A CLINIAL REVIEW ON PHARMACOLOGICAL EVALUATION OF THIAZOLIDINE AND ISATIN IN THE NEW MILLENIUM AS MAGIC MOIETIES

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Abstract

Studies done in the past on the 4-thiazolidinone nucleus have shown that derivatives containing this nucleus have a significant potential to be developed as powerful medicinal agents. Due to these biological actions, medicinal chemists have developed an interest in the structure-activity relationship of these compounds, which has resulted in the discovery of several lead molecules. For the benefit of medicinal chemists working on this nucleus, this review outlines the routes for its synthesis and covers older and more recent studies on its biological activity. The review discusses current findings about thiazolidin-4-ones' anti-inflammatory, analgesic, anticonvulsant, antidiabetic, antiparasitic, antibacterial, antitubercular, antioxidant, and anticancer activities.

Keyword: Thiazolidine, Isatin, Biological Activity, Cancer, Neurological Syndromes, Cardiovascular Diseases.

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INTRODUCTION

Heterocyclic compounds play a significant role in both chemical and biological sciences. In our biological system, heterocyclic molecules play a critical role. In addition, a wide range of therapeutic candidates, including those for antibiotic, anti-tumor, anti-inflammatory, antiviral, antimicrobial, antifungal, and antidiabetic purposes, contain heterocyclic compounds. Due to its numerous biological functions, thiazolidinone is an extremely powerful heterocyclic ring. It is always being researched how to develop and create new molecules using this nucleus. The tetrahydro derivative of thiazole and its oxo counterpart, thiazolidinone, is thiazolidine. The 2, 3 and 5-positions are susceptible to a wide range of replacements, which alter the characteristics of compounds. It is also feasible to create novel derivatives by changing the substituents bound to the nitrogen atom and the methylene carbon atom.[1, 2]

Thiazole (1), whose non-aromatic equivalent is Thiazolidine, is one of these five-membered ring heterocycles (2). The topic of this review is 2,4-thiazolidinedione (3) (TZD), which is created when 2 is further embellished with two carbonyl groups at positions 2 and 4 (Figure 1).[3]

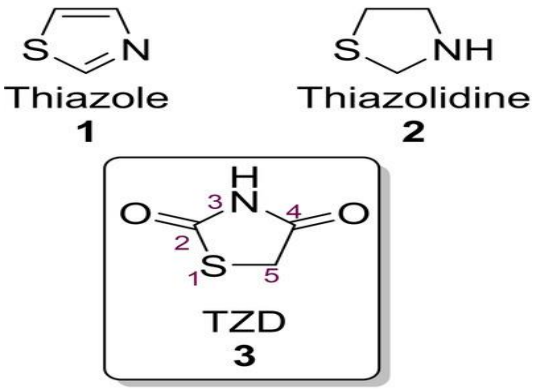


Fig.1 Structure of Thiazole, Thiazolidine, TZD

The potential for 4-thiazolidinones and related heterocyclic-based compounds as a source of anti-inflammatory, anticancer, antimicrobial, antidiabetic, and antibacterial agents has been thoroughly investigated. Since the 1960s, there have been considerable advances in the medicinal chemistry and pharmacology of 4-thiazolidinones, as evidenced by the explosive growth of the number of scholarly papers, reviews, and patents relating to diverse 4-thiazolidinone derivatives.[4]

Heterocyclic compounds are crucial in the treatment of cancer, and TZDs, which are produced from a five-membered thiazole system with three carbon atoms, one nitrogen atom, one sulphur atom, and two double-bonded oxygen atoms on the 2 and 4 positions, have been reported to be a promising scaffold. When coupled with other heterocyclic rings, TZD produces a wide range of biological actions, including anti-diabetic, anti-inflammatory, anti-oxidant, anti-tubercular, anti-microbial, anticonvulsant, and cytotoxic activities, according to a literature review.[5, 6, 7]

A fundamental component of many synthesized molecules of great interest in medical chemistry, is the scaffold 1,3-thiazolidine-4-one. Several natural compounds, including thiamine (vitamin B1), acidomycin (identified from Strepomyces strains), and many metabolic byproducts (cytotoxic cyclopeptides) of fungus and early marine creatures have this scaffold as a structural element. Many thiazolidine-4-one-based medications, including pioglitazone (an oral anti-diabetic medication), etozoline (a loop diuretic), and ralitoline (an anticonvulsant), have already received approval for therapeutic use (Fig. 2 and 3).[8]

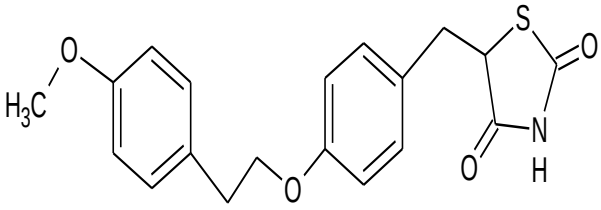


Figure 2. Structure of Rosiglitazone

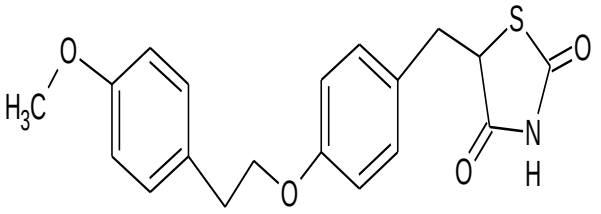


Figure 3. Structure of Pioiglitazone

Other significant biological effects of thiazolidine-4-one scaffold are reported in the literature, including those that are anti-inflammatory, antioxidant, platelet-activating factor (PAF) antagonist, cyclooxygenase (COX) inhibition, tumour necrosis factor antagonist, anticonvulsant, antimicrobial, antiviral, and anti-HIV.[9-14]

4-THIAZOLIDINONE SYNTHESIS

The traditional process for making 4-thiazolidinone derivatives calls for the hazardous catalyst dicyclohexyl carbodimide to condense aldehydes, anilines, and mercaptoacetic acid. Additionally, the method's limitations include the usage of organic solvents, strict experimental guidelines, and low yield. So, it is necessary to create contemporary

techniques that can do away with these drawbacks. Harale and colleagues are working on a method that uses environmentally safe palladium nanoparticles with a diameter of about 5 nm as the catalyst. This procedure successfully produced 2,3-disubstituted-4-thiazolidinones for the first time in good yield.[15]

Another synthesis catalyzed by nanoparticle has been developed that uses $CdZr_4(PO_4)_6$ as the catalyst, and bis-thiazolidinones have been synthesized in excellent yield.[16]

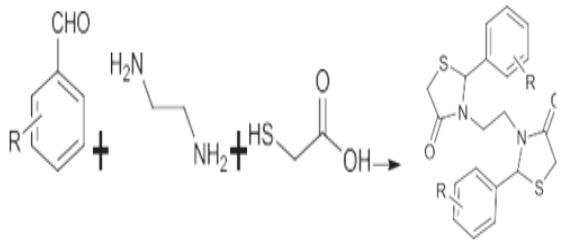


Figure 4. Synthesis of bis-thiazolidinone using $CdZr_4(PO_4)_6$ nanoparticles as the catalyst.

BIOLOGICAL ACTIVITIES

Our main goal in the literature review was to find powerful molecules with a variety of pharmacological activity and fewer side effects. Many investigations have been conducted on thiazolidinone since it is a physiologically significant heterocyclic molecule with a solid reputation in the literature.

PPAR Gamma Receptor Activator

Peroxisome proliferator-activated receptors (PPARs), a class of nuclear receptors, are activated by thiazolidinediones (TZDs), which are frequently used to treat type 2 diabetes. PPAR-gamma is one of these nuclear receptors. In a variety of cancer models, PPAR gamma ligands (TZDs) have recently been discovered to have anticancer action by disrupting the cell cycle, cell proliferation, cell differentiation, and apoptosis in addition to halting tumour angiogenesis.[17]

Anticonvulsant activity

Based on 2-imino-4-thiazolidinone, Mishchenko et al. (2020) produced thiazole-bearing hybrids that were then tested for anticonvulsant activity utilizing the maximum electroshock (MES) test and the pentylenetetrazole-induced seizures test. In all models, compound 6 demonstrated outstanding anticonvulsant activity.[18]

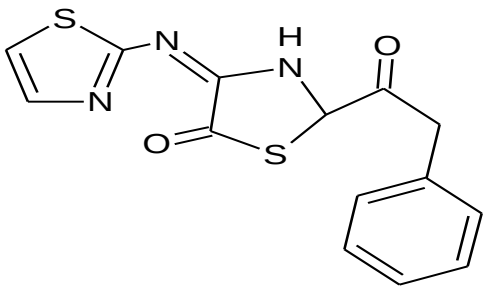


Figure 5. Structure of Pentylenetetrazole

Antidiabetic Activity

In order to determine their antidiabetic potential, Rajalakshmi et al., 2020 produced oxazinyl thiazolidinone compounds and tested them for -α amylase inhibition and -glucosidase inhibition activity. It was discovered that compounds 7 (chloro-substituted) and 8 (bromo-substituted) were more potent than the common medication acarbose.[19]

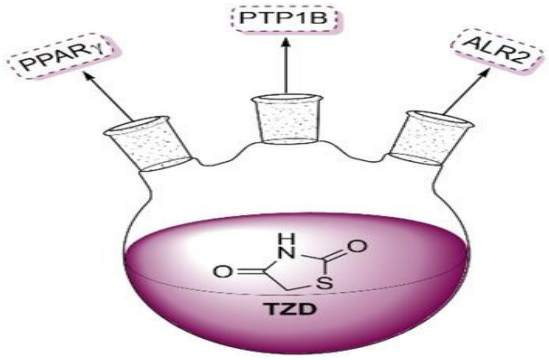


Figure.6. Structure of Oxazinyl Thiazolidinone

Action against cancer and tumours

A series of 2,3-disubstituted 1,3-thiazolidin-4-ones were synthesised by Gawronska-Grzywacz et al. in 2019 and tested for cytotoxicity against human cancer cell types in vitro. The most effective compounds against human renal adenocarcinoma 769-P cells were 9a (IC50 = 2.67 mM) and 9b (IC50 = 2.93 mM). According to a thorough investigation of these compounds' have antiproliferative capabilities, they caused G1 cell cycle arrest in 769-P cells.[20]

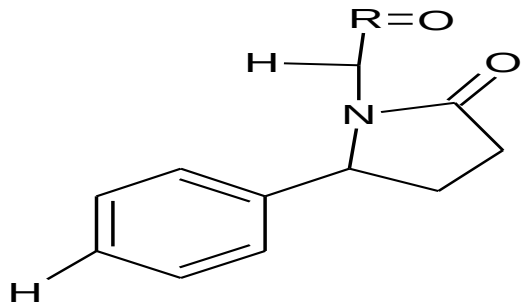


Figure.7. Structure of (9a) R= $-CH_3$ (9b) R= $-C_6H_5$

Anti-inflammatory and Analgesic activities

Shinde et al., 2019 synthesized 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-one derivatives and screened them for their anti-inflammatory activity by measuring the pro-inflammatory cytokine (TNF-α and IL-6) production by lipopolysaccharides in THP-1 cells. The halogenated derivatives displayed better anti-inflammatory activity and among them, compound 10 displayed the highest activity i.e. 72 and 79% inhibition for TNF-α and IL-6, respectively.[21, 22]

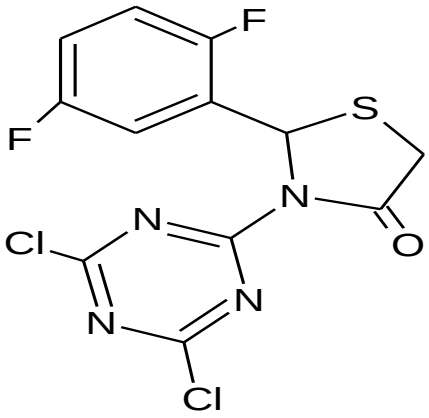


Figure.8. Structure of 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-one

A series of ethyl 2-[2-(2,5-disubstituted-1H-indol-3-yl)-4- oxothiazolid-3-ylamino]-5,6-dihydro-5-oxo-4H-1,3,4-thiadiazine-6-carboxylates were created by Anekal and Biradar in 2017 and tested for their analgesic and anti-inflammatory properties using the tail flick activity using the carrageenan-induced paw edema model. The analgesic effects of compounds 11a and 12b were 97.52% and 96.9%, respectively, and the suppression of edema was 55.08% and 55.50%, respectively.[23]

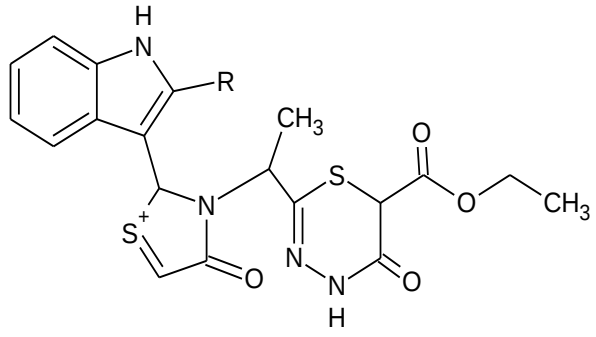


Figure.9. Structure of R=OMe, R_1=Ph & -H, R_1= Me

Antimicrobial activity

In a series of 2-trifluoromethyl benzimidazole-thiazolidinone derivatives created by Cheddie et al. in 2020. Two Gram-positive bacteria, Staphylo coccus aureus and methicillin-resistant Staphylo coccus aureus, and four Gram-negative bacteria, Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia coli, and Salmonella typhimuri As compared to ciprofloxacin and levofloxacin, all of the compounds showed good activity. Compounds 13a, 13b, and 13c, which each have a bromo or nitro group, showed a wide range of activity.[24, 25, 26]

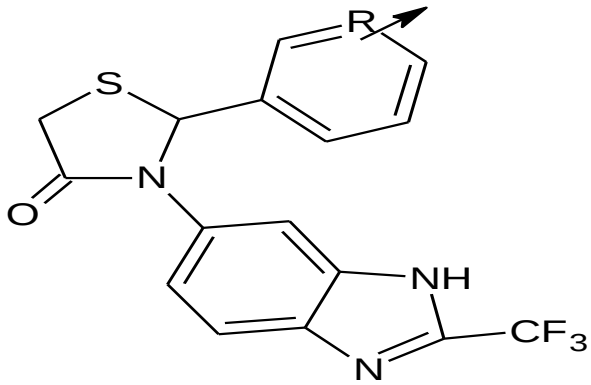


Figure.10. Structure of R= 2-Br, 4-Cl, 4-Br

Antitubercular activity

A series of 5-methyl thiazolidinones were created by Ekinci et al., 2019, and their in vitro antimycobacterial activity against the Mycobacterium TB H37Rv strain were assessed. With a MIC of 12.5 g/mL, Compound 14 emerged as the primary antimycobacterial agent.[27]

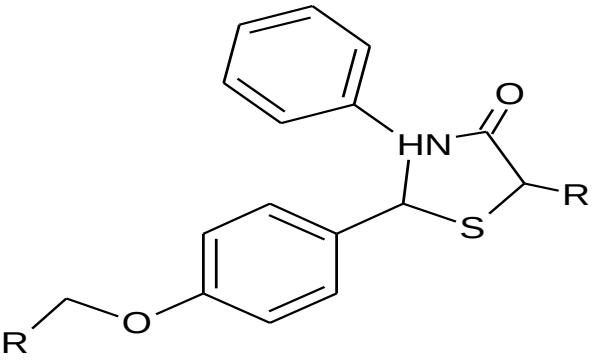


Figure. 11. Structure of 5-methyl thiazolidinones

Antiparasitic Behavior

A tropical disease spread by mosquitoes called leishmaniasis is directly brought on by protozoa belonging to the genus Leishmania spp. The infection may appear in several ways. The disease can manifest in three different ways: cutaneous, visceral, and mucous.[28-29] Conventional medications struggle with issues such toxicity, which causes a variety of side effects, and parasite resistance.[30-31] The importance of creating novel drugs that block the parasitic pathways of the Leishmania genus is thus highlighted.

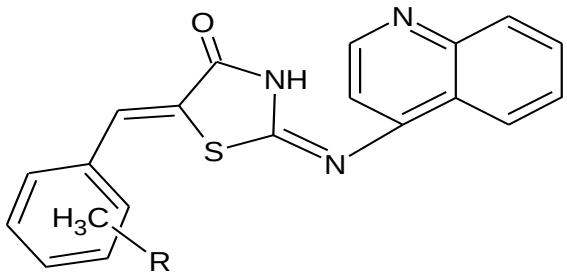


Figure. 12. Structure of **15a**: R=3,4,5-triOCH3, **15b**: R=2,4,6-triOCH$_3$, **15c**: R=4-(CH$_3$)$_2$CH, **15d**: R=4-(CH3)2CH-O, **15e**: R=4-OCH$_3$

Quinoline-thiazolidin-4-one hybrids (15a-15f) were synthesised by Bhat et al. and tested in vitro for their ability to inhibit LdMetAP1 and HsMetAP125. The tested hybrids inhibited LdMetAP1 with IC50 values between 3.0 and 123.4 M and HsMetAP1 with values between 54.2 and 200 M.[32]

Benzodiazepine Agonist

Ali Almasirad1 and others designed, Novel thiazolidinone compounds and synthesised, and subjected to a preliminary pharmacological evaluation as possible benzodiazepine agonists. The inclusion of the thiazolidinone moiety and the absence of BZD agonist characteristics would indicate that our proposed scaffold would have extensive anticonvulsant effects. The maximum electroshock (MES), pentobarbital-induced loss of righting reflex, and open-field locomotor activity tests were carried out in vivo to ascertain the anticonvulsant, sedative-hypnotic, and anxiolytic properties of the synthesised compounds, respectively. The outcomes were contrasted with diazepam, a popular BZD agonist.

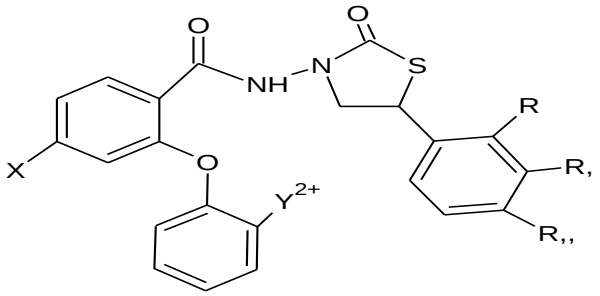


Figure. 13. Structure of Thiazolidinone Compounds

The structure of the novel compounds 5a–p consists of a an aromatic ring, b a coplanar proton-accepting group, c a second out of- plane aromatic ring, d adjunct thiazolidinone pharmacophore.[33]

Divergent activities

Matrix metalloproteinases (MMPs) cause tissue damage by contributing to inflammatory processes. By combining a benzisothiazole with a 4-thiazolidinone, Incerti et al. (2018) created a series of 2-(1,2-benzothiazol-3-yl)-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl) propanamides and assessed their inhibitory effectiveness against MMP-9.27 The most promising profile was displayed by compound 17, which has a 4-carboxyphenyl substituent at C2 of the 4-thiazolidinone ring and can inhibit MMP-9 at a nanomolar level (IC50 = 40 nM). According to docking studies, the carboxylate group of 17 forms H bonds with three of the active site residues and interacts monodentately with three of the active site residues form connections with the Zn atom and H atom (Gly186, Tyr423, and His401). The discovery of novel therapeutic medicines to stop tissue damage can therefore be thought of as starting with this compound as a lead compound. tive site leftovers (Gly186, Tyr423, and His401). The discovery of novel therapeutic medicines to stop tissue damage can therefore be thought of as starting with this compound as a lead compound.[34]

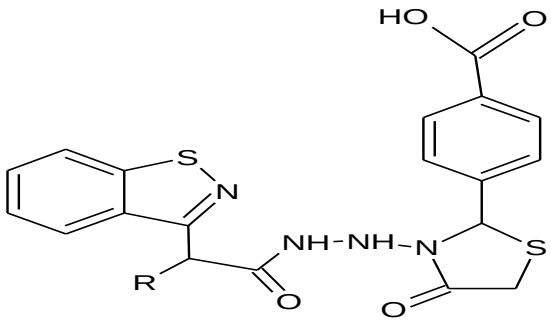


Figure. 14. Structure of 2-(1,2-benzothiazol-3-yl)-N-(4-oxo-2-phenyl- 1,3-thiazolidin-3-yl) propane-mides

In a 2017 study, Genc et al. synthesised derivatives of aminoindane thiazolidinone and assessed how well they inhibited the activity of purified human carbonic anhydrase (hCA) I and II activity. In comparison to compounds substituted with pyridinyl at position 2, phenyl at these positions showed greater activity. The most active substance, compound 18, had an IC50 of 6.75 M for hCAI and 7.55 M for hCAII.[35]

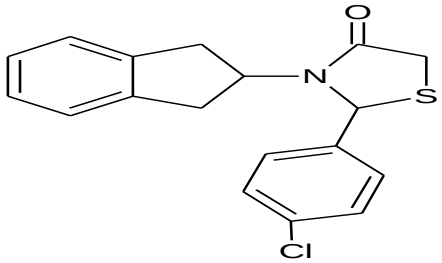


Figure. 15. Structure of Aminoindane Thiazolidinone

In accordance with the right cell culture models, Güzeldemirci et al. (2018) synthesised a series of 4-thiazolidinones with an imidazo[2,1-b]thiazole moiety and tested them against a large and varied panel of RNA- and DNA viruses utilising cytopathic effect (CPE) reduction assays. Some of the substances have a mediocre level of antiviral activity. The 2009 pandemic strain A/H1N1 Virginia/ATCC3/2009 was one of three influenza A virus strains that the compound 66 consistently and moderately showed action against (cytotoxicity >100 M). [36]

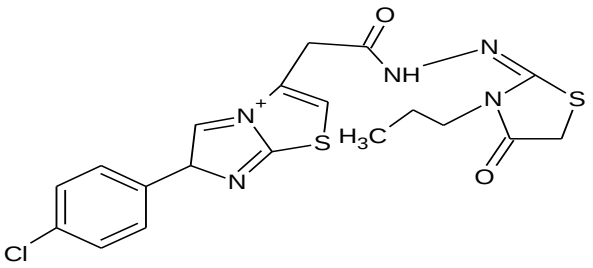


Figure. 16. Structure of 4-thiazolidinones with an imidazo[2,1-b]thiazole moiety

At nanomolar concentrations between 0.84 and 2.81 nM, the piperonal-thiazolidin-4-one hybrids 21a–21f and the 4-nitro counterpart of A (Figure 17) exhibited excellent inhibitory action against AChE. Compound Ad (4-fluoro derivative) had the highest activity, with an IC50 value of 0.84 nM. (Figure 22). The human carbonic anhydrase (hCA) isoforms I and II were inhibited by these derivatives at submicro molar concentrations (IC50 = 91-334.3 nM), however**.**

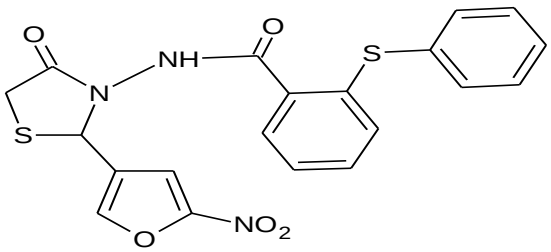
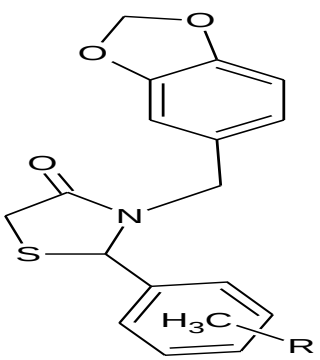


Figure. 17. Structure of piperonal-thiazolidin-4-one hybrids 21a–21f and the 4-nitro counterpart



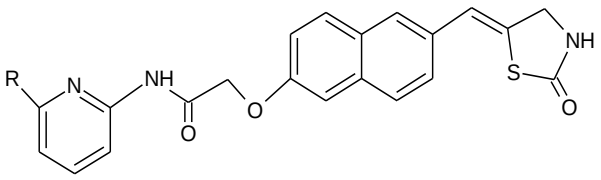


Figure. 18. Structure of Compound Ad (4-fluoro derivative)

CONCLUSION

The information about antioxidant, anticancer, anti-inflammatory, analgesic, anticonvulsant, antidiabetic, antiparasitic, antimicrobial, antitubercular, and antiviral activity that was recently published in 2020 and 2021 is summarised in this article. The thiazolidin-4-one system is very successful in the biological activities listed above. Some of them also shown activity on two or more targets. In the treatment of complex disorders like cancer, neurological syndromes, cardiovascular diseases, or diabetes, these qualities are advantageous. The development of the thiazolidin-4-one derivative group as possible bioactive agents may therefore benefit from this review.

SOURCE OF SUPPORT: Nil

CONFLICT OF INTEREST: None declared

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