Synthetic and therapeutic potential of 4-thiazolidinone and its analogs

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ABSTRACT

Past researches on 4-thiazolidinone nucleus have revealed the prominent potential of derivatives containing this nucleus to be developed as a potent therapeutic agent. Because of these biological activities, their structure-activity relationship has created an interest for medicinal chemists leading to the discovery of a number of lead molecules. This review highlights the routes for its synthesis and summarizes the past and recent studies on its biological activities to guide the medicinal chemists working on this nucleus in the development of clinically viable drugs.

1. Introduction

The chemistry of five-membered rings containing two heteroatoms has been an interesting field of study for decades. Among which 4-thiazolidinone ring system has been studied extensively as it is a core structure in various synthetic compounds and an important scaffold known to be associated with several biological activities. The literature survey revealed that the 4-thiazolidinone moiety can be substituted at positions 2, 3 and 5, but substitution at 2-position specifically results in structurally diverse and potent derivatives.

![Thiazolidinone structure](image)

The 4-thiazolidinone scaffold is not only synthetically important but also possesses diverse therapeutic activities which include antidiabetic, antimicrobial, anticonvulsant, antitubercular, antitumour, antiviral, antiparkinsonian, anti-arthritic, analgesic and anti-inflammatory activities. Some thiazolidinone derivatives have better activity than standard drugs and could become a new drug for the market in the future. The successful introduction of Ralitoline as a potent anticonvulsant, Etozoline as an aldose reductase inhibitor for the treatment of...
diabetic neuropathy\textsuperscript{13} has been demonstrated the therapeutic potential of 4-thiazolidinone derivatives (Fig. 1). With the development of faster new 4-thiazolidinone based therapeutic agents, it is essential to compile the latest information with previously available information in order to understand the status of this chemical moiety in medicinal chemistry research.

Inspired by these observations, this review summarizes the various synthetic methods available for the synthesis of the 4-thiazolidinone core structure and the therapeutic journey of this nucleus to give a flying bird eye-catch view of the 4-thiazolidinone nucleus. Although several reviews have been published earlier on 4-thiazolidinones,\textsuperscript{14–18} the focus was either synthetic routes or chemical reactions of the nucleus or the several biological activities of the thiazolidinone derivatives or published a few years ago. Our effort is an exhaustive and systematic compilation of synthetic, as well as the therapeutic voyage of 4-thiazolidinone and its derivatives in the recent past.

![Fig. 1. Structures of commercially available drugs containing the 4-thiazolidinone nucleus.](image)

2. Syntheses of 4-thiazolidinones

The reaction of acid hydrazide $2$ with aromatic aldehydes yielded corresponding hydrazones $3$ which on further reaction with thiglycolic acid in methanol give 2-substituted 4-thiazolidinones $-4$.\textsuperscript{19}

![Thiazolidinones](image)

Thiazolidinones $5$ can be synthesized by taking three components i.e. an amine, a carbonyl compound and a mercapto acid in two steps. The reactions proceed by initial formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketone), which undergoes attack by sulfur nucleophile followed by intramolecular cyclization on the elimination of water.\textsuperscript{20}

![Hydrazine carbothioamide](image)

Hydrazine carbothioamide $7$ was prepared by condensation of an aromatic ester ($6$) with thiosemicarbazide, which underwent ready heterocyclization upon its reaction with chloroacetic acid in presence of sodium acetate to afford thiazolidin-4-one ($8$).\textsuperscript{21}
Reacting the appropriate amine with chloroacetyl chloride in DMF at room temperature and then cyclization of resulting acetamide in the presence of ammonium thiocyanate affords substituted thiazolidin-4-ones (9).\(^{22}\)

![Chemical structure of thiazolidin-4-ones](image)

### 3. Biological activities

In the literature survey, our main objective was to search the potent compounds for various pharmacological activities with lesser adverse effects. Thiazolidinone is well established in the literature as an important biologically active heterocyclic compound and thus is the subject of many research studies.

#### 3.1. Antidiabetic Activity

Rajalakshmi et al., 2020 synthesized oxazinyl thiazolidinone derivatives and evaluated them for \(\alpha\)-amyrase inhibition and \(\alpha\)-glucosidase inhibition activity to reveal their antidiabetic potential. Compounds 10 (chloro-substituted) and 11 (bromo-substituted) were found to be potent even more than the standard drug acarbose.\(^{1}\)

Ottana et al., 2011, searched for more effective 5-arylidene-4-thiazolidinones as aldose reductase inhibitors for the treatment of diabetic complications. He used molecular docking experiments to support SAR studies. He reported that substitution with lipophilic arylidene moiety in position 5 particularly favored the activity; phenoxo and benzyloxy groups in the para and meta positions of the 5-benzylidene group in compound 12 found to be better substituents for enzyme inhibition.\(^{23}\)

Verma and Kamboj 2010, synthesized a series of N’-[3-(4-alkyl/arylsubstituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy)acetohydrazide and evaluated for antidiabetic activity. The compound 13 showed good antidiabetic activity with reduced toxicity.\(^{24}\)

Sharma et al., 2010, synthesized a series of 2-(substitutedphenyl)-3-\{4-(1-naphthyl)-1,3-thiazole-2-yl\}amino]-5-methyl-1,3-thiazolidin-4-ones from 1-acetyl naphthalene and screened them for antihyperglycemic activity. It was found that compound 14a showed the highest antihyperglycemic activity followed by 14b, 14c and 14d.\(^{25}\)

Firke et al., 2009, synthesized a series of \(\text{N’-}[3-(aryl/alkyl substituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyridin-2-yloxy)\) acetohydrazides 15 using an appropriate route and examined for their antidiabetic activity. The compounds 15a and 15b showed appreciable antidiabetic activity.\(^{26}\)

Imran et al., 2009, synthesized 2-(substituted phenyl)-3-\{4-(1-naphthyl)-1,3-thiazol-2-yl\}amino]-4-oxo-1,3-thiazolidin-5-yl acetic acid derivatives and evaluated for their antihyperglycemic effect. Compound 16 displayed the highest antihyperglycemic activity.\(^{27}\)

Kishore et al., 2009, synthesized thiazolidin-4-ones with nicotinamide substitution and administered to Swiss albino mice with streptozotocin-induced diabetes. Both compounds 17 and 18 produced a significant reduction in fasting blood glucose.\(^{28}\)

Nampurath et al., 2008, evaluated 4-thiazolidinones, with chlorophenoxyacetamide for their hypolipidaemic, hypoglycemic activity in Swiss albino mice. The compounds 19 and 20 were found to possess good hypolipidaemic and glucose-lowering effects.\(^{29}\)
3.2. 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 21 displayed the highest activity i.e. 72 and 79% inhibition for TNF-α and IL-6, respectively.10

Anekal and Biradar, 2017 synthesized 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 and evaluated them for their analgesic activity using the tail flick method and anti-inflammatory activity using the carrageenan-induced paw edema model. Compounds 22a and 22b showed 97.52% and 96.9% of analgesia, respectively, and 55.08% and 55.50% of edema inhibition, respectively.9
Singh et al., 2011, synthesized a series of 2-(substituted)-5-[(N-benzotriazolomethyl)-1,3,4-thiadiazolyl]-4-thiazolidinone 23 and evaluated for analgesic activity. Compounds 23a, 23b and 23c showed very good analgesic activity.

Deep et al., 2010, synthesized some novel biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides and evaluated for anti-inflammatory activity. In general, the compounds bearing electron-withdrawing substituents in compounds 24a, 24b were found to be more active than the others, indicating probable interaction of such groups with receptor sites.

Barros et al., 2010, synthesized a series of 5-arylidene-3-benzyl-thiazolidin-2,4-diones with halide groups on their benzyl rings were synthesized and evaluated in vivo to investigate their anti-inflammatory activities. 3-(2-bromo-benzyl)-5-(4-methanesulfonyl-benzylidene)-thiazolidine-2,4-dione compound 25 had the best anti-inflammatory activity.

Taranalli et al., 2008, synthesized a series of thiazolidin-4-one derivatives from sulfanilamide and evaluated them for anti-inflammatory, analgesic, and anti-ulcer activity. The substitutions at particular places R, R’ and R” with the functional groups Cl, OCH3, NO2 and OH in the aromatic ring in compound 26a resulted in increased activity as compared to unsubstituted thiazolidin-4-ones and substitution at 5-position with spiro group in compound 26b did not improve the activity.

Kumar et al., 2007, synthesized a series of 3-[4'(p-chlorophenyl) thiazol-2'-yl]-2-[(substituted azetidinone/thiazolidinone)-aminomethyl]-6-bromoquinazolin-4-ones and screened them for anti-inflammatory and analgesic activities. Compound 27 was found to be most active in both the activities.
Ottana et al., 2005, synthesized a series of 5-arylidene-2-imino-4-thiazolidinones and screened them for anti-inflammatory activity. In particular, 5-(3-methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone \(28\) displayed high levels of carrageenan-induced paw edema inhibition comparable to those of indomethacin.\(^\text{34}\)

Vigorita et al., 2003, synthesized \(3,3'-(1,2-ethanediyl)-bis[2-(3,4-dimethoxyphenyl)-4-thiazolidinones]\) \(29\), obtained as racemic mixtures and mesoforms. In particular, the dextrorotatory compound is a highly selective COX-2 inhibitor and the levorotatory one is moderately selective. Instead, \(RS\)-\(meso\) isomer exhibited similar levels of inhibitory activity on both COX isozymes.\(^\text{35}\)

3.3. Anticonvulsant activity

Mishchenko et al., 2020 synthesized thiazole-bearing hybrids based on 2-imino-4-thiazolidinone and evaluated for anticonvulsant activity using maximal electroshock (MES) test and pentylenetetrazole-induced seizures test. Compound \(30\) displayed excellent anticonvulsant activity in both models and were found to possess low acute toxicity.\(^3\)

Fig. 4. 4-thiazolidinone derivatives possessing anticonvulsant activity.

Dwivedi et al., 2016 synthesized thiazolidinone derivatives and evaluated for anticonvulsant activity using the MES method and diazepam as standard. The compound \(31\) was found to be most potent that may be due to its greater lipophilicity and thus greater penetrability in the cell.\(^\text{36}\)

Rohini and Manjunath, 2012, synthesized a series of thiazolyl thiazolidinone indole compounds \(32\) and evaluated them for anticonvulsant activity. These compounds showed significant anticonvulsant activity.\(^\text{37}\)

Velmurugan et al., 2012, synthesized a series of 5-(substituted benzyl)-2-iminothiazolidin-4-one and evaluated them for anticonvulsant activity. Out of the synthesized six compounds, compound \(33\) showed good anticonvulsant activity showing good response in flexion, extension, clonus, and stupor.\(^\text{38}\)

Gireesha et al., 2010, synthesized a new series of 4-oxo-thiazolidinone by reacting sulphadiazine with substituted aldehydes in an alcohol medium in presence of a strong base and screened for
antibacterial, anticonvulsant, and analgesic activity. The compounds 34a, 34b and 35 exhibited significant anticonvulsant activity against electrically induced convulsion.39

Gursoy and Terzioglu, 2005, synthesised two regioisomer series of 2-(3-ethyl-4-(3H)-quinazolinone-2-ylmercaptoacetylhydrazono)-3-alkyl/aryl-5-methyl-4-thiazolidinones and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetylamino)-5-methyl-4-thiazolidinones. Only 4-fluorophenyl substituted thiazolidinone derivative 36 was found to be active as anticonvulsant.40

3.4. Antitumor/Anticancer activity

Gawronska-Grzywacz et al., 2019 synthesized a series of 2,3-disubstituted 1,3-thiazolidin-4-one and subjected to in vitro study of cytotoxicity towards human cancer cell lines. The compounds 37a (IC50= 2.67 mM) and 37b (IC50= 2.93 mM) were most active against human renal adenocarcinoma 769-P cells. The detailed analysis of the antiproliferative potential of these compounds revealed that these compounds carried out G1 cell cycle arrest in 769-P cells.5

Mushtaque et al., 2019 synthesized a series of 4-thiazolidinone analogs and screened them for anticancer activity against hepatocellular carcinoma cell line (HepG2). The compound 38 was found to be most cytotoxic (IC50= 75 µM) while others displayed moderate to low activity (85–530 µM).41

Holota et al., 2019 synthesized a series of 2-(5-aminomethylene-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropionic acid ethyl esters and screened them for in vitro anticancer activity within the National Cancer Institute Developmental Therapeutic Program protocol. Compound 39 displayed inhibition against all 59 human tumor cell lines with the average GI50 value of 2.57 µM.42

Some arylidene-4-thiazolidinone derivatives bearing the sulphonamide moiety were synthesized by Kumar et al., 2018 and were screened for their in vitro cytotoxicity on HepG2 and MDA-MB-231 cell lines. Most of the compounds showed potent activity against MDA-MB-231 cell line. Among those, compounds 40a (IC50= 18.35 µM) and 40b (IC50= 17.45 µM) displayed the highest cytotoxicity which was even higher than the reference drug cisplatin. Moreover, these compounds were found to be non-toxic on human erythrocytes even at high concentrations.43

Kulabaş et al., 2017 synthesized 2-imino-1,3-thiazolidin-4-ones and evaluated them for antiviral and anticancer activities. None of the compounds showed significant antiviral activity. The cytotoxic property was evaluated against NIH3T3 cell line and the anticancer activity was evaluated against K562, MCF-7, HT-29, SJSA1, A549, PC-3, HeLa cell lines. The compound 41 was found to be non-toxic and displayed 35.82% cell growth inhibition against HeLa cell line at 10 µM dose.44

Appalanaidu et al., 2016 synthesized a series of 2-imino-4-thiazolidinone derivatives and screened for cytotoxicity against three cancer cell lines i.e., B16F10, A549 and PANC-1 and normal cell line (CHO). The compounds bearing the thiophene ring were more effective than the compounds bearing the furan ring. Three compounds 42a, 42b, 42c were found to be effective against the tested cancer cell lines in the order B16F10 > A549 > PANC-1. Compounds 42a and 42c are nontoxic to non-cancerous CHO cell line whereas the 42b compound exhibits cytotoxicity at high concentration (50–100 µM).45

Wang et al., 2011, synthesized a series of novel 4-thiazolidinone and indolin-2-one hybrid derivatives and evaluated their cytotoxic activities against four human cancer cell lines by MTT assay. Most of the prepared compounds showed moderate to excellent cytotoxic activities against one or more cancer cell lines. Compound 43 showed potent antitumor activity against all four human cancer cell lines.46
Havrylyuk et al., 2010, synthesized 3- or 2- substituted 4-thiazolidinones with benzothiazole moiety and screened in vitro for anticancer activity. Among tested compounds, compound 44 was found to be the most active compound.47

Lv et al., 2010, prepared two series of thiazolidinone derivatives for potential EGFR and HER-2 kinase inhibitory activity. In particular, compound 45 has demonstrated significant EGFR and HER-2 kinase inhibitory activity and inhibitory activity in tumor growth inhibition as a potential anticancer agent.48

Zhou et al., 2008, identified ten cytoselective compounds from 372 thiazolidinone analogs 46 by applying iterative library approaches. These compounds selectively killed both non-small cell lung cancer cell line H460 and its Paclitaxel-resistant variant H460taxR while showing much less toxicity to normal human fibroblasts.49

Fig. 5. 4-thiazolidinone derivatives possessing anticancer/antitumor activity.

3.5. Antiparkinsonian activity

Gomathy et al., 2012 synthesized some 2-(naphthalen-1-yl)-N-[2-substituted (4-oxothiazolidin-3-yl)]acetamide derivatives and evaluated their antiparkinson potential using 6-
hydroxydopamine lesioned rat’s model. The compound 47 possessing a 3-nitro phenyl group displayed maximum activity.7

Kumar et al., 2012, prepared 3-admantadinyi-2-[(substituted phenyl)-4-oxo-thiazolidin-3-yl]methylamino]-quinazolin-4(3H)-ones and screened for their antiparkinsonian activity. Compounds 48 with 3,4-dimethoxyphenyl group at 2- position of thiazolidinone ring were found to be potent as antiparkinsonian agent.50

Kumar et al., 2010, 3-admantyl-2-(2-(2-substitutedphenyl)-5-substituted-1H-indol-3-yl)thiazolidin-4-ones and evaluated for antiparkinsonian activity. Compound 49 have shown maximum response.51

Fig. 6. 4-thiazolidinone derivatives possessing antiparkinsonian activity.

3.6. Antimicrobial activity

Cheddie et al., 2020 synthesized a series of 2-trifluoromethyl benzimidazole-thiazolidinone derivatives and evaluated for antibacterial activity against four Gram-negative bacteria, 

*Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Escherichia coli*, and *Salmonella typhimurium*, and two Gram-positive bacteria, *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus*. In general, all the compounds displayed excellent activity when compared to ciprofloxacin and levofloxacin. Among them, compounds 50a, 50b and 50c having bromo or nitro group displayed a broad spectrum of activity.2

Deep et al., 2014, synthesized novel derivatives of 4-thiazolidinone from biphenyl-4-carboxylic acid and evaluated for their antimicrobial activities. Compound 51a with its electron-withdrawing group substitutions (bromo and nitro group) on aromatic rings was found to be the most active compound against the bacterial strains. Compound 51b with their bromo substitution on both the aromatic rings was the most active compound against the fungal strains.52

Desai et al., 2013, synthesized a series of 2-(2-chloroquinolin-3-yl)-5-((aryl)benzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-ones 52. Some of the newly synthesized compounds exhibited promising antibacterial activities against *E. coli, S. aureus, P. aeruginosa*, and *S. pyogenes*. Some exhibited very good antifungal activity against *C. albicans, A. niger, and A. clavatus*. Compounds 52a and 52b possessed very good activity against both bacterial and fungal species. It seemed that methyl group at the para position and hydroxyl group at the second position are very significant for activity against both bacterial and fungal strains.53

Shukla et al., 2011, synthesized a series of thiazolidinone derivatives and screened them for anti-inflammatory activity. Among them, compound 53 showed the highest anti-inflammatory activity.54

Vats et al., 2010, synthesized a new series of 2-ketophenyl-3-substituted aryl-1-thiazolidin-4-ones 54 by cyclo condensation of ketoazomethines and thioglycolic acid and screened for antifungal activity against hazardous fungi namely *Fusarium oxysporum, Alternaria brassicola, Pythium* and *Sclerotium*
by paper disc method. Compounds 54a and 54b showed the highest inhibition against *Fusarium oxysporum*, *Alternaria brassicola*, *Sclerotium*, and *Pythium*. Compound 54c showed the highest inhibition against *Sclerotium*, compound 54d was effective against *Alternaria brassicola* and *Sclerotium*. Therefore, from the results, it was evident that compounds having electronegative groups are responsible for antifungal activity.\(^{55}\)

Liesen *et al.*, 2010, reported 4-thiazolidinone derivatives obtained from ethyl(5-methyl-1-H-imidazole-4-carboxylate). The whole synthesized compounds were evaluated against a variety of pathogens for their antibacterial and antifungal activities. The results showed that the tested compounds possessed weak antibacterial and antifungal activities compared to standard drugs. Compounds 55 showed MIC of 270 µg/L against *B. subtilis*.\(^{56}\)

Patel and Shaikh 2010, synthesized Schiff’s bases and 4-thiazolidinones from 2-chloro pyridine-3-carboxylic acid and 2-amino-6-methoxy-benzothiazole and screened for their antimicrobial activity. The compounds 56 containing Cl, NO₂ group, and furan nucleus were found to be more active than the remaining synthesized compounds.\(^{57}\)

Palekar *et al.*, 2009, synthesized a novel series of 4-bis(substituted phenyl)-4-thiazolidinone derivatives from terephthalic acid dihydrazide through multistep reaction sequences. Most of the compounds 57 showed moderate antibacterial activity.\(^{58}\)

Vicini *et al.*, 2008, synthesized 2-heteroarylimino-5-benzylidene-4-thiazolidinones, unsubstituted or carrying hydroxyl, methoxy, nitro, and chloro groups on the benzene ring 58 and screened *in vitro* for their antimicrobial activity against Gram +ve and Gram -ve bacteria, yeasts, and mould. They reported that the activities depend on the substituents at the 5-benzylidene moiety.\(^{52}\)

Bondock *et al.*, 2007, synthesized thirteen compounds and screened *in vitro* for their antimicrobial activities against three strains of bacteria *B. subtilis*, *B. megaterium*, *E. coli* and two strains of fungi *A. niger* and *A. oryzae* by the agar diffusion technique. Most of the prepared thiazolidinone derivatives 59 and 60 revealed comparable activity against tested strains by taking Ampicillin and Chloramphenicol in a concentration of 25 mg/mL as a reference drug.\(^{59}\)

Gadre *et al.*, 2007, synthesized some new 4-thiazolidinones bearing 6-carboxy-3-(2H)-pyridazinone 61 moiety and screened for antibacterial and antifungal activities. All the compounds possessed moderate to good antibacterial and antifungal activities.\(^{60}\)

Kumar *et al.*, 2006, synthesized new substituted arylxy-4-thiazolidinones from corresponding Schiff’s bases and thioglycolic acid in benzene and screened for antimicrobial activity. Compound 62 showed good antibacterial as well as good antifungal activity. From the results, it was concluded that electron releasing groups like methyl, hydroxy and methoxy may be responsible for enhancing antibacterial and antifungal activity.\(^{61}\)

Altintas *et al.*, 2005, synthesized various 5-(N,N-disubstituted aminomethyl)-2-[(4-carbethoxyethyl)thiazol-2-yl]imino]-4-thiazolidinones 63. Synthesized compounds were screened for their *in vitro* antibacterial activity against *S. aureus*, *S. epidermidis*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. typhi*, *S. flexneri*, and *P. mirabilis* using disc diffusion, while the antifungal activities of the compounds against *M. gyipseum*, *M. canis*, *T. mentagrophytes*, *T. rubrum*, and *C. albicans* were tested using micro dilution. All of the compounds were inactive for antibacterial activity but active for antifungal activity.\(^{62}\)
Mistry and Desai, 2004, prepared a series of 4-thiazolidinones by the reaction of various substituted Schiff’s bases with thioglycolic acid and thiolactic acid. The synthesized compounds 64 and 65 were tested for antibacterial activity by measuring the inhibition area on agar plates with *S. aureus* and *E. coli*.63

![Chemical structures](image)

**Fig. 7.** 4-thiazolidinone derivatives possessing antimicrobial activity
3.7. Antiviral and Anti-HIV activities

Güzeldemirci et al., 2018 synthesized a series of 4-thiazolidinones bearing an imidazo[2,1-b]thiazole moiety and evaluated them against a broad and diverse panel of RNA- and DNA viruses using cytopathic effect (CPE) reduction assays in an appropriate cell culture models. Some of the compounds displayed moderate antiviral activity. Among them, the compound (66) displayed moderate but consistent activity against three strains of influenza A virus, including the 2009 pandemic virus A/H1N1 Virginia/ATCC3/2009 (cytotoxicity >100 µM).  

Ravichandran et al., 2011, synthesized a series of 1,3-thiazolidin-4-ones and tested against representative members of the virus including Herpes simplex virus-1 (KOS), Herpes simplex virus-2 (G), Influenza A H3N2 subtype, Influenza B, and their cytotoxic concentration was evaluated. None of the synthesized compounds are active against Herpes simplex virus-1 (KOS) and Herpes simplex virus-2 (G). The compound (67) showed better anti-viral activity against Influenza A H3N2 subtype and Influenza B at the concentration of 249–263 µM, whereas cytotoxicity was found to be >283 µM.  

Ravichandran et al., 2009, used the 3D-QSAR approach to explore the structural requirements of thiazolidinone derivatives for anti-HIV activity and concluded that that 3”, 2”, 6” substituted aromatic rings of thiazolidinones (68) are important for anti-HIV activity.  

Balzarini et al., 2007, synthesized a series of novel thiazolidin-4-ones bearing a lipophilic adamantyl substituent at position 2, and versatile substituents on the nitrogen atom of the thiazolidine ring, were synthesized. Whereas several compounds exhibited a modest anti-HIV-1 activity, (+)-2-adamantan-1-yl-3-(4,6-dimethyl-pyridin-2-yl)-thiazolidin-4-one (69) was endowed with remarkable antiviral potency.  

Terzioglu et al., 2006, synthesized a series of 5-nitro-3-[(5-nonsubstituted/methyl-4-thiazolidinone-2-ylidene)hydrazono]-1H-2-indolinones and were evaluated for in vitro antiviral activity against the yellow fever virus (YFV) in vero cells and the bovine viral diarrhea virus (BVDV). In fact, 1-(4-bromophenyl) substituted 5-methyl-4-thiazolidinone derivative (70) showed the most favorable antiviral activity against BVDV.  

![Fig. 8. 4-thiazolidinone derivatives possessing antiviral activity](image-url)
Rawal et al., 2005, synthesized a series of 2-(aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT Inhibitors. Compound 71 was found to be most active.68

Barreca et al., 2001, synthesized a series of 2,3-diaryl-1,3-thiazolidin-4-ones 72 and screened for their anti-HIV activity. The anti-HIV activity was strongly enhanced by introducing a 2-pyridinyl substituent at the N-3 atom of the thiazolidinone ring and in particular by introducing two chlorine atoms at 2’ and 6’ positions of the phenyl ring. In fact, 6-methylpyridin-2-yl derivatives 72a and 72b possessed the most promising activity.69

3.8. Antitubercular activity

Ekinci et al., 2019 synthesized a series of 5-methyl thiazolidinones and evaluated for their in vitro antimycobacterial activities against *Mycobacterium tuberculosis* H37Rv strain. Compound 73 emerged as the lead antimycobacterial agent with an MIC of 12.5 µg/mL.4

Abo-Ashour et al., 2018 designed and synthesized hybrids of 2-amino-4-methylthiazole bearing 5-acetyl/5-ethyl carboxylate functionality with 5-arylidene thiazolidinone moiety and screened for their antitubercular activity. 5-ethyl carboxylate derivatives displayed about half potency than the acetyl derivatives but their selectivity towards *M. tuberculosis* was high over normal human lung cells. On this basis, compound 74 was considered the most promising lead compound for further optimization.70

![Fig. 9. 4-thiazolidinone derivatives possessing antitubercular activity](image)

Ilango and Kumar, 2010, synthesized a series of novel 2-aryl *N*-(3,4,5-trihydroxy benzamido)-4-thiazolidinone derivatives by reacting various Schiff’s bases of galloyl hydrazide with thioglycolic acid in presence of dioxane and screened for antitubercular activity. The compound 75 showed MIC values equivalent to the standard drug isoniazid. The substitution with the chloro group in phenyl ring of thiazolidinone nucleus was highly active which suggested that electron-withdrawing groups enhance the activity.71

Srivastava et al., 2005, synthesized a series of 4-thiazolidinone derivatives and screened them for antimycobacterial activity. Compound 76 was found to be most active.72
Trivedi et al., 2004, synthesized some new potential 4-oxothiazolidinones in which they added 4-quinazolinone to enhance the medicinal value of the 4-thiazolidinone moiety and screened for antitubercular activity. Significant activity was observed in compounds 77 bearing substituents 2-hydroxy-5-bromophenyl, 4-hydroxyphenyl, 2-chlorophenyl, 4-chlorophenyl, 4-methoxy phenyl, 3-nitrophenyl.\textsuperscript{73}

3.9. Miscellaneous activities

Matrix metalloproteinases (MMPs) are involved in inflammatory processes and thus induce tissue damage. Thus, Incerti et al., 2018 synthesized a series of 2-(1,2-benzothiazol-3-yl)-N-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)propanamides combining a benzisothiazole and 4-thiazolidinone and evaluated for their inhibitory activity against MMP-9.\textsuperscript{11} Compound 78, bearing a 4-carboxyphenyl substituent at C2 of the 4-thiazolidinone ring, exhibited the most promising profile, being able to inhibit MMP-9 at nanomolar level (IC\textsubscript{50} = 40 nM). Docking studies revealed that the carboxylate group of 78 has a monodentate interaction with the Zn atom and H bonds with three of the active site residues (Gly186, Tyr423, and His401). This compound can therefore be considered as a lead compound for the development of new therapeutic agents to prevent tissue damage.

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Genc et al., 2017 synthesized aminoindane thiazolidinone derivatives and evaluated their inhibitory effects on the activity of purified human carbonic anhydrase (hCA) I and II activity. The derivatives substituted with phenyl at 2-position of thiazolidinone rings displayed better activity than those substituted with pyridinyl. The most active compound 79 displayed IC\textsubscript{50} 6.75 \(\mu\text{M} \) against hCAI and 7.55 \(\mu\text{M} \) against hCAII.\textsuperscript{74}

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Adhikari et al., 2012, synthesized a series of 5-\{[(6-substituted-2-hydroxy quinolin-3-yl)methyldiene]/5-[(7-substitutedtetrazolo[1,5-a]quinoline-4-yl)methyldiene}\}-2-[(4-substituted phenyl)amino]-1,3-thiazol-4(5H)-one and evaluated for their in vitro antioxidant activity by DPPH method. Compounds 80 and 81 displayed the highest activity which is comparable with the standard butylated hydroxytoluene (BHT).\textsuperscript{75}
Mushtaque et al., 2012, synthesized a series of thiazolidinone derivatives 82 and screened them for \textit{in vitro} antiamoebic activity against HMI: IMSS strain of \textit{E. histolytica}. Out of sixteen compounds, four compounds 82a, 82b, 82c, and 82d exhibited better antiamoebic activity than the reference drug Metronidazole and also showed low cytotoxicity. \(^{76}\)

Panico et al., 2011, investigated 2-benz[d]isothiazolyl-imino-5-benzylidene-4-thiazolidinone derivatives as potential metalloproteinases (MMPs) inhibitors and evaluated for their antidegenerative activity on human chondrocyte cultures. The most potent compound 83 could be considered as a lead compound for the development of novel clinical agents, inhibitors of cartilage degradation, for the treatment of osteoarthritis. \(^{8}\)

4. Conclusion

The ease of the synthesis of 4-thiazolidinone derivatives allows for structure-activity studies of various substitutions at different positions of this versatile chemical moiety and their application in medicinal chemistry and research as illustrated in Table 1. Further studies on this privileged scaffold are going on to explore its potential for the treatment of various diseases. This article is an endeavor to find potential future directions in the design of novel potent analogs of 4-thiazolidinone based compounds for different biological targets.
Table 1. SAR displaying different substituents at various positions of 4-thiazolidinone moiety for different biological activities

| Activity                      | $R_1$                              | $R_2$                              | $R_3$                              |
|-------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Antidiabetic                  | substituted aryl, aryl or benzyl amido | substituted aryl                   | unsubstituted, short alkyl         |
| Anti-inflammatory and analgesic| substituted aryl or heteroaryl      | dialkyl, substituted aryl or heteroaryl | unsubstituted, substituted benzylidene |
| Anticonvulsant                | unsubstituted, substituted ryl      | unsubstituted, substituted aryl, imine | unsubstituted, substituted arylidene or benzylidene |
| Antitumor/anticancer          | unsubstituted, substituted aryl     | substituted aryl$_N$, $N$-substituted imine | unsubstituted, substituted arylidene or benzylidene |
| Antiparkinsonian              | azetidine, substituted amine or amido | substituted aryl or heteroaryl     | unsubstituted                       |
| Antimicrobial                 | substituted aryl or heteroaryl linked via amido | substituted aryl or hydrazinyl | unsubstituted, substituted benzylidene, short alkyl group |
| Antiviral                     | substituted aryl or heteroaryl      | substituted aryl or hydrazinyl     | unsubstituted, methyl               |
| Antitubercular                | unsubstituted, substituted benzamido or phenylamino | substituted aryl                   | unsubstituted, short alkyl         |

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