REVIEW ON SYNTHESIS AND THERAPEUTIC IMPORTANCE OF THIAZOLIDINONE AS ANTIDIABETIC, ANTIMICROBIAL AND ANTIOXIDANT AGENTS IN LAST TWO DECADES

Mohd Hussain[1], and Mahesh Kumar[2]*

Abstract

Heterocyclic compounds are an integral part of the chemical, life sciences and constitute a considerable quantum of the modern research that is being currently pursued throughout the world. Heterocyclic compounds, having atoms other than carbon in the ring, have long been proven to have vivid biological activities. Thiazolidinone scaffold has become a highly powerful scaffold in the current era when it comes to its clinical importance. Its wide variety of biological functions have piqued the researcher's intense curiosity. It is a five-membered heterocyclic ring having almost all types of biological activities. A wide range of pharmacological actions, including anti-cancer, anti-diabetic, anti-microbial, anti-viral, anti-inflammatory, and anti-convulsant, are present in thiazolidinones. In the recent years, several innovative synthetic techniques have been developed to create a variety of scaffolds to investigate a range of biological activities. The authors have attempted to summarize various thiazolidinone derivative their synthetic approach as well as their biological importance in this review.

Keywords: Thiazolidinone derivatives, Molecular Modeling, Antimicrobial, Antioxidant, and Antidiabetic Activity

[1,2*]Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India – 124001
Email: mohdhussain1206@gmail.com

[2]*Corresponding Author
*Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India – 124001
Email: drmaheshkumar.pharma@mdurohtak.ac.in

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Introduction

Thiazolidinones are a biologically significant class of heterocyclic compounds with a wide range of biological activities. Heterocyclic compounds are those that contain atoms other than carbon in their rings. They have long been known to have important biological activities, and the biological activities of many different heterocyclic compounds have been studied extensively.

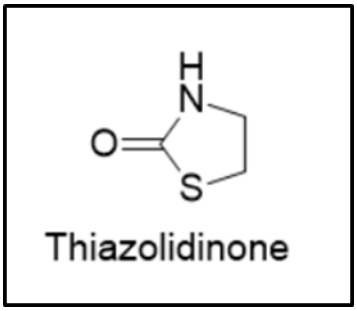
The 2, 3, and 5 positions of the thiazolidinone ring are all susceptible to substitution, which can change the properties of the compound. It is also possible to modify the substituents bound to the nitrogen atom and the carbon atom of methylene. The 4 thiazolidinone carbonyl group is relatively inert [1]. The increasing resistance of microbes to existing antimicrobial drugs is a major public health concern. This has led to a demand for the search and synthesis of new antimicrobial compounds. Thiazolidinones are a promising class of compounds with a wide range of antimicrobial activities [2].

The antimicrobial activities of thiazolidinones have been studied against a wide range of bacteria, fungi, and viruses. Some thiazolidinones have been shown to be effective against multidrug resistant bacteria, such as methicillin resistant Staphylococcus aureus (MRSA). The antimicrobial properties of thiazolidinones are thought to be due to their ability to inhibit the growth of microbes by interfering with their metabolism. For example, some thiazolidinones have been shown to inhibit the synthesis of bacterial cell walls.

Their antidiabetic properties is another significant field of research. Thiazolidinones have been used to develop a number of new drugs, including rosiglitazone, pioglitazone, lobeglitazone, and troglitazone. These drugs are used to treat diabetes, cancer, arthritis, inflammation, and other conditions. The peroxisome proliferator activated receptor gamma (PPAR), a transcription factor that controls the expression of genes involved in glucose metabolism, is activated by these medications [3].

Thiazolidinones are particularly interesting because they can be modified to exhibit a wide range of different biological activities. For example, thiazolidinones can be modified to have antidiabetic, anticancer, antiarthritic, antiinflammatory, antimicrobial, and antimelanoma activities. The potential of thiazolidinones to treat various diseases like cancer, arthritis, and inflammation is also being researched. Thiazolidinones' biological actions are currently being researched, and it's conceivable that more medications based on them may be created in the future.

Chemistry of Thiazolidinone



Thiazolidinones, also known as thiazolidines, are saturated forms of the thiazole that have a carbonyl group. Heterocycles known as 1,3 thiazolidine 4 ones have a carbonyl group at position 4, a nitrogen atom at position 3, and a sulphur atom at position 1. The primary structure of 4 thiazolidinones has been altered in a variety of ways to produce new derivatives.

- Although several substitutes may be used in the 2, 3, and 5 positions, the group bound to the carbon atom in the 2 position makes the biggest impact in the structure and characteristics.
- The structures are susceptible to changes in the substituents bound to the nitrogen atom and the methylene carbon atom.
- The carbonyl group of the 4 thiazolidinone is highly inert. However, occasionally, the combination of 4 thiazolidinone with the unsubstituted 4-thiazolidinones are typically solids that frequently melt upon decomposition; however, the melting point is lowered by the addition of an alkyl group to the nitrogen. The 4 Thiazolidinones without aryl or higher alkyl substituents have a moderate water solubility.

Molecular Modeling

Molecular Modeling study has been one of the most basic and relevant action for drug discovery. The most interesting case is the protein ligand interaction because of its function in medicine. Molecular modeling is integral part of the drug discovery process. It allows forecast of molecular interactions that hold together a protein and a ligand in the bound state (**Cohen *et al.*, 1990**) [4]. Molecular modeling is a collection of computer based techniques for starting, showing and determining the structures and reactions of molecules, and those properties are dependent on these three dimensional structures. For the study of molecular recognition, one of the most well known and popular structure based methods is molecular modelling, which seeks to forecast the binding mechanism and binding affinity of a complex

produced by two or more constituent molecules. It makes predictions about the three dimensional structure of any complex based on the binding characteristics of ligands and targets.

One of the areas of science with the fastest growth is molecular modelling (MM). It can range from performing intricate computer simulations on large proteins and nanostructures to building and visualizing simple molecules in three dimensions (3D). MM is a group of computer based methods for controlling, visualizing, and modifying the 3D structures and reactions of molecules as well as the qualities that depend on them. Computational chemistry, drug design, computational biology, nanostructures, and material science are some of the topics covered by MM methods. Eight papers covering five topics new methods in MM, computational chemistry, computational biology, nanostructures, and material science are collected in this issue. This issue includes descriptions of two novel procedures (**Ghelfi *et al.*, 2011**) [5]. **D. J. Medieiros *et al.*,** developed the utility software to compute the ab initio charges of each atom for reasonably big molecules, and they describe the first technique (**Medeiros et al., 2013**) [6]. The second method is provided by **K. Dedachi *et al.*,** who created a new all-atom force field for use in applications for short peptide 3D structure prediction [7]. The authors of two pieces in this issue that deal with computational chemistry are S. Arshadi et al. The electrical structure of Zigzag boron nitride nanotubes and two models of diborinin-doped boron nitride nanotubes are investigated in one study using applications of density functional theory (DFT) (**Keshavarzi Arshadi *et al.*, 2020**) [8]. The second study describes the use of DFT to compute the nuclear magnetic resonance (NMR) parameters of pyrazinedroped nitride nanotubes and analyse their electronic structure. MM of critical micelle concentration for a single chain and a double chain of a surfactant with amphiphilic capabilities are illustrated in the study by R. Behjatmanesh Ardakani and M. Farsad. Monte Carlo simulations are used to compare the self assembly processes of the single chain and double chain surfactants. In order to comprehend biological mechanisms, two studies use computational biology. In one study, used a mix of MM and spectroscopic approaches to show how transresveratrol interacts with bovine serum albumin (**Tu *et al.*, 2021**) [9]. The second publication by illustrates the use of guided molecular dynamics simulations to look at the mechanism of the p VEC peptide's membrane translocation (**Rathnayake *et al.*, 2017**) [10]. The mouse vascular endothelial cadherin protein, which is responsible for the physical contact between neighbouring cells, is the source of this short peptide. Last but not least, one of the major developments in the last five years is the use of MM in the study of material science. This development is demonstrated inthe study by **Da Silva *et al.*,** combining DFT with periodic boundary conditions. Understanding the 3D structure of the biological target is essential for computer aided and structure based drug design. Iterative drug design is a procedure that starts when a molecule is found to have an intriguing biological profile and concludes when the chemical synthesis and activity profile are perfected. MM now penetrates all facet of drug development (**Da Silva *et al.*, 2018**) [11]. In order to describe activity profiles, geometries, and relativities, scientists have used computer models of novel chemical substances. Virtual screening, hit to lead optimization of affinity and selectivity, and lead optimization of additional pharmacological qualities while maintaining affinity are the three stages of drug development that can be accomplishedvia MM (**Lasri *et al.*, 2020**) [12].

Rapid Overlay of Chemical Structures (ROCS) is a technique used to identify compounds that are similar based on their three dimensional shapes. Shape similarity is regarded as a critical characteristic for computational drug development in order to accurately predict and comprehend the interactions between protein ligands. Shape displays friendly neighbourhoodbehaviours that are very reflective of biological similarities and are in no way similar in 2D. The target compounds thiazolidindiones and the must be in the database as well as the query molecules celecoxib and rosiglitazone. The Tanimoto Combo score, which is the total of the Shape Tanimoto and the Color Tanimoto, was used to determine the degree of alignment between the database and the query. Shape Tanimoto has a scale from 0 to 1.0 and represents the shared volume and mismatch volume. 0 to 1.0. Utilizing fragment unconnected molecules with nonchemically meaningful bits, the query and database molecules are united into a single species (**Kasam *et al.*, 2009**) [13].

Molecular Docking

A computer technique called molecular docking is used in molecular biology and drug development to forecast the most effective orientation or conformation of the small-molecule ligand, such as a drug candidate, when it binds to a target receptor, such as a protein. It entails investigating several potential binding configurations between the receptor and the ligand in order to identify the binding conformation that is both energetically

advantageous and physiologically significant [14,15].

Molecular Docking Functions

- ***Drug Discovery***

The development of new drugs is one of the main uses of molecular docking. By electronically screening huge databases of compounds against a target protein, it aids researchers in identifying possible therapeutic candidates. The choice of molecules that are most likely to bind to the target with high affinity and specificity is made possible via docking [16].

- ***Binding Mode Prediction***

Molecular docking sheds light on the physical configuration and interactions between a ligand and its receptor. Binding Mode Prediction. To comprehend the molecular underpinnings of drug target interactions, it is crucial to be able to predict the precise amino acid residues involved in ligand binding.

- ***Lead Optimisation***

Molecular docking can be utilised to improve the chemical structure of a prospective drug candidate to increase binding affinity and potency. To better match and interact with the target receptor, the ligand might be altered repeatedly.

- ***Virtual Screening***

Docking is a technique used in online screening to sort and prioritise a huge library of compounds according to how likely they are to be effective against a specific target. This enables scientists to concentrate their experimental efforts on the candidates that show the most promise [17].

Application for Molecular Docking

- ***Drug Design and Discovery***

To find possible lead compounds and improve their interactions with the target protein, molecular docking is frequently used in the early stages of drug development.

- ***Target Identification***

The prediction of probable binding partners for a given ligand via docking can help in the discovery of new therapeutic targets.

- ***Polypharmacology***

Docking enables researchers to examine a ligand's binding to a variety of protein targets, which is essential for comprehending a compound's polypharmacological effects.

- ***Protein Engineering***

Docking can help with the design of variants in target proteins to improve their binding to certain ligands or to research the effects of mutations on ligand-receptor interactions.

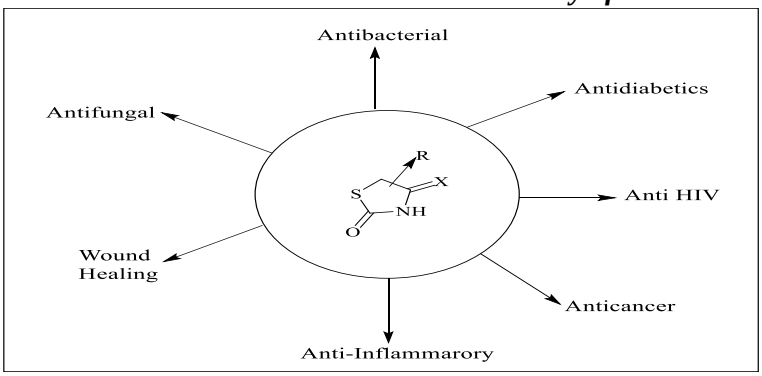
- ***Toxicity Prediction***

Docking can be used to evaluate the likelihood that small compounds will attach to unwanted off target proteins, assisting in the prediction of negative effects and enhancing drug safety.

- ***Natural Product Studies***

In order to find new bioactive compounds, docking is used to examine the interactions among natural products & target proteins [18].

Thiazolidinones and their derivatives have a variety of medicinal uses



Thiazolidinone medicinal uses

General method

The title compounds were prepared in following steps

2.2.1. Synthesis of hydrazone

Biphenyl-4-carboxylic acid hydrazide (0.025 mol, 5.3 g) and the necessary aromatic aldehydes (0.025 mol) were mixed together and heated in methanol (50 ml) in the presence of glacial acetic acid for around two hours. After that the mixture was cooled, the resulting solid was filtered, and recrystallized from the methanol and produced the matching hydrazones.

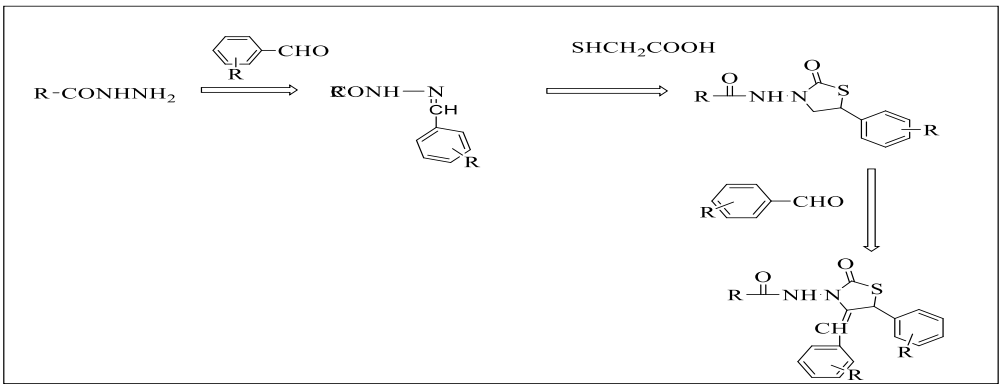
2.2.2. Synthesis of 2-substituted-4-thiazolidinone

The desired amount of thioglycolic acid (0.015 mol, 1.40 ml) and the appropriate Schiff's base (0.015 mol) (2) were mixed in 50 ml of N,N-dimethylformamide (DMF), together with a trace amount of anhydrous ZnCl2, and refluxed for roughly 6 hours. The reaction mixture was cooled, then poured over ice that had been crushed. The

product resulting was recrystallized from rectified spirit after that resulting solid had been filtered and washed with water.

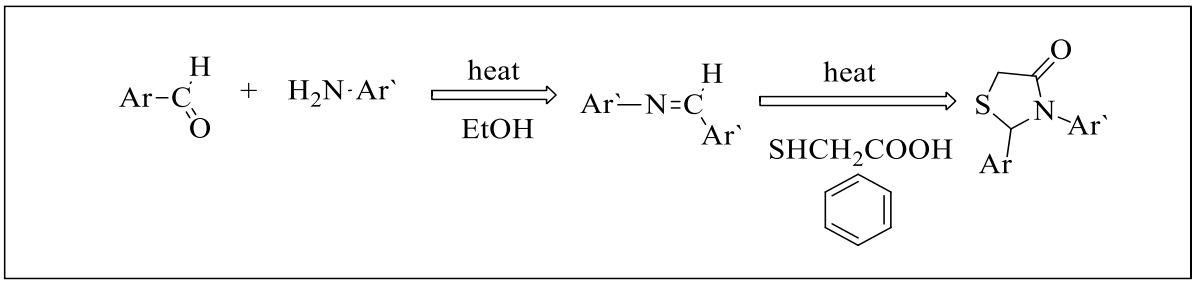
2.2.3. Synthesis of 2,5-disubstituted-4-thiazolidinone

Anhydrous sodium acetate was produced in glacial acetic acid and then refluxed for 5-7 hours with 2-substituted-4-thiazolidinone (0.01 mol), aromatic aldehydes (0.01mol) and anhydrous sodium acetate (0.01mol) [19]. The resulting product was precipitated by pouring the solution with ethanol in crushed ice and recrystallized with ethanol. The title compounds synthetic process is depicted in ***Scheme 1***.



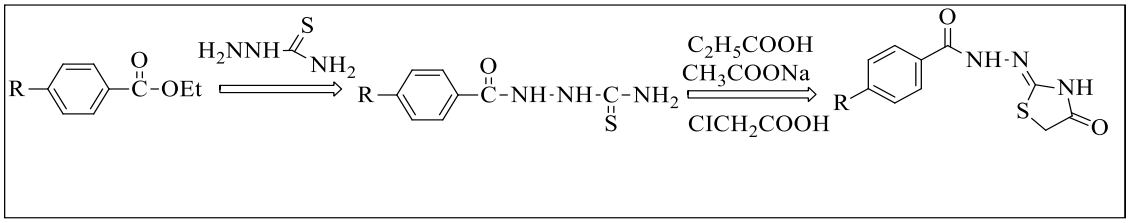
Scheme 1 *Synthesis of Thiazolidinone derivatives by biphenyl-4-carboxylic acid*

Three ingredients an amine a carbonyl molecule and a mercapto acid can be combined to create thiazolidinones in two processes. The first step in the reactions is the creation of an imine (the nitrogen in the amine attacks the carbonyl in the aldehyde or ketone), which is then attacked by the sulphur nucleophile and undergoes intramolecular cyclization upon the removal of water (**Agrawal *et al.*, 2021**) [20].



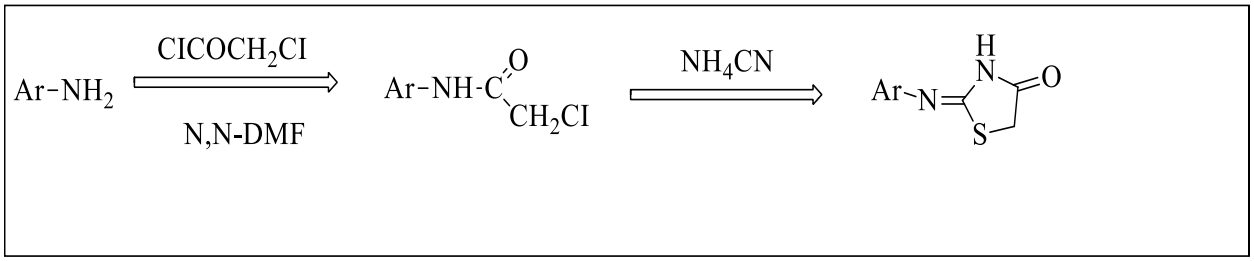
Scheme 2 *Synthesis of Thiazolidinone nitrogen of amine attacks the carbonyl of aldehyde or ketone*

By combining an aromatic ester with thiosemicarbazide, which readily heterocycle when it reacted with chloroacetic acid in the presence of sodium acetate to produce thiazolidin-4-one, hydrazine carbothioamide was created.



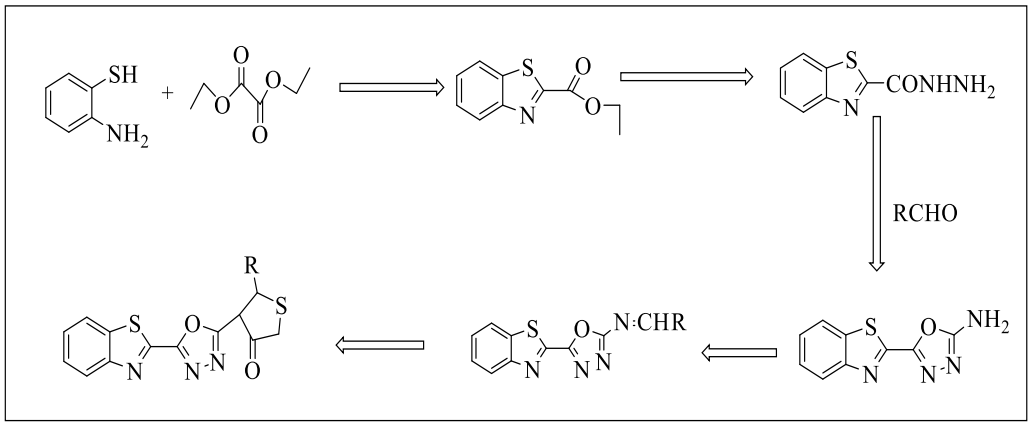
Scheme 3 *Synthesis of Thiazolidinone aromatic ester with thiosemicarbazide*

The right amine can be made into substituted thiazolidin-4-ones by reacting it with chloroacetyl chloride in DMF at room temperature, followed by cyclizing the acetamide that results in the presence of ammonium thiocyanate.



Scheme 4 *Synthesis of Thiazolidinone amine with chloroacetyl chloride*

A reaction mixture containing mercaptoacetic acid and the relevant Schiff bases (4a-z) in dimethylformamide (25-30 mL) and a zinc chloride was refluxed with stirring for 15 hours. The mixture was chilled and then poured over crushed ice after the reaction was finished. The resulting product was filtered, rinsed multiple times in cold water after being treated with an excess of 10% sodium bicarbonate solution, dried and recrystallized from ethanol to obtained the required product (**Ates *et al.*, 2011**) [21].



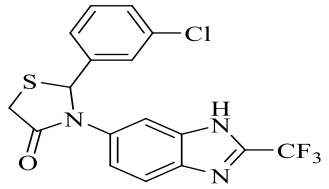
Scheme 5 *Synthesis of Thiazolidinonemercaptoacetic acid (0.1 mol) in dimethylformamide*

Antimicrobial Activity

Microbe based infections are one of the main killers in the world. A significant problem is posed by the limited number of antibiotics that are available for the treatment of illnesses and the ongoing emergence of antimicrobial agent resistance. Therefore, the development of successful treatments for infectious disorders may only be possible through the discovery of novel and strong antimicrobial medicines. Recent studies have shown that 4-thiazolidinones can prevent several bacterial pathogenic pathways as well as the bacterial enzyme Mur B, which is a precursor for the manufacture of peptidoglycan. Thiazolidine derivatives having a carbonyl group in the fourth position are known as 4-thiazolidinones. Treatment of infectious diseases continues to be a significant and difficult issue because Drugs, chemicals, and other substances that kill or inhibit the growth of bacteria are known as antimicrobial agents. Due to the growth of multidrug resistance in common pathogens, the quick introduction of new infectious diseases, and the possibility for usage of multidrug resistant agents, the need for new antimicrobial drugs is higher than ever (**Sadowski *et al.*, 2022**) [22]. The management of illnesses like pneumonia, TB, malaria, and AIDS is in danger due to antimicrobial resistance. In the treatment of infectious diseases brought on by bacteria, fungi, and viruses, medication resistance has grown to be a significant issue. Millions of patients worldwide perish as a result of infections that they cause. Finding new antimicrobial medications has become urgently necessary. There are many antibiotics and chemotherapeutics that can be used for medical purposes. Any agent, whether natural, semi-synthetic, or synthetic, that kills or slows the growth of germs while causing little or no harm to the host is considered an antimicrobial. Although all antimicrobials are antibiotics, not all antibiotics are antimicrobials.There has been a noticeable surge in the emergence of bacteria that are resistant to antibiotic usage in recent years. For millions of people around the world, improved health was made possible by the discovery of antimicrobials like penicillin and tetracycline. The 4-Thiazolidinone derivatives are a significant class of heterocyclic compounds with a wide range of biological activities, including antibacterial, antifungal, antiproliferative, antiviral,

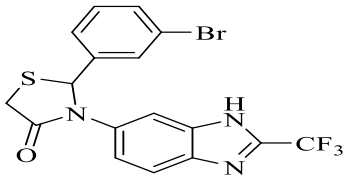
anticonvulsant, antidiabetic, and anti hyperlipidemic effects. Leukemia, melanoma, lung, colon, CNS, ovarian, and renal 4-thiazolidinone derivatives with anticancer activity have been developed recently (**Balouiri *et al.*, 2016**) [23].

Cheddie *et al.*, 2020 synthesised a series of 2-trifluoromethyl benzimidazole-thiazolidinone derivatives and tested them for antibacterial activity against two Grampositive bacteria, Staphylococcus aureus, and methicillin-resistant Staphylococcus aureus, as well as four Gramnegative bacteria, including Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia When compared to ciprofloxacin and levofloxacin. Compounds (1) and (2) showed good antibacterial activity. The compounds contain bromo, nitro group exhibited a wide range of activity (**Cheddie *et al.*, 2020**) [24].



2-(3-chlorophenyl)-3-(2-(trifluoromethyl) -1*H*-benzo[*d*]imidazol-6-yl)thiazolidin-4-one

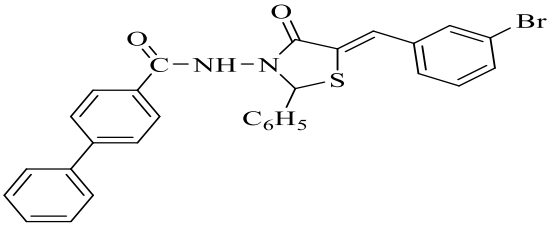
(1)



2-(3-bromophenyl)-3-(2-(trifluoromethyl) -1*H*-benzo[*d*]imidazol-6-yl)thiazolidin-4-one

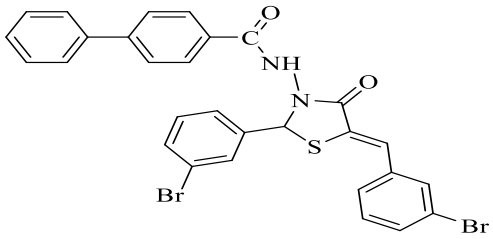
(2)

The antibacterial activity of new 4-thiazolidinone compounds exhibited from biphenyl-4- carboxylic acid. The compounds (3) and (4) showed good antibacterial activity. They substituted bromo and nitro groups, which pull electrons from aromatic rings. The chemical with their bromo substitution on both aromatic rings was the most efficient one against the various fungus strains (**Rocha Roa *et al.*, and Cardona *et al.*, 2018**) [25].



(*Z*)-*N*-(5-(3-bromobenzylidene)-4-oxo -2-phenylthiazolidin-3-yl)-[1,1'-biphenyl]-4-carboxamide

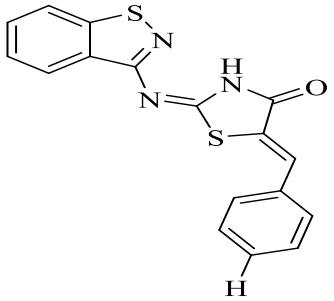
(3)



(*Z*)-*N*-(5-(3-bromobenzylidene)-2-(3-bromophenyl) -4-oxothiazolidin-3-yl)-[1,1'-biphenyl]-4-carboxamide

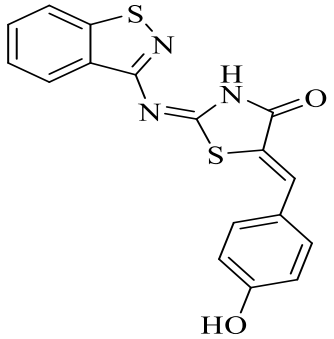
(4)

On 2-heteroarylimino-5-benzylidene-4-thiazolidinones that were either unsubstituted or hydroxyl, methoxy, nitro, and chloro groups on the benzene ring. Antibacterial activity tests against Gram +ve and Gram -ve bacteria, yeasts, and mould were performed in vitro. Compounds (5) and (6) showed good antibacterial activity (**Deep *et al.*, 2014**) [26].



(*E*)-2-(benzo[*d*]isothiazol-3-ylimino)
-5-((*Z*)-benzylidene)thiazolidin-4-one

(5)

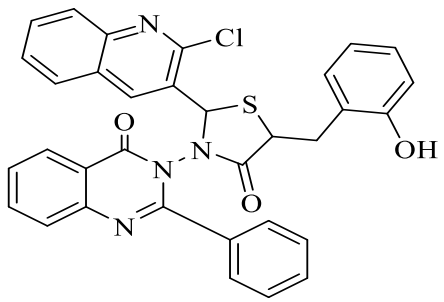


(*E*)-2-(benzo[*d*]isothiazol-3-ylimino)
-5-((*Z*)-4-hydroxybenzylidene)thiazolidin-4-one

(6)

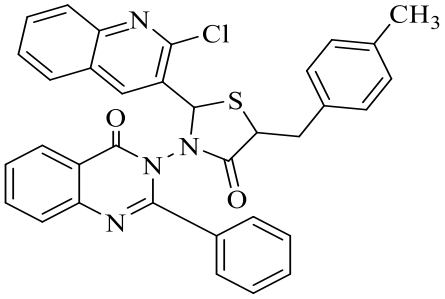
Synthesized derivatives of 2-(2-chloroquinolin-3-yl)-5-((aryl)benzylidene)-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiazolidin-4-ones.

Some of the recently created compounds demonstrated potential antibacterial activity against *E. coli*, *S. aureus*, *P. aeruginosa*, and *S. pyogenus*. Some displayed remarkably potent antifungal activity against *C. albicans*, *A. niger*, and *A. clavatus*. It seemed that the paramethyl group and the hydroxyl group in the second position are particularly crucial for activity against bacterial and fungal strains. Compounds (7) and (8) showed good antibacterial activity (**Desai *et al.*, and Shihory *et al.*, 2013**) [27].



2-(2-chloroquinolin-3-yl)-5-(2-hydroxybenzyl)
-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiazolidin-4-one

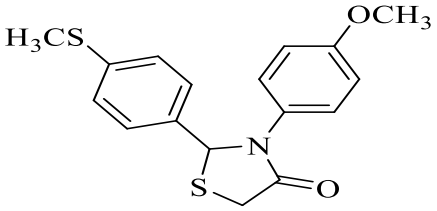
(7)



2-(2-chloroquinolin-3-yl)-5-(4-methylbenzyl)
-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiazolidin-4-one

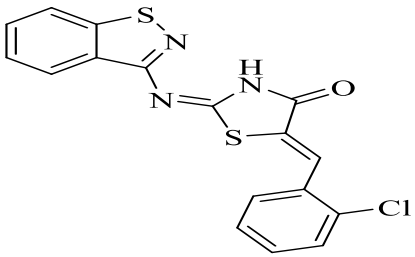
(8)

Synthesized thiazolidinone compounds and evaluated their anti-inflammatory and antibacterial activity (**Castro *et al.*, 2016**) [28].



3-(4-methoxyphenyl)-2-(4-(methylthio)phenyl)
thiazolidin-4-one

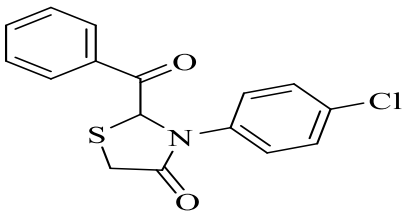
(9)



(*E*)-2-(benzo[*d*]isothiazol-3-ylimino)
-5-((*Z*)-2-chlorobenzylidene)thiazolidin-4-one

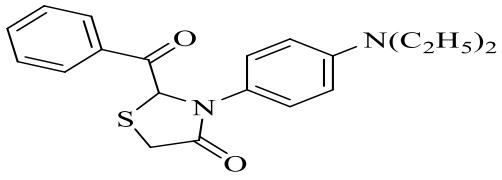
(10)

2-ketophenyl-3-substituted aryl-1-thiazolidin-4-ones by cyclo condensation of ketoazomethines and thioglycolic acid. These compounds were tested against antifungal (Fusariumoxysporum) and antibacterial (Alternariabrassicola, Pythium, and Sclerotium) activity by using paper disc method. The compound demonstrated the best inhibition against Sclerotium and against Alternariabrassicola. Compounds (11) and (12) showed good antibacterial activity (**Vats *et al.*, 2010**) [29].



2-benzoyl-3-(4-chlorophenyl)thiazolidin-4-one

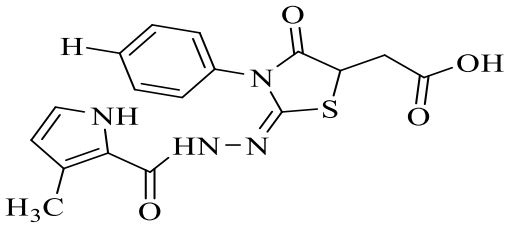
(11)



2-benzoyl-3-(4-(diethylamino) phenyl)thiazolidin-4-one

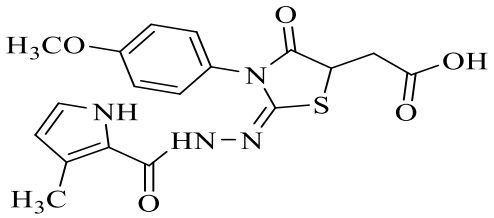
(12)

These compound of 4-thiazolidinone from ethyl (5-methyl-1-Himidazole- 4-carboxylate). The antibacterial and antifungal efficacy against a range of illnesses was evaluated. The MIC of the compound for B. subtilis was 270 g/L. Compounds (13) and (14) showed good antibacterial activity (**Liesen *et al.*, 2010**) [30].



(*E*)-2-(2-(2-(3-methyl-1*H*-pyrrole-2-carbonyl) hydrazineylidene)-4-oxo-3-phenylthiazolidin -5-yl)acetic acid

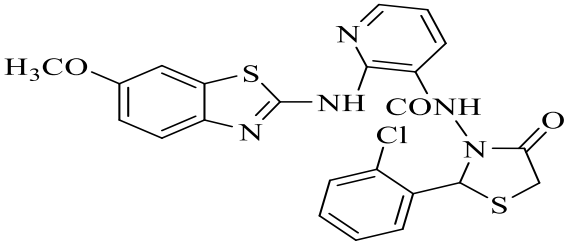
(13)



(*E*)-2-(3-(4-methoxyphenyl)-2-(2-(3-methyl-1*H*-pyrrole -2-carbonyl)hydrazineylidene)-4-oxothiazolidin -5-yl)acetic acid

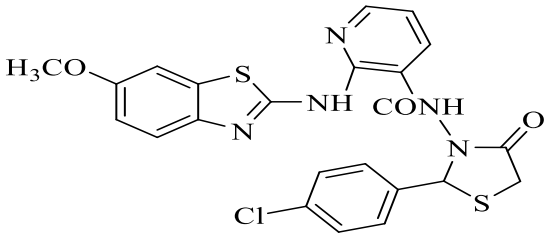
(14)

Synthesized Schiff's bases and 4-thiazolidinones from 2-chloro pyridine-3-carboxylic acid and 2-amino-6-methoxybenzothiazole and evaluated their antibacterial potency. Compounds (15) and (16) showed good antibacterial activity (**Patel *et al.*, 2010**) [31].



N-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl) -2-((6-methoxybenzo[*d*]thiazol-2-yl) amino)nicotinamide

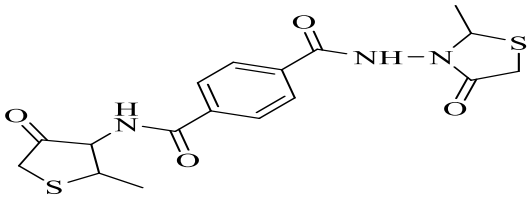
(15)



N-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-((6-methoxybenzo[*d*]thiazol-2-yl) amino)nicotinamide

(16)

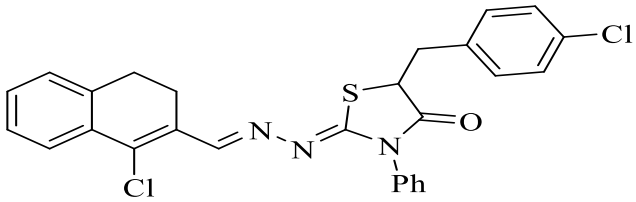
Developed a novel series of 4-bis(substituted phenyl)-4-thiazolidinone derivatives from terephthalic acid dihydrazide using antibacterial activity. Compound (17) showed good antibacterial activity (**Palekar *et al.*, and Shukla *et al.*, 2009**) [32].



N^1-(2-methyl-4-oxotetrahydrothiophen-3-yl) -N^4-(2-methyl-4-oxothiazolidin-3-yl) terephthalamide

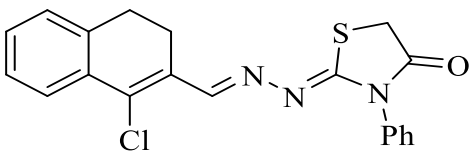
(17)

Synthesized the compounds using the agar diffusion method and evaluated their antibacterial activity in vitro against the B. subtilis, B. megaterium, and E. coli bacterial strains, as well as the A. niger and A. oryzae fungal strains and three strains of viruses. the synthesized thiazolidinone derivatives showed equivalent activity against tested bacteria when compared to Ampicillin and Chloramphenicol at a concentration of 25 mg/mL as a reference drug. Compounds (18) and (19) showed good antibacterial activity (**Bondock *et al.*, 2007**) [33].



(*Z*)-2-(((*E*)-(1-chloro-3,4-dihydronaphthalen-2-yl) methylene)hydrazineylidene)-5-(4-chlorobenzyl) -3-phenylthiazolidin-4-one

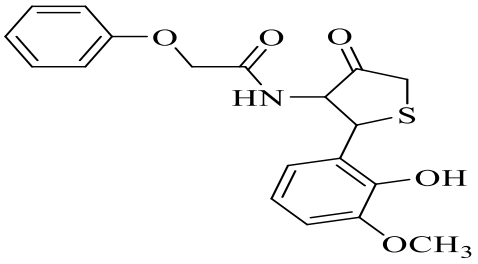
(18)



(*Z*)-2-(((*E*)-(1-chloro-3,4-dihydronaphthalen-2-yl)methylene)hydrazineylidene) -3-phenylthiazolidin-4-one

(19)

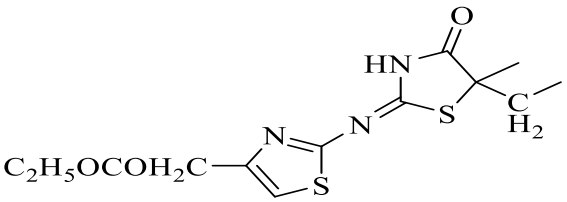
Synthesized substituted aryloxy-4-thiazolidinones and investigated them for antibacterial activity by matching Schiff's bases and thioglycolic acid in benzene. The compound showed high antibacterial and good antifungal activity. The electron-releasing groups like methyl, hydroxy, and methoxy may be responsible for an increase in antibacterial and antifungal activity. Compound (20) showed good antibacterial activity (**Kumar *et al.*, 2006**) [34].



N-(2-(2-hydroxy-3-methoxyphenyl) -4-oxotetrahydrothiophen-3-yl) -2-phenoxyacetamide

(20)

Synthesized substituted 5- (N,N-disubstitutedaminomethyl) The synthesis of -4-[(4-carbethoxymethylthiazol-2-yl)imino]. Compounds was carried out using thiazolidinones. In vitro antibacterial activity of synthetic compounds was evaluated using disc diffusion against S. aureus, S. epidermidis, E. coli, K. pneumoniae, P. aeruginosa, S. typhi, S. flexneri, and P. mirabilis, and in vitro antifungal activity was evaluated using micro dilution against M. gypseum, M. canis, T. mentagrophytes, T. mentagrophytes. Compound (21) showed good antibacterial activity (**Bondock *et al.*, 2007**) [33].



(2-((5-ethyl-5-methyl-4-oxothiazolidin -2-ylidene)amino)thiazol-4-yl) methyl propionate

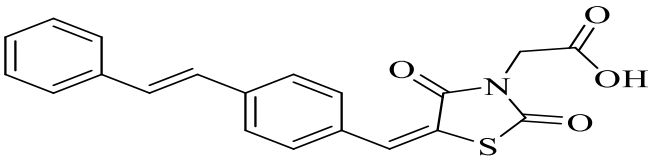
(21)

Antioxidant Activity

During typical cellular metabolism and bioorganic redox processes, free radicals and reactive oxygen species (ROS), such as superoxide anion, hydrogen peroxide, and hydroxyl radical, are produced. Radical reactions also contribute significantly to the emergence of chronic illnesses that are fatal, including cancer, hypertension, cardiac infarction, stroke, arteriosclerosis, rheumatoid arthritis, cataracts, Alzheimer's and Parkinson diseases. It is known that exposing a healthy cell to free radicals damages its structural integrity and impairs the activity of enzymes and other macromolecules (e.g., lipids, proteins and nucleic acids). Superoxide dismutase, catalase, and glutathione peroxidase are just a few of the enzymes that the human body naturally produces to fight against free radicals. The development of chronic and degenerative diseases is caused by an imbalance between the generation and detoxification of free radical species, which intensifies oxidative stress. Therefore, preventing oxidative damage by taking an antioxidant supplement and/or free radical scavengers may lower the risk of developing these illnesses. As a preventive measure against these diseases by lowering and/or suppressing free radical reactions, medicinal chemists, food chemists, and biologists have increased their focus on research and testing for new and effective natural or synthetic antioxidants over the past ten years (**Geronikaki *et al.*, 2013**) [35].

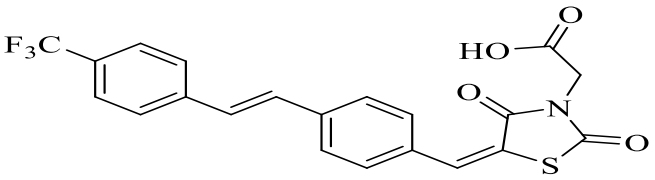
Ottana *et al.*, created several compounds of 5-arylidene-4-thiazolidinone and assessed their antioxidant and anti-diabetic properties. The highly

pure enzyme from the lens of a bovine animal was used to evaluate the inhibitory action of drugs against aldose reductase (ALR2) in vitro. D,L-glyceraldehyde was used as the substrate, and the reference medicines were sorbinil and epalrestat. The investigated substances were found to inhibit ALR2 according to the in vitro inhibition findings. The best inhibitors of these were (5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids, with IC50 values of 0.25 Mand 0.30 M showing the significance of the acetic acid group in the interaction with the enzyme. All substances had more activity than sorbinil. These substances have been shown to be intriguing enzyme inhibitors as well as superior antioxidants that may be able topotentially effective antioxidants and intriguing enzyme inhibitors are needed to combat the oxidative stress brought on by both diabetic complications and other illnesses.Compounds (22) and (23) showed good antioxidant activity (**Ottana *et al.*, 2011**) [36].



2-(2,4-dioxo-5-((*E*)-4-((*E*)-styryl) benzylidene)thiazolidin-3-yl)acetic acid

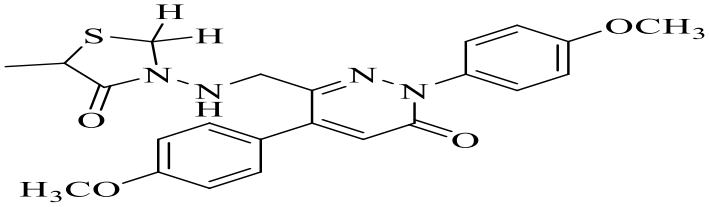
(22)



2-(2,4-dioxo-5-((*E*)-4-((*E*)-4-(trifluoromethyl) styryl)benzylidene)thiazolidin-3-yl)acetic acid

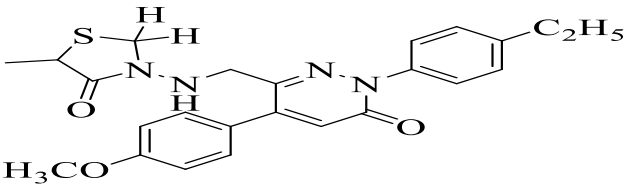
(23)

Synthesized 4-thiazolidinones with a 6-carboxy-3-(2H)-pyridazinone moiety, and they evaluated them for their antioxidant activities. Compounds (24) and (25) showed good antioxidant activity (**Gadre *et al.*, and Chitre *et al.*, 2007**) [37].



3-(((1,4-bis(4-methoxyphenyl)-6-oxo-1,6-dihydropyridazin-3-yl)methyl)amino) -5-methylthiazolidin-4-one

(24)



3-(((1-(4-ethylphenyl)-4-(4-methoxyphenyl) -6-oxo-1,6-dihydropyridazin-3-yl)methyl)amino) -5-methylthiazolidin-4-one

(25)

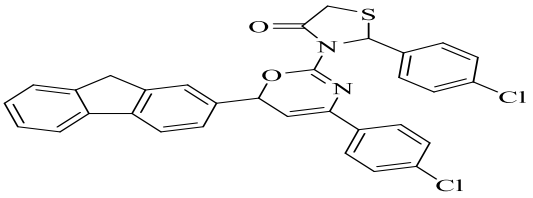
Antidiabetic Activity

Diabetes is treated clinically with pioglitazone and rosiglitazone, two examples of thiazolidine compounds having saturated thiazole rings that act as insulin sensitizers. The FDA has limited the broad use of these two medications in diabetic patients, nevertheless, because of the cardiovascular side effects of rosiglitazone and the risk that pioglitazone poses for bladder cancer. One essential method for developing novel drugs is target-based drug design. Researchers have switched their focus to creating PTP1B inhibitors with such scaffolds as cutting-edge anti-diabetes medications in light of the pharmacological properties of PTP1B and the numerous biological activities of thiazole and thiazolidine moieties. Here, a brief summary of the structural characteristics of PTP1B and the current state of diabetes has been provided (**Nirwan *et al.*, 2019**) [38].

In the last ten years, we have mainly concentrated on the chemical compositions and biological properties of thiazoles and thiazolidines as PTP1B inhibitors. Additionally, the connection between these PTP1B inhibitors' structure and activity was examined. It is planned to provide more information on the logical development and successful use of anti-diabetic medications based on PTP1B inhibitors.

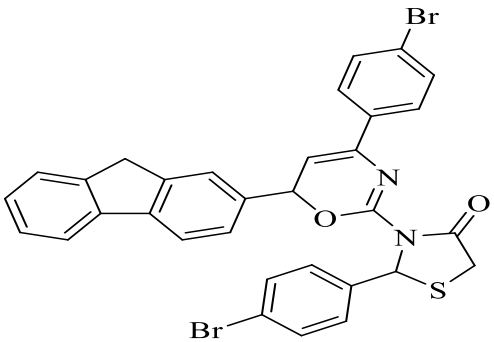
Diabetes is a metabolic problem disease linked to lifestyle that is spreading alarmingly quickly throughout the world. Type-I and Type-II diabetes are two subtypes that result from insulin resistance in human tissues. Obesity, stress, nutrition, and inactivity all contribute to the development of these conditions. For the treatment of Type-II diabetes mellitus, thiazolidin-4-one ring system and thiazolidindiones (TZDs, glitazones) have been utilised extensively. A class of anti-hyperglycemic drugs known as TZDs, which are agonists of the peroxisome proliferator activated receptor-(PPAR-), decrease insulin resistance and increase insulin action to maintain normoglycemia and maybe protect -cell function (**Kishore *et al.*, 2009**) [39]. In recent times, TZDs have also been linked to the management of several inflammatory illnesses. There is growing evidence to supportcompounds of benzylidene-2,4-thiazolidinedione having exceptional PTP1B inhibitory action. Compound, which has an IC50 value of 5.0 0.1 M and is the most potent compound against PTP1B, is one of the most noteworthy. The drug could activate peroxisome proliferator-activated receptors and showed significant selectivity to PTP1B across a panel of PTPs (PTP1B, TCPTP, LAR-D1, and YPTP1) (PPARs). The chemical can attach to the PTP1B catalytic site by forming hydrophobic contacts and hydrogen bonds with amino acid residues like Gln266, Ser216, and Tyr46, according to a molecular docking investigation. Additionally, the substance has the power to prevent diet-related weight gain and improve triglyceride, total cholesterol, and non-esterified free fatty acid levels without having any negative side effects. To produce more active chemicals. Additionally, the compounds' inhibitory effect was enhanced by the presence of the sulfonic ester group. Liu et al. suggested using PEG-combined aniline as a traceless linker to create 5-arylidene thiazolidinone and pyrimidinone derivatives. The capacity to boost anti-PTP1B activity was discovered in several compounds with thiazolidinedione scaffold and substituted biphenyl moiety. Mahapatra et al. reported a variety of N-alkylated thiazolidine-2,4-dione analogues and assessed their actions against PTP1B. Further structural modification was also made. Notably, compound 18a exhibited notable PTP1B inhibitory action. Compound 18a's low lipophilicity and smaller substituent (-CH3) improve its inhibitory action against PTP1B. Studies using molecular docking have shown that the compound's carbonyl oxygen at positions C-2 and C-4 may interact (**Gu *et al.*, 2012**) [40].

Synthesized thiazolidinone compounds and evaluated their amylase inhibition and glucosidase inhibitory activity to ascertain their antidiabetic potential. These compounds were shown to be more powerful than the widely used drug acarbose. Compounds (26) and (27) showed good anti-diabetic activity (**Rajalakshmi *et al.*, and Elakkiya *et al.*, 2020**) [41].



2-(4-chlorophenyl)-3-(4-(4-chlorophenyl)-6-(9*H*-fluoren-2-yl)-6*H*-1,3-oxazin-2-yl) thiazolidin-4-one

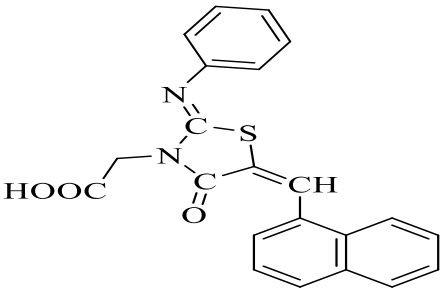
(26)



2-(4-bromophenyl)-3-(4-(4-bromophenyl)
-6-(9*H*-fluoren-2-yl)-6*H*-1,3-oxazin-2-yl)
thiazolidin-4-one

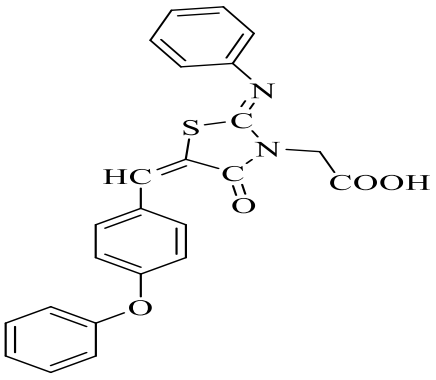
(27)

5-arylidene-4-thiazolidinones to treat diabetes-related problems. He performed molecular docking experiments to support his SAR findings. He claimed that changing the position 5 of the compound's 5-benzylidene group to a lipophilic arylidene moiety specifically increased activity; however, it was later demonstrated that substituting phenoxy and benzyloxy groups in the compound's para and meta positions of the 5-benzylidene group provided greater enzyme inhibition Compounds (28) and (29) showed good anti-diabetic activity (**Ottana *et al.*, 2011**) [36].



2-((2*Z*,5*E*)-5-(naphthalen-1-ylmethylene)
-4-oxo-2-(phenylimino)thiazolidin-3-yl)
acetic acid

(28)

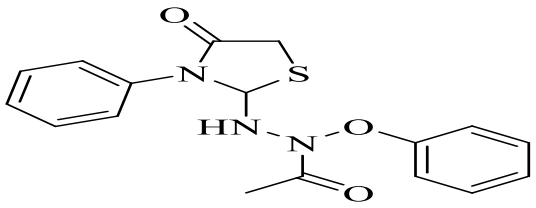


2-((*Z*)-4-oxo-5-((*E*)-4-phenoxybenzylidene)
-2-(phenylimino)thiazolidin-3-yl)acetic acid

(29)

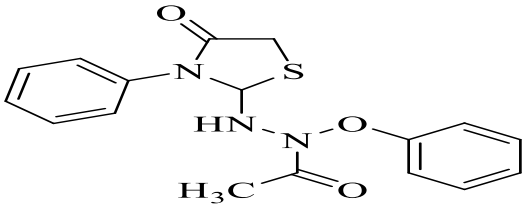
N'-[3-(4-alkyl/arylsubstituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy)acetohydrazides and evaluated their effectiveness in the treatment of diabetes. The medication was safe and had effective antidiabetic

properties. Compounds (30) and (31) showed good anti-diabetic activity (**Bennett *et al.*, 2011**) [42].



N'-(4-oxo-3-phenylthiazolidin-2-yl) -*N*-phenoxyacetohydrazide

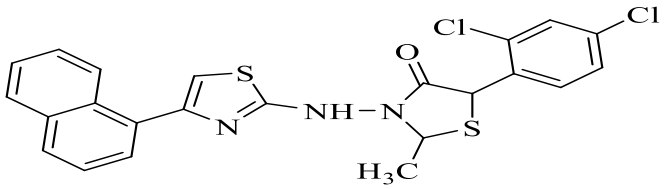
(30)



N'-(4-oxo-3-phenylthiazolidin-2-yl) -*N*-phenoxyacetohydrazide

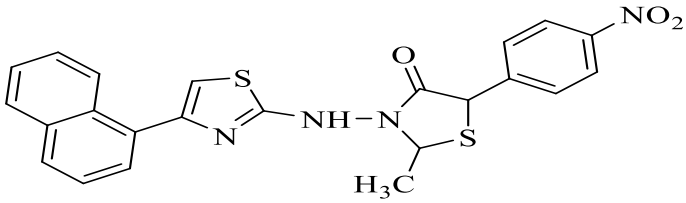
(31)

Synthesized a number of 2-(substitutedphenyl)-3-[4-(1-naphthyl)-1,3-thiazole- 2-ylamino] compounds from 1-acetyl naphthalene and examined them for their ability to lower blood sugar. 5-methyl-1,3-thiazolidin-4-ones. Compounds (32) and (33) showed good antidiabetic activity (**Imran *et al.*, 2009**) [43 .



5-(2,4-dichlorophenyl)-2-methyl-3-(4-(naphthalen-1-yl)thiazol-2-ylamino) thiazolidin-4-one

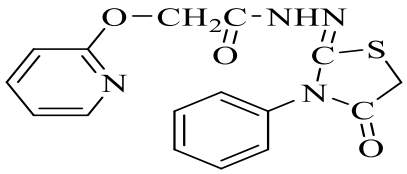
(32)



2-methyl-3-(4-(naphthalen-1-yl)thiazol-2-ylamino) -5-(4-nitrophenyl)thiazolidin-4-one

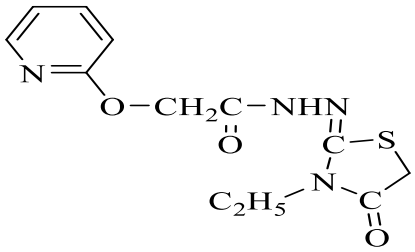
(33)

N'-[3-(aryl/alkyl substituted)-4-oxo-1,3-thiazolidin-2-ylidene] compounds were created. Using the proper method, prepare 2-(pyridin-2-yloxy) acetohydrazides, and test them for their ability to lower blood sugar. Compounds (34) and (35) showed good anti-diabetic activity (**Firke *et al.*, 2009**) [44].



(*E*)-*N*'-(4-oxo-3-phenylthiazolidin-2-ylidene)
-2-(pyridin-2-yloxy)acetohydrazide

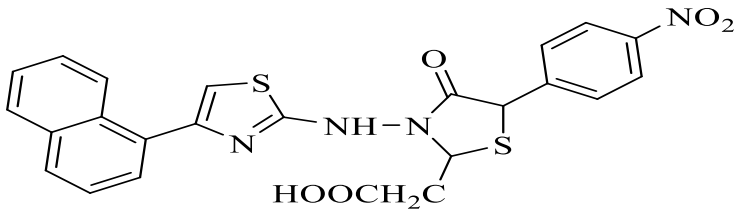
(34)



(*E*)-*N*'-(3-ethyl-4-oxothiazolidin-2-ylidene)
-2-(pyridin-2-yloxy)acetohydrazide

(35)

2-(substituted phenyl)-3-[4-(1-naphthyl)-1,3-thiazol-2-yl]amino synthesised compounds of -4-oxo-1,3-thiazolidin-5-yl acetic acid were examined for their potential antihyperglycemic properties. Compound (36) showed good antidiabetic activity (**Imran *et al.*, 2009**) [43].



2-(3-(4-(naphthalen-1-yl)thiazol-2-ylamino)
-5-(4-nitrophenyl)-4-oxothiazolidin-2-yl)
acetic acid

(36)

Conclusion

The goal of this study is to discuss numerous biological activities, such as antibacterial, antioxidant, and antidiabetic ones. For additional research on this scaffold, the information offered in this publication might be helpful.

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Authors' Contributions

MK designed and finalized the scheme; MH performed review work and 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

Author details

[1,2*]Faculty of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak, Haryana, India - 124001.

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