RECENT PERSPECTIVES OF THIAZOLIDINE-2,4-DIONES AS ANTIBACTERIAL ANTIFUNGAL AGENTS AND ANTIOXIDANT ACTIVITY

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ABSTRACT

The widespread presence of nitrogen- and sulfur-containing heterocyclic compounds in pharmacologically dynamic natural products and as overwhelmingly powerful agrochemicals and pharmaceuticals has piqued interest in their synthetic chemistry. The thiazolidine-2,4-dione (TZD) moiety is crucial to the operation of several vital molecules. The TZD scaffold is extensively employed and adaptable due to the availability of substitutions at the third and fifth positions, allowing for a broad variety of biological activities to be shown by this moiety. The antibacterial activity of TZD analogues is shown by the suppression of cytoplasmic Mur ligases. In this publication, we attempt to summarize the literature on TZD derivatives as prospective antibacterial agents from the beginning of 2012 to the end of 2022, including a discussion of their molecular mechanisms and details on patents awarded to TZD analogs.

Keywords: *Thiazolidin-2,4-dione; Antimicrobial; Antibacterial; Antifungal; Mechanism of actions*

1. Introduction

In the recent era, treating infectious diseases is still of serious concern because of a combination of factors including growing infectious diseases and an increasing number of multi-drug resistant microbial pathogens with particular relevance for Gram-positive bacteria [1]. Antimicrobial resistance has emerged as the major danger, which is mostly attributed to changing microbial characteristics, antimicrobial misuse, adaptation of harmful microbes to antimicrobials, bacterial genetic mutation, and the spread of drug-resistant germs among individuals [2]. *Methicillin-resistant Staphylococcus aureus* (MRSA), Staphylococcus epidermidis, and *vancomycin-resistant enterococci* (VRE) are only a few examples of the multi-drug resistance bacteria that are spreading and becoming increasingly difficult to treat in a clinical setting [3]. The World Health Organization (WHO) asserts that illnesses brought on by resistant microorganisms frequently do not respond to standard antibiotic therapy, leading to persistent infection and a greater risk of mortality. Therefore, there is still a need for advancements in innovative antimicrobial medications that are different from the established class of antibacterial medicines [4]. Heterocycles with new structures are significant pharmacophores and make up an elite class of bioactive components and natural products, especially in drug research and innovation programmes [5]. Heterocyclic compounds are acknowledged as essential lead chemicals in medicinal chemistry, particularly those containing heterocycles of nitrogen, sulphur, and oxygen [6].

Glitazone, also known as thiazolidin-2,4-dione (**Figure 1**), is a heterocyclic moiety made up of a five-membered, saturated thiazolidine ring, sulfur at position 1, nitrogen at position 3, and two carbonyl functional groups at positions 2 and 4. Only at the 3-5 locations of the Thiazolidin-2,4-dione (TZD) scaffold are substitutions of other moieties feasible. The TZD analogues come in a variety of structural forms [7] and have a variety of therapeutic potentials that have been demonstrated, including, anti-diabetic [8-10], analgesic, anti-inflammatory [11-12], wound healing [13], antiproliferative [14-15], antimalarial [16], anti-tubercular [17], hypolipidemic [18], antiviral [19], antimicrobial, antifungal [20-23], and antioxidant properties [24,25], etc.

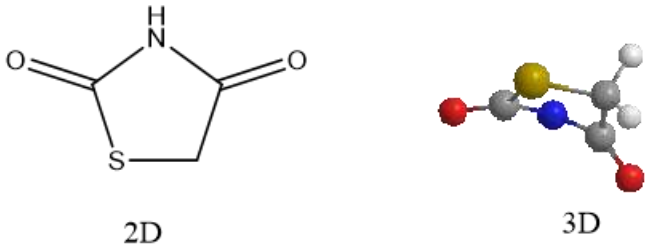


Figure 1. Core structure of Thiazolidine-2,4-dione show in 2D or 3D

2. Antimicrobial Activity

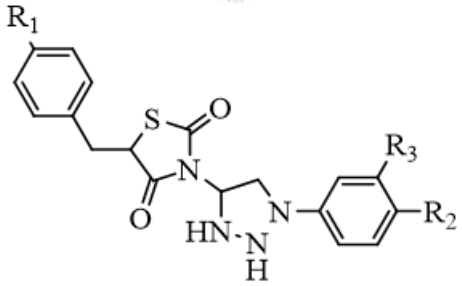
Antibiotics were first developed in the 1940s, and their widespread use was widely celebrated as the beginning of the end for infectious illnesses. One of the most pressing public health concerns, however, is antibiotic resistance, which has emerged as a result of the inappropriate abuse of antibiotics by various bacterial strains. Vancomycin-resistant enterococci (VRE) and multidrug-resistant Staphylococcus aureus (MRSA) are two examples of antibiotic-resistant bacterial strains that are able to persist in the presence of the vast majority of commonly used antibiotics. There is an immediate need for novel chemical entities for the treatment of microbial illnesses with a distinct mode of action due to the emergence of multidrug-resistant microbial infections that are resistant to presently existing antibiotics/antimicrobials [26,27].

2.1. Mechanism of TZD as Antimicrobial Agent

The bacterial cell wall is essential for bacterial survival because it provides structure and shields the cell from the environment. Peptidoglycan, which is located on the outer wall of the cytoplasmic membrane, is a key component of the bacterial cell wall. Cell death may occur as a result of its ability to block biosynthetic enzymes. Membrane-bound extracellular enzymes (penicillin-binding proteins) and cytoplasmic enzymes (Mur enzymes) are both capable of catalyzing this production. The Mur ligases (Mur C-F) are a family of four ATP-dependent enzymes involved in the production of peptide stems in peptidoglycans. They facilitate the addition of the amino acids L-alanine, D-glutamic acid, L-lysine, and D-alanyl-D-alanine (D-Ala-D-Ala) to the D-lactoyl group of UDP-N-acetylmuramic acid, resulting in the pentapeptide UDP-MurNAc. These cytoplasmic ligases are thought to be inhibited by TZD molecules, leading to infections and cells dying [28,29].

2.2 Specific studies

Sindhu *et al.* (2015) The *in vitro* antibacterial activity of a novel series of thiazolidine-2,4-diones comprising a 1,2,3-triazole scaffold was tested against two bacterial and two fungus strains by Sindhu *et al.* utilizing the disc diffusion and poisoned food techniques. Compound **(1a-1h)** was shown to have higher antibacterial and antifungal activity than the gold standards, ciprofloxacin, and fluconazole, respectively, in an antimicrobial assessment [30].

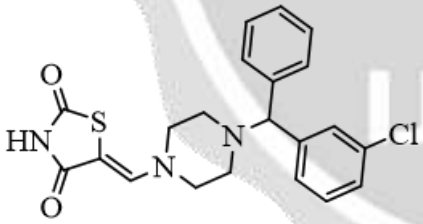


(1a-1h)

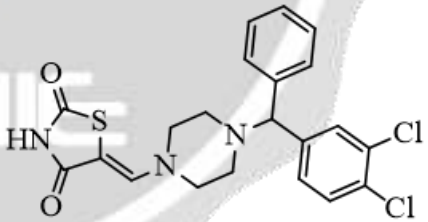
Compounds	R_1	R_2	R_3
1a	Me	Me	H
1b	Me	F	H
1c	Me	OMe	H
1d	Me	F	Cl
1e	Me	H	Cl
1f	Br	Me	H
1g	Br	H	Cl
1h	Br	F	Cl

Table 2.1: Series of 5-(arylidene)-3-((1-aryl-1H-1,2,3-triazol-4-yl) methyl) thiazolidine-2,4-diones

Mohanty *et al.* (2015) assessed the *in vitro* antimicrobial potential of a series of substituted 5-(amino methylene) thiazolidine-2,4-diones derivatives against various strains of bacteria and fungi using the two-fold serial dilution method and the poisoned food method. The antibacterial activity of the compound **(2)** was modest, whereas the antifungal activity of the compound **(3)** was promising in comparison to the gold standards, ciprofloxacin and fluconazole [31].

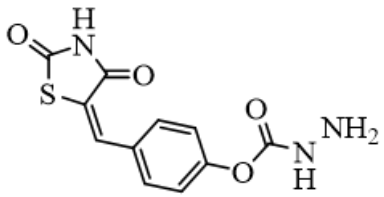


(2)



(3)

Rekha *et al*. (2015) synthesized analogs of 5-arylidene-thiazolidine-2,4-dione and measured their zone of inhibition against various microbial strains was measured using a modified cup plate technique. Based on the findings, compound **(4)** was shown to be more effective than the gold standard antibiotic Amoxycillin at inhibiting *B. subtilis* and *S. aureus*, while compound **(5)** had remarkable effectiveness against *P. vulgaris* [32].



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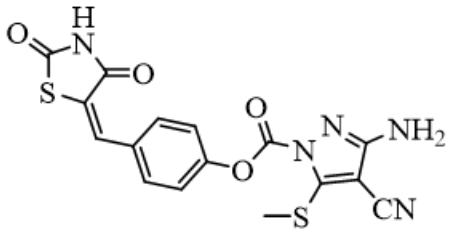
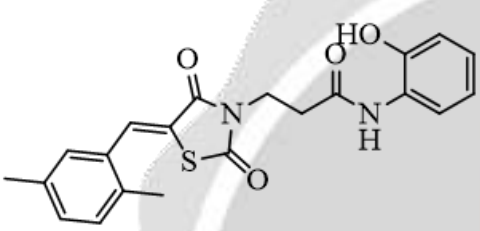


(5)

Bahare *et al*. (2015) synthesized derivative name N-substituted 5-benzylidine-2,4-thiazolidinediones compounds evaluated for their HIV-1 RT inhibitory activity for antibacterial and antifungal activity. The compound **(6)** showed significant HIV-1 RT inhibitory activity with 73% inhibition, with an IC_{50} value of 1.31 µm. The results of the antimicrobial activity revealed that compound **(7)** have the highest activity against all bacterial strains [33].



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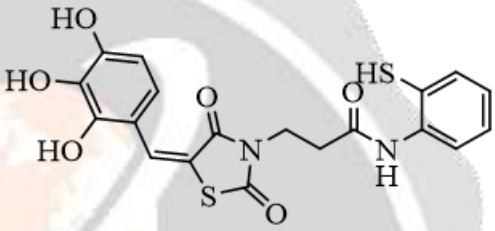
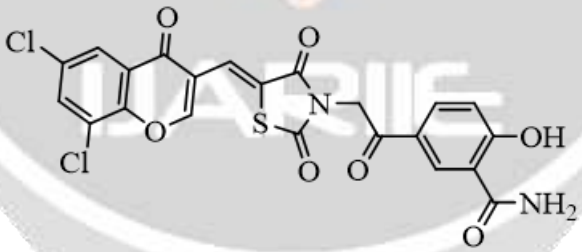


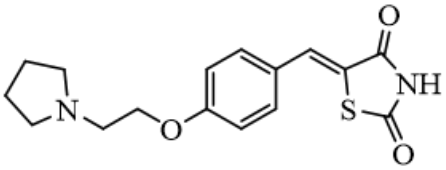
(7)

Nastasa *et al.* (2016) synthesized many 2,4-thiazolidinedione derivatives with a chromene scaffold and evaluated their *in vitro* antibacterial activity against certain strains of bacteria and fungi using the disk diffusion technique. After testing their efficacy against various microorganisms, researchers found that compound **(8)** was more effective than the commercial medications gentamicin and fluconazole [34].



(8)

Laxmi *et al*. (2016) They synthesized for 5-(4-alkylbenzyledene) thiazolidine-2,4-dione derivatives. These compounds have been successfully synthesized, characterized, and tested for anticancer and antibacterial activity utilizing DNA cleavage tests. From these compounds **(9)** and **(10)** were found to be active. These substances make superior prospects for brand-new antibacterial and anticancer drugs [35].



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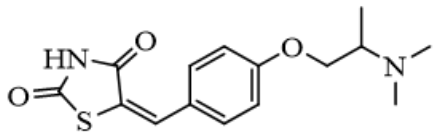
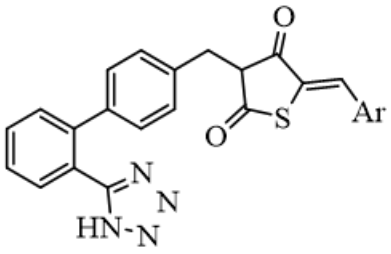


(10)

Firoz *et al.* (2016) Synthesized biphenyl tetrazole-thiazolidinediones as bacterial peptide deformylase (PDF) enzyme inhibitors. These compounds **(11a-11h)** showed IC_{50} value and good PDF inhibition activity. Compared with the standard ciprofloxacin (MIC range = 25-50 µg/ml), these compounds exhibited potent antibacterial activity [36].

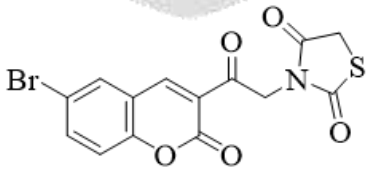


(11a-11h)

Compounds	**Ar**	**IC_{50}**
11a	Phenyl	20.50
11b	4-chlorophenyl	16.25
11c	2-chlorophenyl	18.00
11d	4-flourophenyl	26.25
11e	4-methoxyphenyl	26.00
11f	2,4-dimethoxyphenyl	35.50
11g	2,5-dimethoxyphenyl	26.50
11h	2,6-dichlorophenyl	17.25

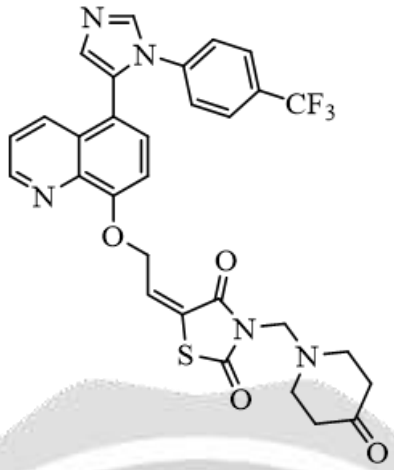
Table 2.2: IC_{50} (Half maximal inhibitory concentration) of biphenyl tetrazole-thiazolidinediones.

Valadbeigi *et al*. (2017) synthesized some new thiazolidinedione derivatives containing a coumarin moiety and evaluated them for their antibacterial and antifungal activities. Since there are several natural products with heterocyclic nuclei, synthetic coumarin and its derivatives have drawn a lot of interest from organic and medical chemistry fields. Among all the synthesized compound **(12)** have shown high antibacterial and antifungal activity [37].



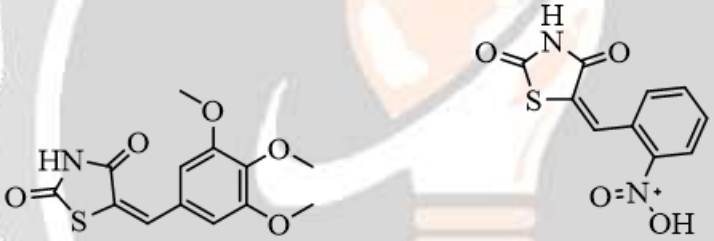
(12)

Vellalacheruvu *et al.* (2017) synthesized and characterized, mannich bases of quinoline-attached imidazoline thiazolidine 2,4-one derivatives. Additionally, sulfonyl derivatives of thiazolidine-2,4-dione were synthesized and characterized using alkylation conditions. This compound **(13)** showed good antimicrobial activity [38].



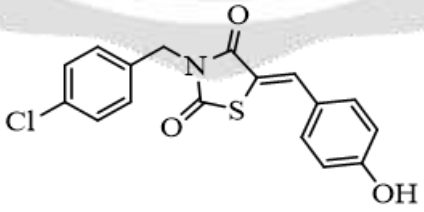
(13)

Sucheta *et al.* (2018) synthesized**,** novel thiazolidine-2,4-diones derivatives and screened them for their *in vitro* antimicrobial potential against Gram (positive and negative) bacterial and fungal strains by tube dilution technique. The compound **(14)** showed good potent antibacterial activity and the compound **(15)** showed good antifungal activity [39].



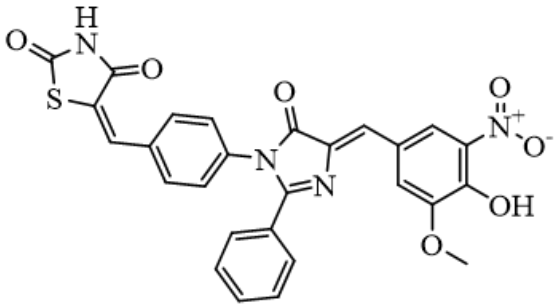
(14) **(15)**

Sethi *et al.* (2018) synthesized a set of 3,5-disudstituted-2,4-thiazolidinediones derivatives and screened them for their antimicrobial potential. These derivatives were synthesized through the use of benzyl halides and aromatic aldehydes. The enhancement of antimicrobial activity can be achieved by attaching more heterocyclic rings containing nitrogen to the 3rd position of 2,4-thiazolidinedione. Additionally, increasing the bioavailability and efficacy of the drug can be achieved by incorporating more lipophilic agents. Compound **(16)** showed good antimicrobial activity [40].



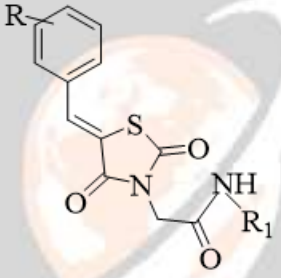
(16)

Khan *et al.* (2018) synthesized 5-(4-((Z)-4-substituted benzylidene-2-thienyl methylene-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-1-yl) benzylidene) thiazolidine-2,4-diones derivatives. Antimicrobial activity against two gram-positive bacteria (*S. aureus, S. pyogenes*), two gram-negative bacteria (*E. coli, P. aeruginosa*) and three fungal species (*C. albicans, A. niger, A. clavatus)* using the broth microdilution method This compound **(17)** showed very good antimicrobial activity along with Gilde docking score (-8.864) [41].



(17)

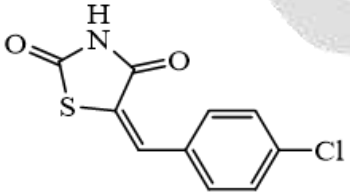
Alhameed R.A *et al.* (2019) synthesized and evaluated antimicrobial activity of a new series of thiazoldinediones with carboxamide and amino acid derivatives. This compound **(18)** having the substituent on arylidene group with amino acid derivatives was found to be potent among these compounds [42].



R= H, 4-Br, 2-Cl R_1= Ph, Ph, $-CH_2CH_2Ph$

(18)

De Paiva *et al.* (2019) The thiazolidine-2,4-dione core represents a heterocyclic class with several correlated properties. The goal was to synthesize 10 different derivatives of 5-arylidene-thiazolidine-2,4-dione, utilizing urea as the catalyst in a solvent-free reaction medium, with good results. Notably, compounds **19** and **20** exhibited the most significant effects against *S. aureus* [43].



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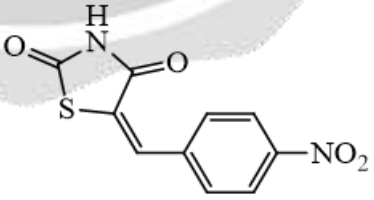
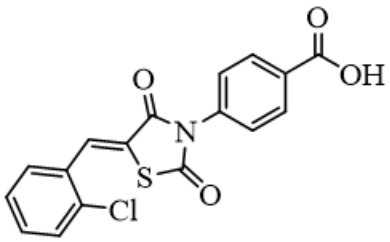


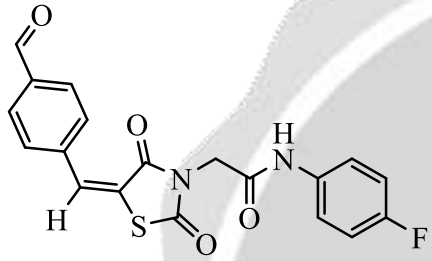
(20)

Shukla *et al.* (2019) Derivatives of 5-benzylidene-2,4-dioxothiazolidin-3-yl benzoic acid were synthesized using both conventional and microwave methods. The antimicrobial potential of the synthesized derivatives was evaluated. Compound 4-(5-(2-chlorobenzylidene)-2,4-dioxothiazolidin-3-yl)benzoic acid **(21)** exhibited potent antimicrobial activities against all microbial strains in this study, with MIC values ranging between 0.6-0.8 µg/ml. The zone of inhibition diameter was measured between 17.2-19.5 mm at a concentration of 200 µg/ml [44].



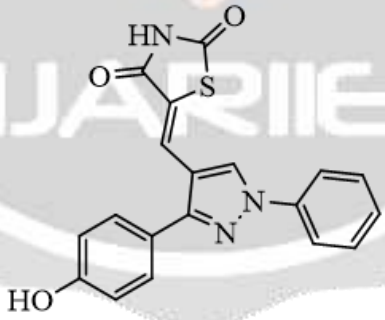
(21)

Joshi *et al.* (2020) Novel 5-ethylidene-thiazolidine-2,4-dione was synthesized through the Knoevenagel condensation of aromatic ketone and N-substituted thiazolidinedione-2,4-diones. The antimicrobial activity of the synthesized compound **(22)** was evaluated, showing moderate to very good activity against the tested microorganisms, including both gram-positive and gram-negative bacteria. The thiazolidine ring is attached with para fluoroaniline via a nitrogen atom, and substituted with different arylidene group at 5th position [45].



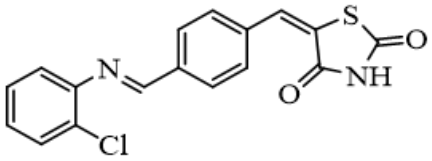
(22)

Tummalacharla S *et al.* (2020) synthesized pyrazolyl-thiazolidinedione hybrid analogues and evaluated them for their antimicrobial activity. The in vitro antimicrobial activity of the synthesized compounds was assessed against four bacterial and two fungal pathogens. Compound **(23)** demonstrated a moderate to good zone of inhibition against the tested organisms. The findings from microbial screening studies were further supported by the results obtained from molecular docking studies [46].



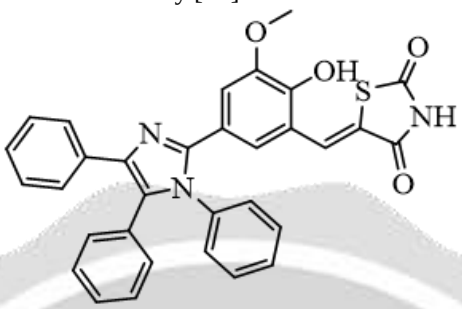
(23)

Kumar *et al.* (2020) A new series of thiazolidine-2,4-dione analogs were synthesized. These synthesized compounds were screened for their antioxidant and antimicrobial potential. Molecular docking studies were conducted to explore the interaction between the synthesized thiazolidine-2,4-dione compounds and DNA gyrase. This compound **(24)** showed good antimicrobial activity and docking score [47].



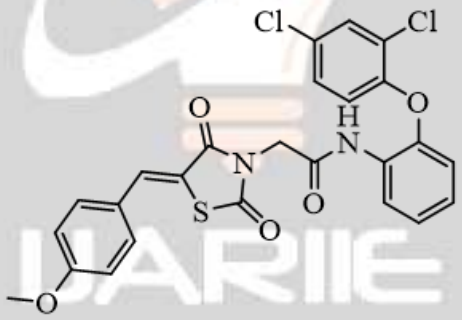
(24)

Nyaki H.Y. *et al.* (2021) Newly synthesized derivatives of thiazolidine-2,4-dione and 1-H-imidazole were prepared. The antimicrobial activity of these compounds **(25)** against gram-positive bacteria, including *Bacillus anthracis* (*B. anthracis*) and *Staphylococcus aureus (S. aureus*), as well as gram-negative bacteria, including *Escherichia coli (E. coli)* and *Pseudomonas aeruginosa (P. aeruginosa),* was evaluated using the inhibition zone diameter assay method. All the derivatives showed good antimicrobial activity [48].



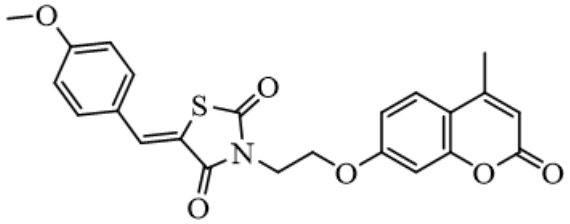
(25)

Patel J.A *et al*. (2021) Thiazolidine-2,4-dione is a toxophoric unit and its derivatives showed antimicrobial activity. Computational approach two-dimensional quantitative structure-activity relationship (2D-QSAR) was used to predict the antitubercular activity of the thiazolidine-2,4-dione derivatives. This derivatives have thiazolidine-2,4-dione and **(26)** (2-(2,4-dichlorophenoxy)phenyl as antimicrobial and antitubercular toxophores which increase the biological activity. From the biological activity, it was revealed that substitution with the electron-withdrawing group enhanced biological activity [49].



(26)

Mangasuli S.N. *et al*. (2021) Synthesized novel coumarin-thiazolidine-2,4-dione derivatives. The synthesized compounds were subjected for computational studies and biological evaluation. These compounds (**27, 28**) were tested for their *in-vitro* antibacterial and antifungal activities, revealing promising results. Compound **(27)** demonstrated excellent antibacterial activity, with a MIC of 0.5 µg/mL against *Staphylococcus aureus* and *Bacillus subtilis*, and 1 µg/mL for *Escherichia coli* and *Pseudomonas aeruginosa*. Compound **(28)** exhibited antifungal activity, with a MIC of 1 µg/mL against Aspergillus flavus [50].



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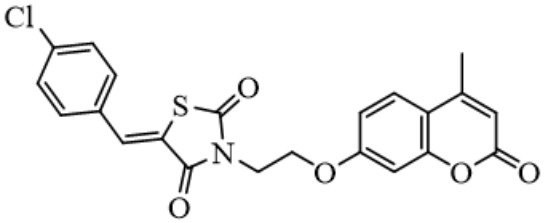
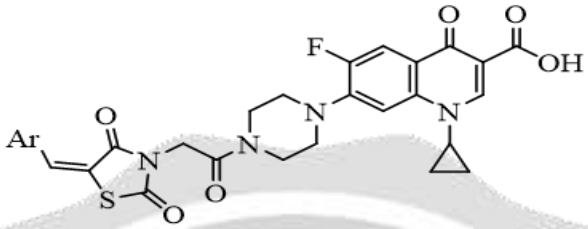


(28)

Aziz H.A. *et al.* (2022) Thiazolidine-2,4-dione linked ciprofloxacin derivatives were synthesized, exhibiting broad-spectrum antibacterial activity. The introduction of thiazolidine-2,4-dione to the N-4 piperazinyl moiety of ciprofloxacin in these hybrids proved effective against both Gram-positive and Gram-negative bacteria. Compounds **(29a-29l)** highlighted the crucial role of extending a small aromatic or heteroaromatic group beyond the thiazolidine ring for optimal DNA gyrase enzyme active site interaction. Compounds **29a, 29g**, and **29l** demonstrated greater potency than ciprofloxacin for topoisomerase IV (IC_{50}=0.3–1.9 μM) and gyrase (IC_{50}=0.22–0.31 μM) inhibition, aligning with their enhanced antibacterial activity against *S. aureus* [51].



(29a-29l)

Compounds	Ar
29a	Phenyl
29b	2-CH_3-phenyl
29c	4-CH_3-phenyl
29d	3-NO_2-phenyl
29e	4-OCH_3-phenyl
29f	3,4-di OCH_3-phenyl
29g	3,4,5-di OCH_3-phenyl
29h	4-Cl- phenyl
29i	4-F-phenyl
29j	naphthayl
29k	4-NO_2-phenyl
29l	furyl

Table 2.2: Thiazolidine-2,4-dione derivatives

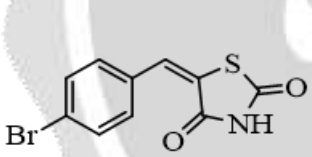
3. Antioxidant activity

When utilised at low quantities, antioxidants are substances that stop or slow the oxidation of an oxidizable substrate. Antioxidants neutralise free radicals, rendering them harmless, so preventing their damage to cells. Standard chemical constituents (polycyclic aromatic hydrocarbon, lead, cadmium, etc.) and environmental contaminants also produce free radicals, aberrant cellular processes, several biochemical responses, and illnesses like atherosclerosis, tumours, heart disorders, diabetes, etc. By giving up a proton to reactive oxygen species (ROS), antioxidants may stop the chain reaction that would otherwise occur. Antioxidants stop free radicals in their tracks before they may damage a cell. Antioxidants found in nature are excellent for cleaning and detoxifying the body. Toxins in the body are neutralised and eliminated as waste. Therefore, it is necessary to create new, extremely effective antioxidant compounds by chemical synthesis [52].

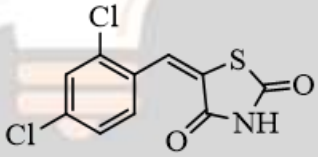
3.1. Mechanism of TZD as an Antioxidant

The release of free radicals causes oxidative stress. Chemically reactive free radicals are molecules with an uneven amount of electrons. The most important kind of free radicals are oxygen-containing radicals, sometimes called reactive oxygen species (ROS). Reactive oxygen species (ROS) are produced when oxidants such as superoxide dismutase (SOD), catalase, and NADPH oxidase are activated (**Figure 3**) [53]. Damage to DNA, proteins, and cells is caused when ROS scavenge for cells to grab or contribute protons. TZD derivatives are hypothesized to be effective because they donate their proton to ROS, therefore stopping the ROS from propagating and causing a cascade effect [54].

Sucheta *et al.* (2018) Using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging technique and ascorbic acid as a reference, synthesized substituted 5-benzylidene-3-(2-oxo-2-(2-oxo-2*H*-chromen-3-yl)ethyl)thiazolidine-2,4-dione derivatives and tested them *in vitro* for antioxidant activity. Based on the laboratory findings, compounds **(30)** and **(31)** were found to be the most potent compounds [55].

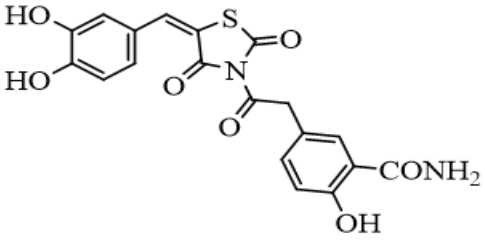


(30)

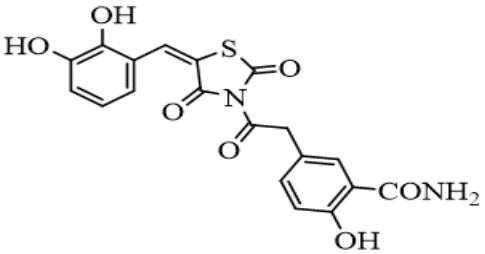


(31)

Marc *et al.* (2019) Using ABTS and DPPH radical scavenging experiments, Marc *et al.* developed a novel series of (*E*)-5-(2-(5-(substitutedbenzylidene)-2,4-dioxothiazolidin-3-yl)acetyl)-2-hydroxybenzamide and screened them for *in vitro* antioxidant capacity. All of the compounds showed moderate to powerful radical scavenging action compared to the reference chemicals Trolox (6-hydroxy-2,5,7,8-tetramethylchroman- 2-carboxylic acid), ascorbic acid, and butylated hydroxytoluene (BHT). Compounds **(32)** and **(33)** also showed potent activity compared to standard [56].

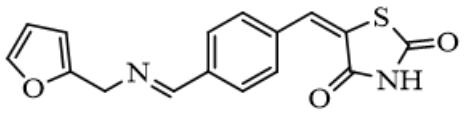


(32)

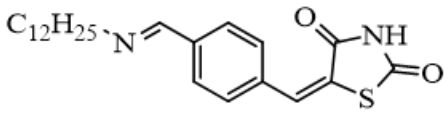


(33)

Kumar *et al.* (2020) Different thiazolidine-2,4-dione derivatives with 5-substituted aryl/alkyl moieties were synthesized by Kumar *et al.* for the development of new antioxidant compounds, and their *in vitro* antioxidant potential was evaluated using a 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging method, with ascorbic acid serving as a reference drug. All of the synthesised compounds showed very high levels of antioxidant activity in the assay. The most effective derivatives in the series were determined to be compounds **(34)** and **(35) [47].**

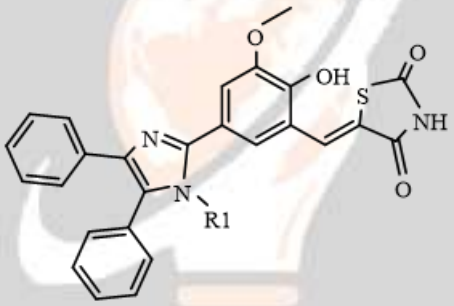


(34)



(35)

Nyaki H Y. et al. (2021) The new derivatives of thiazolidine-2,4-dione and 1-H-imidazole were prepared using imidazole. The antioxidant activity of the final products was assessed through DPPH radical scavenging activity, exhibiting relatively good activity compared to ascorbic acid. Notably, compounds **36d, 36e**, and **36f** demonstrated the highest antioxidant activity. Compound **36e**, with a NO2 group, exhibited stronger antioxidant properties in the DPPH method. Overall, the synthesized product **(36a-36f)** showed good antioxidant activity, particularly the compound (5-(2-hydroxy-3-methoxy-5-(1-(3-nitrophenyl)-4,5-diphenyl-1H-imidazole-2-yl)benzylidene) thiazolidine-2,4-dione) [48].



(36a-36f)

Compounds	**R_1**
36a	C_6H_5
36b	4- ClC_6H_4
36c	4-$OEtC_6H_4$
36d	4-MeC_6H_4
36e	3-$NO_2C_6H_4$
36f	H

Table 3.1: Series of (4,5-diphenyl-1*H*-imidazol-2-yl)benzylidene)thiazolidine-2,4-dione)

4. Conclusion

The TZD moiety is very medicinally promising due to its pivotal involvement in the biological functioning of various vital substances. Since the synthetic methods are flexible and easy to use, finding novel TZD analogues is a realistic goal. The medicinal chemist has the opportunity to develop new TZD compounds by substituting different moieties at the third and fifth locations of the TZD scaffold. TZDs have other therapeutic applications outside their

primary usage as antidiabetic medicines, including antibacterial activity. This review article aimed to investigate the pharmacological potential of TZDs as well as their mechanism of action for use as antimicrobial, antibacterial, and antifungal drugs. Recent patents awarded to TZDs for their various biological actions were also briefly described. Researchers using medicinal chemistry to create novel TZD analogues will find this review study useful, and future drug molecule designers will find it useful as well. It is possible that if we look at TZD molecules with other heteroatoms in the future, we will find some promising leads.

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