BIOLOGICAL POTENTIAL OF THIAZOLIDINONE DERIVATIVES OF SYNTHETIC ORIGIN

Mohd Hussain[1], Mohit Verma[2], and Mahesh Kumar[3]*

Abstract

Thiazolidinone derivatives have garnered a lot of focus lately because of their various biological functions and possible applications in the field of medicinal chemistry. Thiazolidinone derivatives of synthetic origin have shown significant biological potential in medicinal chemistry, with antimicrobial, antioxidant, and antidiabetic activities. Antimicrobial properties have been demonstrated against various pathogenic microorganisms, such as bacteria, fungi, and protozoa. These derivatives have been extensively investigated for their ability to scavenge free radicals and mitigate oxidative stress-induced cellular damage. Antidiabetic properties have emerged as potential candidates for managing diabetes mellitus, modulating key enzymes involved in glucose metabolism and improving insulin sensitivity. Understanding their structure-activity relationships and mechanisms of action can help in developing new therapeutic agents for treating various diseases. Utilizing these biological activities holds great promise for addressing challenges posed by infectious diseases, oxidative stress-related conditions, and diabetes, potentially pave the way for the development of innovative pharmaceutical interventions in the future. This paper focuses on efforts to synthesized and probe their structure activity relationships and mechanisms for the future study. The diverse biological activities, the potential for structural modification, and the need for new therapeutic agents in various disease areas contribute to the prominence of thiazolidinone derivatives in pharmaceutical and chemical research. Continued research in this field has the potential to yield novel drug candidates and contribute to advancements in the pharmaceutical industry.

Keywords: Thiazolidinone derivatives, Synthetic origin, Antimicrobial activity, Antioxidant activity, Antidiabetic activity, Biological potential, Medicinal chemistry

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1.1 Introduction

One of the most crucial goals in "medicinal chemistry" is the development and improvement of drugs. Several areas of chemistry and biology have influenced medicinal chemistry. It deals with the investigation, recognition, and synthesis of pharmacological and related substance metabolic products. Additionally, it makes an effort to connect physical qualities, chemical reactivity, and biodynamic behaviour in order to determine how structure and function are related.. However, the understanding of medication action processes is really what it's about. Additionally, medicinal chemistry entails the isolation, characterisation, and synthesis of substances that is capable of being used for the prevention, treatment, and diagnosis of disease. Consequently, it offers a chemical foundation for the multidisciplinary field of therapeutics [1, 2].

Nitrogen containing heterocycles have drawn substantial attention in a number of bio (organic) investigations due to their broad bioactivity spectrum. Widely present in nature, heterocyclic substances are necessary for life. Numerous heterocyclic compounds are pharmacologically active and often used in clinical settings.

The family of chemical compounds known as thiazolidinone derivatives has received a lot of interest in sector of "medicinal chemistry" because of the wide range of biological qualities it exhibits. A "five-membered heterocyclic ring" with a sulphur atom and a nitrogen atom gives these molecules their structural identity. Four-thiazolidinones (4-TZD), which are regarded as potential molecules as preferred scaffolds for novel drug creation, are one of the well-known heterocycle groups [3]. The different compounds, including 2-thiazolidinone (A), 4-thiazolidinone (B), 5-thiazolidinone (C), 2-thioxo-4-thiazolidinone (D), and thiazolidine-2,4-dione (E), are linked to a variety of pharmacological features [4, 5].

Thiazolidinone derivatives have a long history that began with their initial synthesis and investigation in the early 20th century [6]. Thiazolidinones were initially mainly studied for their antibacterial properties. However, with improvements in chemical synthesis and a better understanding of the links between structure and activity, scientists started to investigate the diverse biological potential of thiazolidinone derivatives [7-9].

Thiazolidinones are synthetically flexible, which has enabled researchers to develop a variety of compounds with better pharmacological qualities during the past few decades. Researchers may easily create these derivatives by making changes to the original thiazolidinone structure, allowing them to modify the biological activities to meet certain needs. Alkyl, aryl, or heteroaryl groups have all been used as substituents to modify the physicochemical and biological characteristics of thiazolidinones [10, 11]. Numerous in vitro and in vivo investigations have proven the biological quality of thiazolidinone derivatives. These substances have shown positive antibacterial effects against a variety of pathogens, such as bacteria, fungus, and parasites. Furthermore, by blocking important enzymes and signalling pathways involved in inflammation, thiazolidinone derivatives have demonstrated notable anti-inflammatory benefits. This qualifies them as possible alternatives for inflammatory disease treatment illnesses for instance, inflammatory bowel disease and rheumatoid arthritis [12-14].

Thiazolidinones have also shown anticancer efficacy by preventing the development of cancer cells and triggering apoptosis [15]. Additionally, they have shown antiviral abilities against a number of infections, such as the flu, hepatitis, and HIV. The antioxidant activity of thiazolidinone derivatives has also been researched for its potential use in treating oxidative stress-related illnesses, such as cardiovascular and neurological diseases [16].

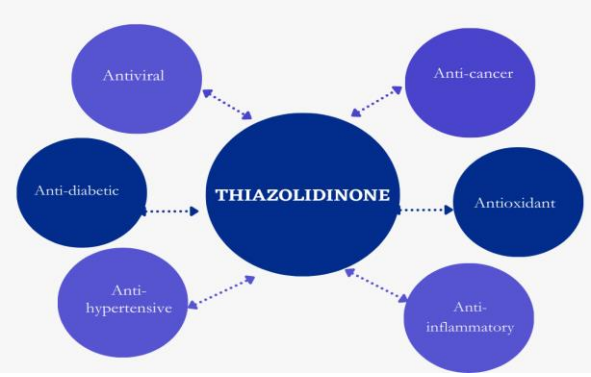


Fig 1

Beyond their biological actions, thiazolidinone derivatives are extremely versatile. Researchers have been able to investigate their potential as enzyme inhibitors, receptor modulators, and imaging agents in diagnostic procedures thanks to their distinctive structural characteristics. A number of molecules have advanced to the preclinical and clinical stages of review, demonstrating the significant impetus that the development of thiazolidinone-based therapeutic candidates has experienced [17].

The study on the "biological potential of thiazolidinone derivatives of synthetic origin" encompasses a multidisciplinary approach, combining organic synthesis, medicinal chemistry, and pharmacology. Researchers in this field aim to design, synthesize, and evaluate novel thiazolidinone derivatives to uncover their therapeutic potential and understand the underlying mechanisms of action. This study aims to do the same.

Organic synthesis plays a crucial role in the study of thiazolidinone derivatives. Chemists employ various synthetic strategies to access a wide range of derivatives with different structural features and substitution patterns. These synthetic methods involve the modification of the thiazolidinone core structure, introduction of functional groups, and exploration of stereochemistry. The synthesis of these derivatives often requires expertise in heterocyclic chemistry, organic transformations, and purification techniques [18].

Once synthesized, thiazolidinone derivatives undergo rigorous evaluation of their biological activities. In vitro assays are commonly employed to assess their antimicrobial, anti-inflammatory, antitumor, antiviral, and antioxidant properties. These assays involve testing the compounds against a panel of microorganisms, evaluating their ability to inhibit specific enzymes or signaling pathways, and measuring their antioxidant capacity. Promising derivatives identified through in vitro studies are further investigated in animal models to evaluate their pharmacokinetics, toxicity, and therapeutic efficacy [19, 20].

Understanding the structure-activity relationships (SAR) of thiazolidinone derivatives is another essential aspect of this field. By systematically modifying the chemical structure of these compounds, researchers aim to elucidate the key molecular features responsible for their biological activities. This knowledge helps in designing and synthesizing derivatives with improved potency, selectivity, and pharmacokinetic properties.

Computational methods, such as molecular dynamics simulations, quantitative structure-activity relationships (QSAR), and molecular docking, are also employed to complement experimental studies. These computational tools provide insights into the interactions between thiazolidinone derivatives and their target biomolecules, aiding in rational drug design and optimization.

THIAZOLIDINONE

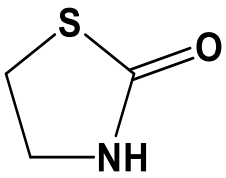


Fig 2 Molecular Structure of Thiazolidinone

Molecular Formula: C_3H_5NOS
Monoisotopic mass: 103.009186 Da
Average mass: 103.143 Da

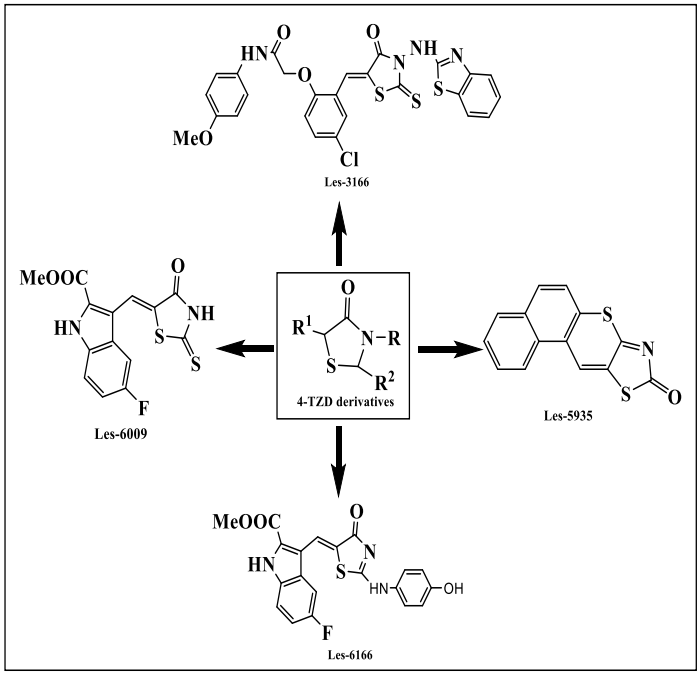


Fig 3 Various derivatives of 4-TZD

1.2 Physical Properties

The chemical structure and substitution patterns of thiazolidinones have an impact on a variety of physical characteristics that they display. Here are some typical thiazolidinone compound physicochemical characteristics:

1. **State:** Thiazolidinones are typically solid compounds at room temperature. However, the melting points of thiazolidinones can vary depending on their specific chemical structure and substituents. Some thiazolidinones may have low melting points, while others may have higher melting points, indicating a more rigid and crystalline nature. An analysis of the compound 3-phenyl-2,4-thiazolidione has shown that it can exist in two polymorphic forms, the first of which melts at 143-144°C and stores well at room temperature, and the second of which melts at "147-148°C" and stores well at temperature above 100°C [21].
2. **Color:** Thiazolidinones can exhibit various colors, ranging from colorless to pale yellow, light brown, or even darker shades. The color of a thiazolidinone compound is determined by its molecular structure, conjugated systems, and the presence of chromophores or functional groups that absorb or reflect light at specific wavelengths.
3. **Solubility:** The solubility of thiazolidinones depends on their molecular structure and the nature of the substituents present. Generally, thiazolidinones are sparingly soluble or insoluble in water due to their hydrophobic nature. However, they can be soluble with several different organic solvents, such as methanol, ethanol, acetone, chloroform, and dimethyl sulfoxide (DMSO).
4. **Stability:** Thiazolidinone compounds are generally stable under standard laboratory conditions. They exhibit good thermal stability, but their stability can change based on the kind of alternatives. Thiazolidinones may undergo chemical reactions under extreme conditions, such as high temperatures or strong acids or bases. Some derivatives may also be sensitive to light and undergo photodegradation.
5. **Crystallinity:** Thiazolidinone compounds can form well-defined crystals due to their rigid structure and the presence of hydrogen bonding sites. Crystalline thiazolidinones often exhibit better solid-state properties, such as improved stability and bioavailability. The crystallinity of thiazolidinone derivatives can be influenced by factors such as the presence of functional groups, molecular symmetry, and intermolecular interactions.
6. **Molecular Weight:** Thiazolidinones have different molecular weights based on their chemical makeup and substituents. Thiazolidinone derivatives can have molecular weights of a few hundred to several thousand atomic mass units (AMU). The molecular weight has an impact on the compound's solubility, permeability, and pharmacokinetics, among other aspects.

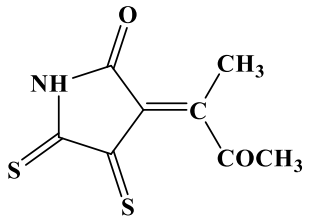
Stereochemistry

Optimal Isomerism

Optical isomerism is a phenomenon where thiazolidinone compounds exhibit the biological process in its purest visual state. In the rhodanine series, tautomerism is limited and optically active when Alkyl or modified alkyl group replacement. Active amines in rhodanine derivative synthesis and these amines' thiourea derivatives result in optically active cyclized compounds. The racemate, a racemic mixture with antibiotic activity, can be resolved by Brucine salt fractionally crystallised.

Dimensional Isomerism

Thiazolidinones and their cpmpounds display geometric isomerism as well. The synthesis of the "rhodanine (2-thioxo-4-thiazolidinone)" derivative demonstrates that it is a transisomer Fig. 3), as opposed to the cyclic structure [22]. The molecule 5-(3-phenyl-2-propenylidene)- 2-thioxo-4-thiazoli dinone (4) occurs in four viable isomers, due to rotation around the CC double bonds. The most stable isomer is discovered to be (Z,E). Furthermore, due to the compound's "2-thioxo-4-thiazolidinone ring's" strong polarity in the N-H bond and the potential for either proton migration to an oxygenation or a sulphur atom, the ring of carbon may exist in thione, thiol, and enol, three distinct tautomeric forms [23].



Rhodanine

1.3. Thiazolidinone derivatives' Biological Activities

A. Antimicrobial Activity

Microbes are the cause of a number of illnesses, including amoebiasis, typhoid, pneumonia, malaria, the common cold, & other viral & infections, as well as certain serious illnesses that include acquired immune deficiency syndrome, syphilis, influenza, TB, and the flu. Micro-

organisms that have acquired the ability to prevent, inactivate, or block the inhibitory or fatal effects of antimicrobial drugs are said to have developed antimicrobial resistance. Life-threatening infectious illnesses were brought on by antimicrobial resistance to both "Gram-positive and Gram-negative strains" in several nations. The most effective tools for avoiding bacterial disease are antimicrobial medications.

There are many antimicrobial medications on the market, but more new antimicrobial agents need to be developed with superior pharmacodynamic and pharmacokinetic features and fewer or no side effects. The majority of thiazolidinediones are effective at killing a variety of microbiological species, both Gram-negative & Gram-positive. Thiazolidinedione derivatives' instead of the aromatic moiety, the type of substitution introduced to the heterocyclic thiazolidinering determines the bactericidal action [24, 25].

Mechanism as anti-microbial agent

The wall of a bacterial cell is crucial for the survival of bacteria because it keeps the cell protected and in good form. A crucial element of the cell wall of bacteria, peptidoglycan, is located at the cytoplasmic membrane's external wall. Cell death may result from the suppression of biosynthetic enzymes. Penicillin-binding proteins, which are membrane-bound extracellular enzymes, or Mur enzymes, which are cytoplasmic enzymes, can both be involved in the production. The Mur ligases (Mur C-F), a group of four ATT-dependent enzymes, are involved in the formation of peptididoglycan peptide stems. Typically a meso-diaminopimelic acid, a diamino acid that is "MurC (L-alanine)" & "MurD (D-glutamic acid)" added in succession is produced, they promote the formation of UDP-MurNAc-pentapeptide. These cytoplasmic ligases are meant to be inhibited by TZD molecules, which will cause the bacterial cells to die.

The research work carried by Shelke *et al.*, and he proposed a new series of thiazolidinone derivatives Scheme 1, [26]. Using the disc diffusion method, the synthesised compounds' antibacterial activity was assessed in vitro against two pathogenic fungi, Candida albicans and Aspergillus niger, as well as Escherichia coli and Pseudomonas aeruginosa are Gram-negative bacteria, while Staphylococcus aureus is a Gram-positive & Bacillus subtilis are sensitive microorganisms.

By combining "4,6-diphenyl-6H-1,3-thiazin-2-amine", aromatic aldehyde, and thioglycolic acid in polypropylene glycol, a novel series of potentially biologically active 3-(4,6-diphenyl-6H-1,3-thiazin-2-yl)-2- (4-methoxyphenyl)thiazolidin-4-one compounds have been created. Their antimicrobial activity has been tested.

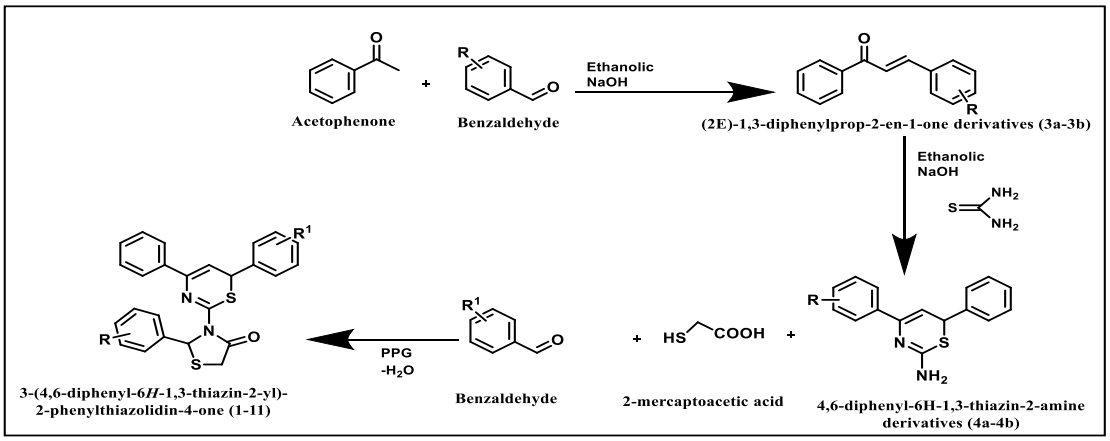


Fig 4 Synthesis of compound 1-11 (Scheme 1)

Compound	R	R_1
1	4-OCH_3	C_6H_4
2	4-Cl	C_6H_4
3	2-Cl	C_6H_4
4	4-OH	C_6H_4
5	4-OCH_3	C_6H_5
6	2-NO_2	C_6H_4
7	4-OCH_3	C_6H_5
8	4-OCH_3	C_6H_4
9	4-OCH_3	4-Cl
10	4-OCH_3	4-OH
11	4-OCH_3	2-NO_2

Compounds (1-11)

The result of the synthesized compounds is shown in Table I

Table I Antimicrobial Activity

Compound	Antibacterial Activity (B. Subtilis)	Antibacterial Activity (E. Coli)	Antibacterial Activity (P.aeruginosa)	Antibacterial Activity (S. Aureus)	Antifungal Activity (C.albicans)	Antifungal Activity (A. niger)
1	15	13	9	19	19	20
2	20	19	23	22	20	21
3	21	23	19	19	18	19
4	23	19	22	18	10	11
5	14	12	19	15	11	13
6	7	11	8	13	13	10
7	11	15	17	13	20	18
8	9	13	11	10	21	20
9	19	23	20	22	22	19
10	17	20	23	22	13	10
11	9	17	15	14	10	9
Ciprofloxacin	26	28	25	24	-	-
Fluconazole	-	-	-	-	26	25

Hence, by reacting 4,6-diphenyl-6H-1,3-thiazin-2-amine, aromaticaldehyde, and thioglycolic acid in polypropylene glycol at 110°C temperature, they accomplished the development of an innovative class of compounds that could be biologically active 3-(4,6-diphenyl-6H-1,3-thiazin-2-yl)-2-(4-methoxyphenyl)thiazolidin-4-one derivatives. The findings show that some of the series' chemicals showed promising antibacterial and antifungal efficacy when compared to conventional medicines.

(Nawale *et al.*, 2012) created the in vitro antibacterial efficacy of a new family of "5-substituted 2,4-thiazolidinedione derivatives" against Bacillus subtilis, Staphylococcus aureus, and Pseudomonas aeruginosa, two species of "Gram-positive and Gram-negative bacteria", respectively. (Scheme 2) Compounds 12, 13, 14, and 15 showed the most active of all evaluated microbes among the synthetic derivatives. Table II shows the results of synthesised chemicals [27].

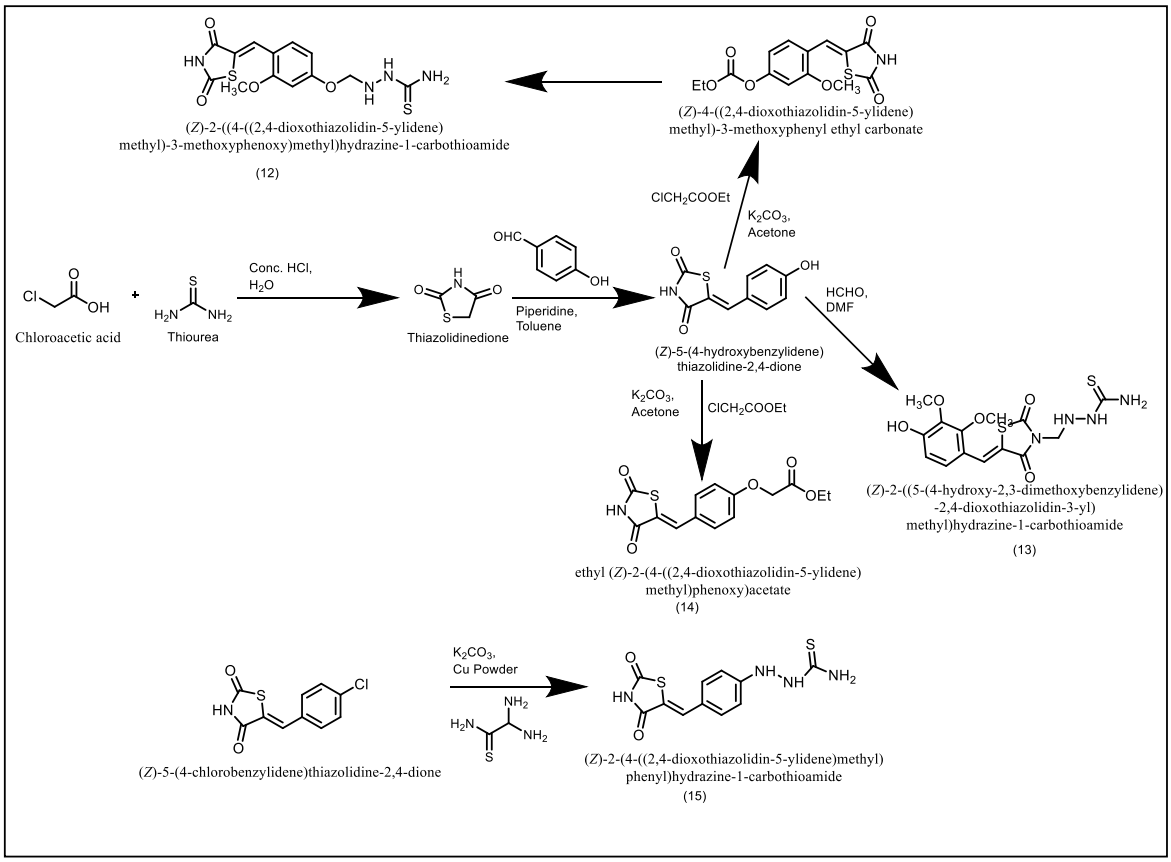


Fig 5 Synthesis of Compound 12-15 (Scheme 2)

Table II Result of synthesized Compounds (12-15)

Compounds	"Bacillus subtilis"	"Staphylococcus aureus"	"Pseudomonas aeruginosa"
12	31.25	31.25	31.25
13	31.25	31.25	31.25
14	62.5	125	62.5
15	31.25	62.5	125
Streptomycin	3.9	3.9	3.9

As a result compounds 12, 13, 14, and 15 were evaluated for their effectiveness against Pseudomonas aeruginosa, Bacillus subtilis, and Staphylococcus aureus. The results showed varying levels of activity, with compound 43 exhibiting the highest potency against all tested microorganisms. Streptomycin, used as a positive control, demonstrated significant bacterial resistance in the tested strains.

In order to test their in vitro bacterial resistance against "Gram-positive" & "Gram-negative bacteria" as well as fungi (A. niger and A. fumigates), [28] synthesised a number of new compounds of imidazolyl thiazolidinedione Compounds (Scheme 3) (by Moorthy et al.,). They were contrasted with ketoconazole and ciprofloxacin, two common medications. In the research, the imidazolyl thiazolidinedione derivatives were created using a multi-step reaction sequence. The compounds were then characterized using various techniques including infrared spectroscopy, mass spectrometry, and nuclear magnetic resonance. The "antimicrobial evaluation" of the synthesized compounds was performed contrary to a variety of bacteria using standard methods. Table III shows the outcomes of the synthetic substance.

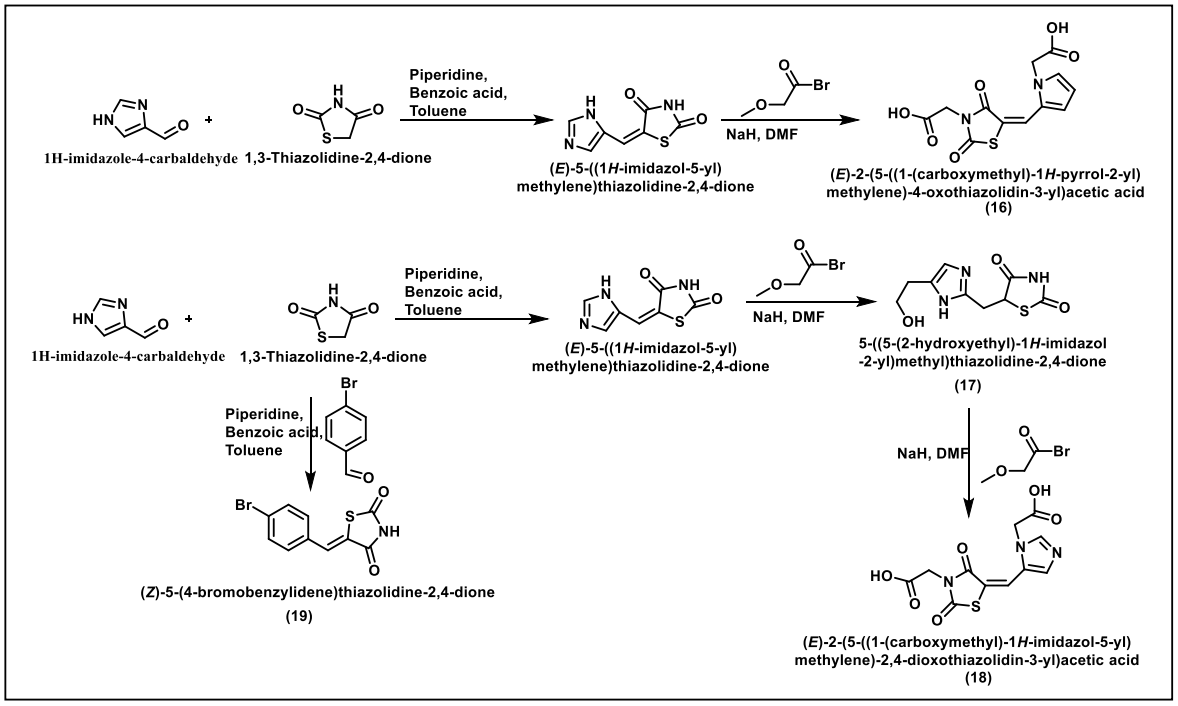


Fig 6 Synthesis of Compound 16-19 (Scheme 3)

Table III Outcomes of the synthetic substance

Compounds	Gram Positive bacteria		Gram Negative bacteria		Fungi	
16	18 (1.9)	16 (1.4)	28 (1.6)	28 (0.56)	20 (8.8)	26 (2.3)
17	21 (22.1)	27 (22.2)	27 (21.5)	21 (21.5)	24 (20.7)	20 (22.6)
18	16 (2.7)	18 (3.39)	22 (9.2)	16 (1.4)	22 (8.2)	26 (3.4)
19	21 (22.1)	25 (22.2)	25 (21.5)	21 (21.5)	28 (21.6)	25 (21.7)
Ciprofloxacin	29 (0.2)	31 (0.39)	32 (0.2)	33 (0.25)	-	-
Ketoconazole	-	-	-	-	26 (6.1)	24 (0.23)

The outcome of the research showed that the imidazolyl thiazolidinedione compounds had a substantial antibacterial effect on the tested microorganisms. The compounds demonstrated varying degrees of efficacy against both "Gram-positive" and "Gram-negative bacteria" as well as

fungi. The antimicrobial activity of the derivatives was comparable to or even superior to that of standard antimicrobial agents used as positive controls in the study.

The antibacterial activity of certain new biphenyl tetrazole thiazolidinedione derivatives (Scheme 4) was tested by Khan et al. against the bacterial strains Escherichia coli and Bacillus subtilis [29]. The research involved the creation of several biphenyl tetrazole compounds -thiazolidinedione compounds using established synthetic methods. These compounds were then subjected to various biological evaluations to determine their inhibitory activity against bacterial peptide deformylase.

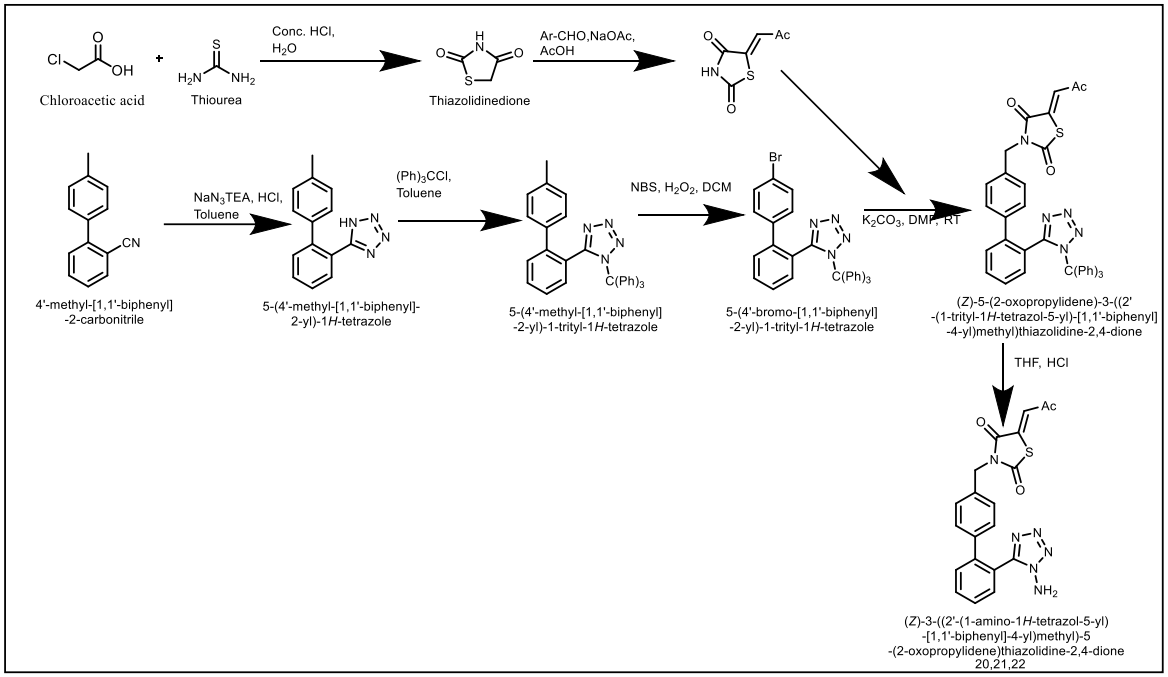
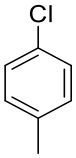
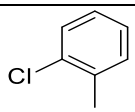
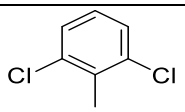


Fig 7 Synthesis of Compound 20-22 (Scheme 4)

Compound	Ar
20	
21	
22	

Different types of bacteria are utilized to test the compounds' antibacterial property, and the MIC ("minimum inhibitory concentration") values were calculated, it shown in table VI.

Table VI Results of Synthesize compounds for the anti-microbial activity

Compounds	E. coli (MIC ± SLM)	B. subtilis (MIC ± SLM)
20	20.75 ± 1.55	35.41 ± 2.41
21	19.41 ± 1.27	26.00 ± 1.96
22	8.58 ± 0.42	8.42 ± 0.51
Ciprofloxacin	25.00 ± 0.95	50.00 ± 1.75

The outcomes of the work indicate several of the created compounds exhibited major inhibitory properties against bacterial peptide deformylase. Furthermore, some of the compounds displayed potent antimicrobial opposition to the verified bacterial strains, including both "Gram-positive"

and "Gram-negative bacteria". The researchers also performed molecular docking studies to gain insights into the binding interactions among the synthesized mixtures, as well as the site of action of bacterial peptide deformylase.

B. Antioxidant activity

The need for oxidation inhibitor compounds arises from the harmful effects of oxidative stress on biological systems. When the amount of "Reactive oxygen species (ROS)" produced and their ability to be neutralised by the body's antioxidant defence mechanisms are out of balance, oxidative stress is the result. ROS are incredibly reactive molecules that could harm things to cellular components such as proteins, lipids, and DNA [30].

Oxidative stress has been linked to various diseases and conditions, including cardiovascular diseases, neurodegenerative disorders, cancer, diabetes, and aging. The accumulation of oxidative damage in cells and tissues can lead to malfunction and speed up the onset and spread of various illnesses [31].

Oxidation inhibitor compounds, such as the thiazolidinedione derivatives mentioned in the research work, play a crucial role in mitigating the harmful effects of oxidative stress. These compounds have the ability to scavenge or neutralize ROS, thereby reducing oxidative damage to cells and tissues.

By acting as antioxidants, oxidation inhibitor compounds help maintain the balance between ROS production and antioxidant defense systems, preventing or minimizing the detrimental effects of oxidative stress. They protect cellular components from oxidation, maintain cellular integrity, and promote overall cellular health.

In addition to their antioxidant properties, oxidation inhibitor compounds may also possess other beneficial properties, such as α-amylase inhibitory and antidiabetic activities, as demonstrated in the mentioned research work. This highlights their potential as multifunctional agents for managing oxidative stress-related disorders and associated complications.

Mechanisms of Anti-oxidation agent

The generation of free radicals leads to oxidative stress. Free radicals are chemically active molecules with excess or insufficient amounts of electrons. The most harmful free radicals, often referred to as reactive reactive oxygen species (ROS), are those that include oxygen. To turn oxygen into reactive oxygen species (ROS), oxidants trigger a number of important enzymes, including SOD, catalase, and NADPH oxidase. ROS harm cells, proteins, and DNA by scavenging bodily cells in order to give or grab protons. In order to prevent the cascade effect brought on by ROS propagation, TZD derivatives are meant to donate their proton to the ROS.

A study conducted by (**Sameeh *et al.*, 2021**) created a number of compounds of thiazolidinedione. and evaluated their antioxidant activity using established assays. They also investigated the α-amylase inhibitory activity of the compounds, which is an important target for the management of diabetes. In addition, the antidiabetic potential of the synthesized derivatives was assessed through in vitro and in vivo experiments [32] (Scheme 5).

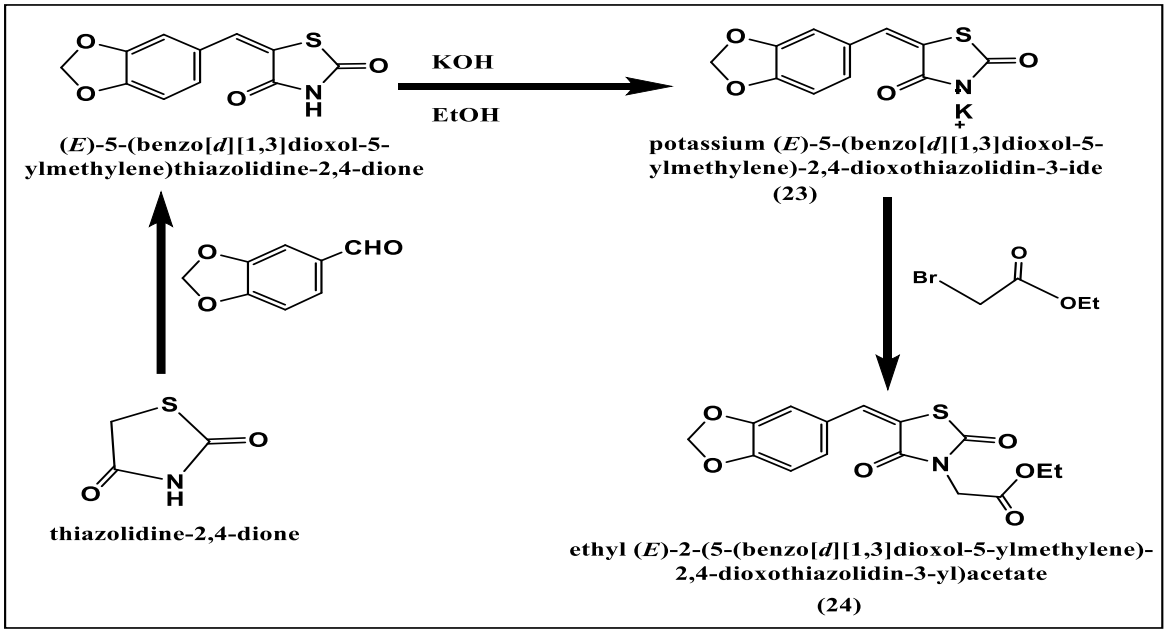


Fig 8 Synthesis of Compound 23, and 24 (Scheme 5)

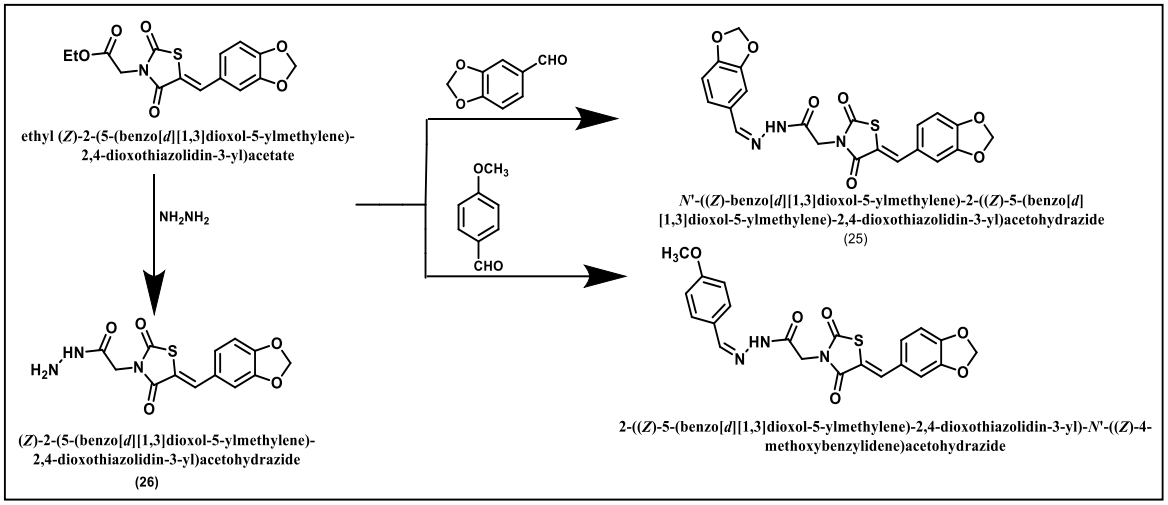


Fig 9 Synthesis of Compound 25, and 26 (Scheme 6)

(Scheme 6) Chloroacetyl thiazolidine-2,4-dione 24 was created by further reacting the molecule 23 with chloro-acetyl chloride. A "5-(benzo[d] [1, 3]dioxol-5-ylmethylene-3-(2-oxopropyl)thiazolidine -2,4-dione" (25), shown in (Scheme 6), was produced by the reaction In the refluxing DMF solution of the equimolar salt of potassium (23) and chloroacetone conditions. Similar to how the potassium salt (23) and chloroacetic acid reacted to produce an excellent yield of "2-(5-(benzo[d] [1,3]dioxol-5-ylmethylene)-2,4-dioxothiazolidin-3-yl) acetic acid" (26),

Table V shows the IC_{50} for the synthesized compounds. The anti-oxidant activity is analysed utilizing the DPPH assay.

Table V Result of synthesized compound

Compound	IC50 1000 µg/mL
23	0.16
24	0.8
25	4
26	20

The findings of the study indicated that the thiazolidinedione compounds exhibited significant antioxidant property, as well as potent α-amylase inhibitory effects.

Lupascu *et al.,* [33] used in vitro models such as the "DPPH radical scavenging assay" and the "ABTS [2,2-azino-bis-(3-ethyl benzothiazoline-6-sulfonic acid] radical scavenging assay method" to create a chain of novel thiazolidinediones with a xanthine moiety and evaluate their antioxidant potential. The maximum antioxidant activity was seen in derivatives 27, 28, 29, and 30 of the synthesised compounds. The outcomes of the most effective derivatives are presented in Table VI (Scheme 7).

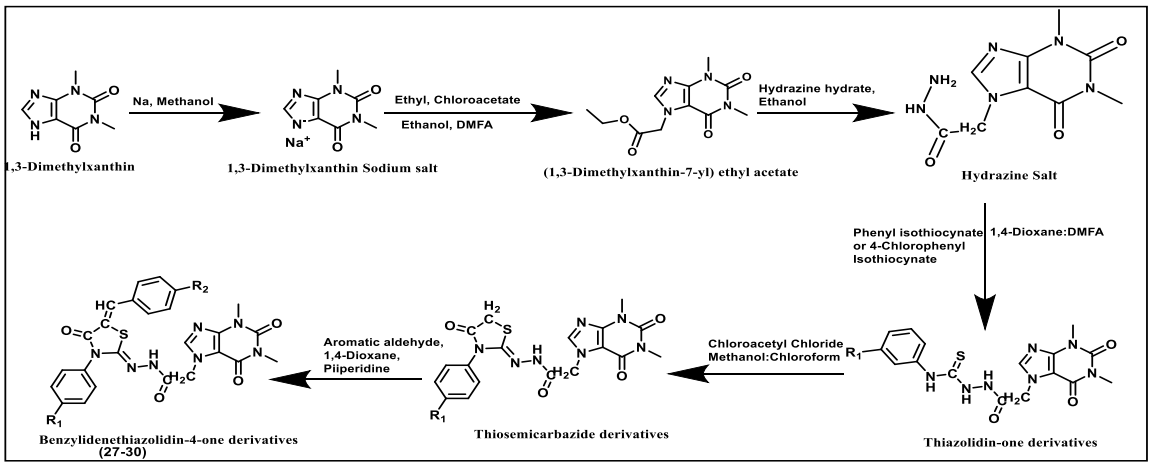


Fig 10 Synthesis of Compound 27-30 (Scheme 7)

Compounds	R_1	R_2
27	H	4-hydroxy
28	H	$4-N(CH_3)_2$
29	Cl	4-hydroxy
30	Cl	$4-N(CH_3)_2$

Table VI Anti-oxidants result

Compounds	**EC50 (mg/mL)**	**Compounds**
27	0.025 ± 0.0012	27
28	0.022 ± 0.0013	28
29	0.033 ± 0.0014	29
30	0.026 ± 0.0028	30
Ascorbic acid	0.0067 ± 0.0003	**Ascorbic acid**

All tested compounds are more effective than 3-phenlythiazolidin-4-one and 3-(4-chlorophenyl) thiazolidin-4-one, respectively, but they are less effective than ascorbic acid (AA) at the same concentration thanks to the chemical modification of the parent thiazolidin-4-one derivatives.

C. Anti-diabetic Activity

Despite the existence of conventional pharmaco-logical therapies, the burden of DM on healthcare systems worldwide remains significant. Therefore, there is a continuous need to explore and develop novel molecules that can effectively manage this metabolic condition. Healthcare professionals are seeking novel molecules to expand treatment options for diabetes management, improve efficacy, target specific mechanisms, minimize side effects, and prevent or delay complications. By exploring new molecules, researchers aim to develop safer, more effective treatments that achieve better glycemic control and minimize complications. This approach can help individuals with diabetes manage their condition and improve long-term health outcomes. By exploring new molecules, researchers can develop compounds with improved safety profiles and reduced risk of adverse effects, ultimately improving the overall quality of treatment for individuals with diabetes.

In the development of new drugs, a major heterocyclic unit is the thiazole moiety.. A brief survey of past works reveals that there have been inquiries into the creation of thiazolidinediones. Numerous pharmacological properties of thiazolid-iones molecules include antibacterial, antitumor, anti-viral, anti-inflammatory, anti-diabetic effects and antitubercular. Thiazolidinediones (TZDs) have shown great potential as anti-diabetic agents.

Mechanism of TZD as anti-diabetic agent

Thiazolidinediones (TZDs) work as anti-diabetic drugs by activating the PPAR-gamma peroxisome proliferator-activated receptor. Transactivation and transrepression are the two basic methods through which PPAR- functions.

TZDs bind to PPAR- and activate it during transactivation. Exogenous ligands (IZD) or endogenous ligands like prostaglandins (PGs) and fatty acids are both capable of mediating this binding. The PPAR-RXR complex is formed when the retinoid X factor (RXR) and PPAR- create a heterodimer. The target genes' peroxisome proliferator response elements (PPRE) are specifically targeted by this complex. The PPAR--RXR complex along with a coactivator with chromatin acetylase activity, promotes the transcription of genes that regulate differentiation of cells, the breakdown of glucose, and the breakdown of lipids. By improving cellular insulin sensitivity and glucose uptake, these target genes are activated, assisting in the lowering of blood sugar levels. Figure 11 shows the PPAR transcription of genes processes [34].

PPAR- adversely interacts with other signalling routes like the NFKB (nuclear factor kappa beta) pathway, which regulates a number of genes involved in inflammation, when transrepressing. Figure 12 shows the pathway of gene trans-repression. Leukocytes and cytokines, which are examples of inflammatory mediators, are expressed less when NFKB is inhibited by PPAR-. This anti-inflammatory impact helps to reduce insulin resistance and enhance glucose metabolism as a whole [35].

Additionally, TZDs cause varied effects by activating PPAR- in various tissues. PPAR-activation increases lipid uptake and triglyceride storage in adipose tissues, enhancing insulin sensitivity. Additionally, TZDs encourage the growth of fresh adipocytes. By stimulating the anti-inflammatory M2 phenotype in macrophages, TZDs reduce inflammation and macrophage infiltration in fat tissues. In addition to acting on PPAR- in liver cells, TZDs can also inhibit liver

fibrosis and inflammation. By interacting with PPAR-, TZDs can prevent atherosclerosis in macrophages. Improved insulin sensitivity, glucose absorption, and lipid metabolism are all benefits of TZDs on PPAR- activation, which lower blood glucose levels in people with type 2 diabetes.

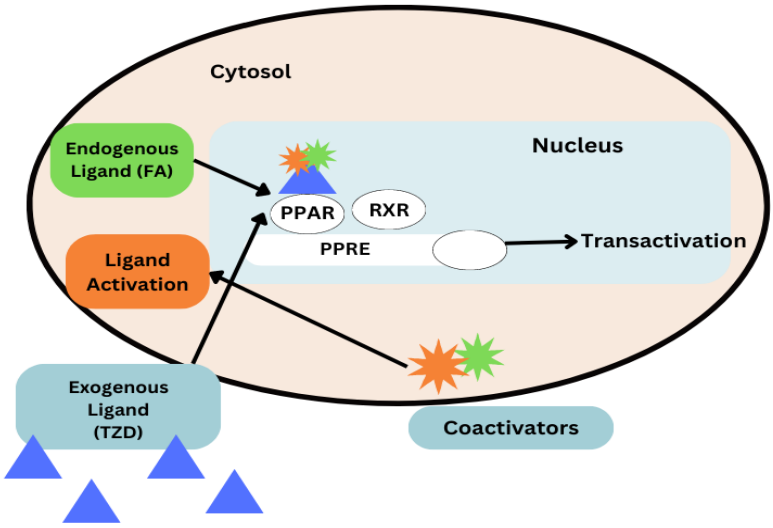


Figure 11 shows the PPAR transcription of genes processes

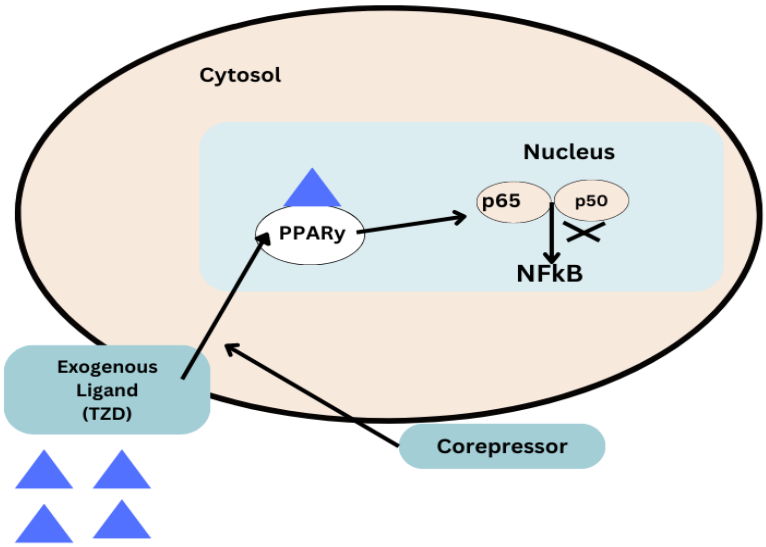


Figure 12 PPAR's gene trans-repression pathways

(**D *et al.*, 2016**) worked on deriving the anti-diabetic property of TZD. A noval family of 2, 4-thiazolidinedione-based compounds has been created via the reaction between 4'-chlorosulphonyl -5-benzylidene-2, 4-thiazolidinedione and different substituted phenoxy benzene amines. (Scheme 8). On albino rats, these novel compounds (31-37) had their anti-diabetic potential assessed. When compared to the common medication metformin, the majority of the compounds had considerable antidiabetic efficacy [36].

Wistar albino rats were used in the study, and their blood sugar levels ranged from 200 to 400 mg/dl. Alloxan monohydrate was given intraperitoneally after the subject had fasted for 24 hours. Rats were separated into test, standard, and control groups after 72 hours and had high blood glucose levels. In a 0.25% w/v CMC solution, test substances were given orally at a dosage of 50 mg/kg. The study's objectives were to pinpoint precise pathways, reduce side effects, and stop or postpone diabetes-related problems. For those with diabetes, long-term health outcomes may be improved by the creation of innovative diabetic agent molecules.

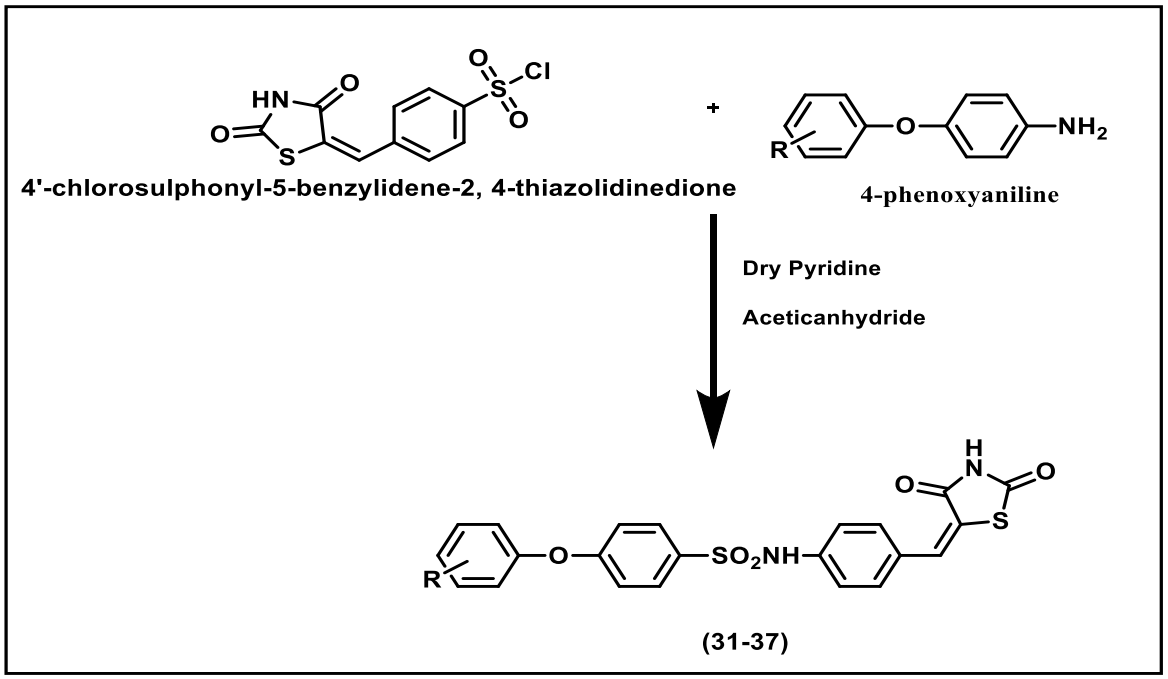


Figure 13 Synthesis of Compound 31-37 (Scheme 8)

Compounds	R
31	H
32	$4-OH_3$
33	4-Cl
34	4-CH_3
35	4-OC_2H_5
36	2-OCH_3
37	2-Cl

Table VII shows the blood glucose alterations that occurred after diabetic rats were treated with synthetic TZD derivatives

Table VII Blood glucose level for compounds 31-37

Compound	**Blood glucose**	**level**	**mg/dl (Mean + SE)**
	0 hr.	**3hr**	**6hr**
31	354.2±5.856	342.5±5.464	321.7±10.96*
32	343±5.797	313.8±9.411**	303.2±9.827***
33	351.8±7.007	340.3±4.580	318±9.299*
34	341.5±6.158	320.5±6.737	313.3±9.500**
35	353.7±6.026	315.8±8.109*	311.2±9.297**
36	357.7±6.677	348.0±5.882	340.7±3.593
37	358.3±8.597	346.3±5.981	342.8±3.544
Positive Control	335.7±5.168	345.5±5.488	354.3±8.135
Normal Control	125.0±4.494	126.3±4.047	127.7±3.703
Standard (Metformin)	343.3±6.206	322.8±4.989**	292.0±7.767****

Eight compounds were synthesised, and seven of them (31-37) were tested for their antidiabetic efficacy. Significant antidiabetic effects were seen in medication 32, 34, and 35.

On oral administration, the medications 31 and 33 displayed a modest level of anti-diabetic action. After six hours, the compound 32 significantly decreased blood glucose levels (p0.0001), and 34, 35 significantly increased hypoglycemic activity (p0.05).The values in the tables represent the blood glucose levels (in mg/dL) at different time points. The Mean ± SE indicates the average blood glucose level for each compound, along with the standard error of the mean.

Yasmin *et al.*, 2017 created and put to the test a library of brand-new "5-benzylidene-thiazolidin-2,4-dione" (BTZD) substituted compounds on the TZD nucleus' nitrogen. BTZDs were prepared using Knoevenagel condensation and piperidine as a catalyst. 2- By mixing amines in triethylamine with 2-chloroacetylchloride, chloroacetamide derivatives were created (Scheme 9) [37].

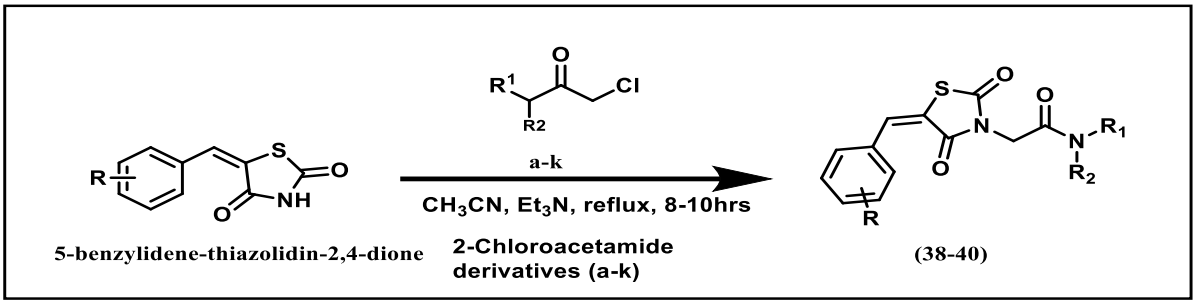


Figure 14 Synthesis of Compound 38-40 (Scheme 9)

Compound	R	R_1	R_2
38		-H	$-(CH_2)_3CH_3$
39		$-C_2H5$	$-C_2H_5$
40	4-Cl		

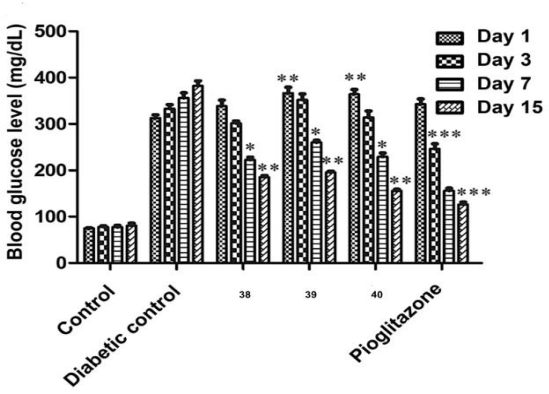


Figure 15 Blood glucose level for the compounds 38, 39, and 40

In a rat model of diabetes caused by streptozotocin and nicotinamide, the study examined the anti-diabetic effect of PPAR partial agonists 38, 39, and 40. Rats received the substances orally for 15 days while fasting blood glucose levels were measured. After 15 days, diabetic rats treated with compounds 38–40 and pioglitazone had considerably lower blood glucose levels than the rats in the control group. The in vitro and in vivo results were in agreement, demonstrating that these drugs had a decreasing effect on blood sugar by activating PPAR receptors. The activity of compound 40 was comparable to that of the study's reference medication, pioglitazone. Figure 15 shows the result of the research work.

Pattan *et al.,* created a noval series of "thiazolidinedione derivatives", including 5-(4-substitutedsulfonylbenzylidene)-2,4-thiazolidinedione. The "ANOVA and Dunnet's 't' test" were used to analyse the in vitro anti-diabetic activity. From this series, compounds 41, 42, and 43 shown modest activity and were similar to the common medication glibenclamide (Scheme 10). Table VIII presents the active compound's data [38-40].

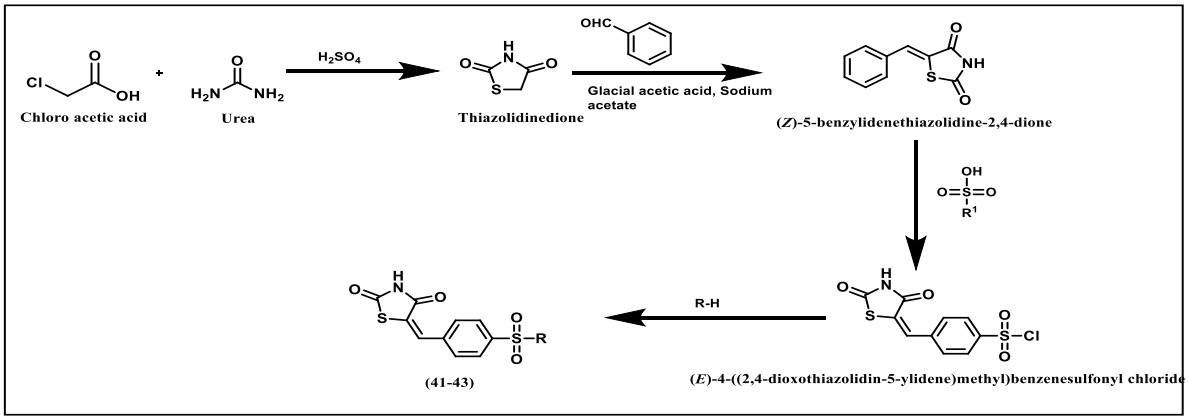


Figure 16 Synthesis of Compound 41-43 (Scheme 10)

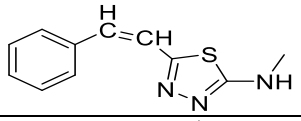
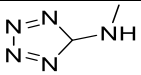
Compounds	R
41	
42	
43	

Table VIII Blood glucose level of the compounds

Compounds	Blood Glucose Level (mean ± SE)		
	0 hr	**3hr**	**6hr**
41	320.5 ± 15.81	137.0 ± 3.80	123.5 ± 1.10
42	213.5 ± 8.78	106.3 ± 6.91	95.75 ± 6.06
43	283.5 ± 43.76	166.3 ± 38.92	124.5 ± 13.16
Standard	385.8 ± 21.37	156.8 ± 10.87	93.4 ± 4.98

1.4 Conclusion

This study report concludes by highlighting the biological potential of synthetic thiazolidinone derivatives, with a focus on their antibacterial, antioxidant, and antidiabetic actions. The extensive data supporting the potential of Thiazolidinone derivatives in these fields comes from the literature review that was done for this study.

First off, the antimicrobial capacity of derivatives of thiazolidinone has been thoroughly investigated and described in the literature. Numerous studies have documented how these compounds can stop the growth of different microbes, including fungus, "Gram-positive bacteria," and "Gram-negative bacteria". The research that is being presented supports these conclusions by proving the antibacterial effectiveness of the chemical derivatives versus Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, and other microbes. This demonstrates the potential of derivatives of thiazolidinones as powerful antimicrobials.

Secondly, the literature survey reveals the antioxidant potential of Thiazolidinone derivatives. Oxidative stress, Reactive oxygen species (ROS) generation and the body's antioxidant defence system are out of balance, which is a major factor in the onset of many diseases.. Thiazolidinone derivatives have shown remarkable antioxidant activity, effectively scavenging ROS and protecting cells from oxidative damage. The current research work reinforces these findings by demonstrating the antioxidant activity of the synthesized derivatives, further substantiating their value in combating oxidative stress-related disorders.

Additionally, the literature survey highlights the antidiabetic activity of Thiazolidinone derivatives. Diabetes is a common metabolic condition marked by elevated "blood glucose levels," α-amylase inhibitors are key targets in the management of diabetes as they inhibit the breakdown of complex carbohydrates, leading to reduced glucose absorption and lower postprandial glucose levels. Thiazolidinone derivatives have been reported to possess α-amylase inhibitory activity, making them potential candidates for developing antidiabetic agents. The research work supports these findings by evaluating the "α-amylase inhibitory activity" of the synthesized derivatives, providing further evidence of their potential in diabetes management.

Overall, the comprehensive literature survey conducted for this research paper strongly supports the "biological potential of Thiazolidinone derivatives of synthetic origin." The antimicrobial, antioxidant, & antidiabetic activities demonstrated by these derivatives highlight their versatility and therapeutic potential.

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Authors' Contributions

MK designed and finalized the scheme; MH performed review work and MV wrote the paper. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate
Not applicable

Conflict of interest
The authors declare no conflict of interest

Consent for publication
All authors of the research paper have approved the manuscript for submission.

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