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Synthetic and therapeutic potential of 4-thiazolidinone and its analogs

Neetu Agrawal[a*]

[a]*Institute of Pharmaceutical Research, GLA University, Mathura, Uttar Pradesh 281406, India*

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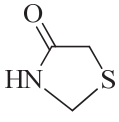
A B S T R A C T

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 **1** 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.



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The 4-thiazolidinone scaffold is not only synthetically important but also possesses diverse therapeutic activities which include antidiabetic,[1] antimicrobial,[2] anticonvulsant,[3] antitubercular,[4] antitumour,[5] antiviral,[6] antiparkinsonian,[7] anti-arthritic,[8] analgesic and anti-inflammatory[9,10] 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,[11] Etozoline as an antihypertensive[12] and Epalrestat as an aldose reductase inhibitor for the treatment of

* Corresponding author.
E-mail address: neetu.agrawal@gla.ac.in (N. Agrawal)

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diabetic neuropathy[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,[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.

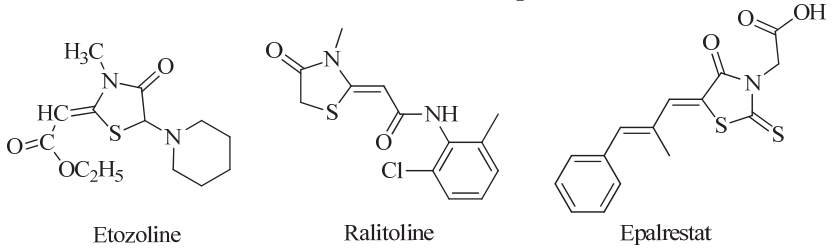
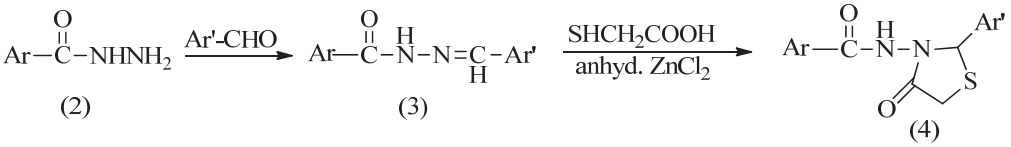


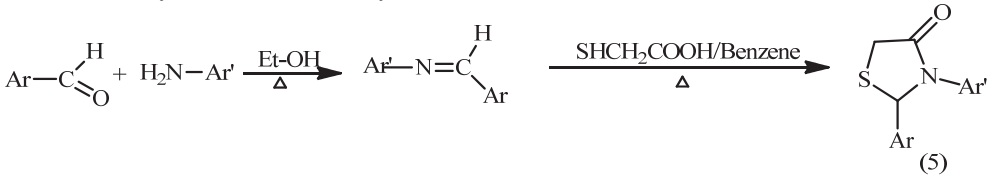
Fig. 1. Structures of commercially available drugs containing the 4-thiazolidinone nucleus.

2. Syntheses of 4-thiazolidinones

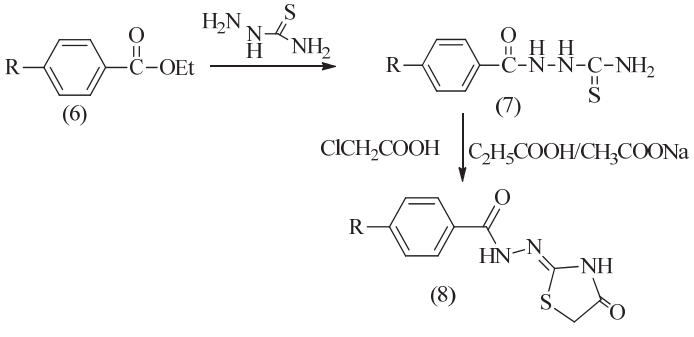
The reaction of acid hydrazide **2** with aromatic aldehydes yielded corresponding hydrazones **3** which on further reaction with thioglycolic acid in methanol give 2-substituted 4-thiazolidinones -**4**.[19]



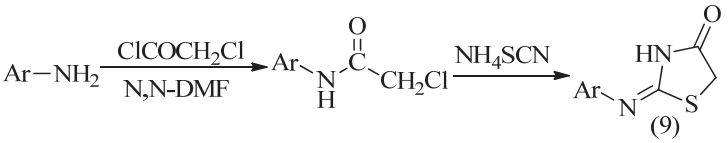
Thiazolidinones **5** can be synthesized by taking three components i.e. an amine, a carbonyl compound and a mercapto acid in two steps. The reactions proceed by initial formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketone), which undergoes attack by sulfur nucleophile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



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**).[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]



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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 α-amylase inhibition and α-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; phenoxy 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 *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]

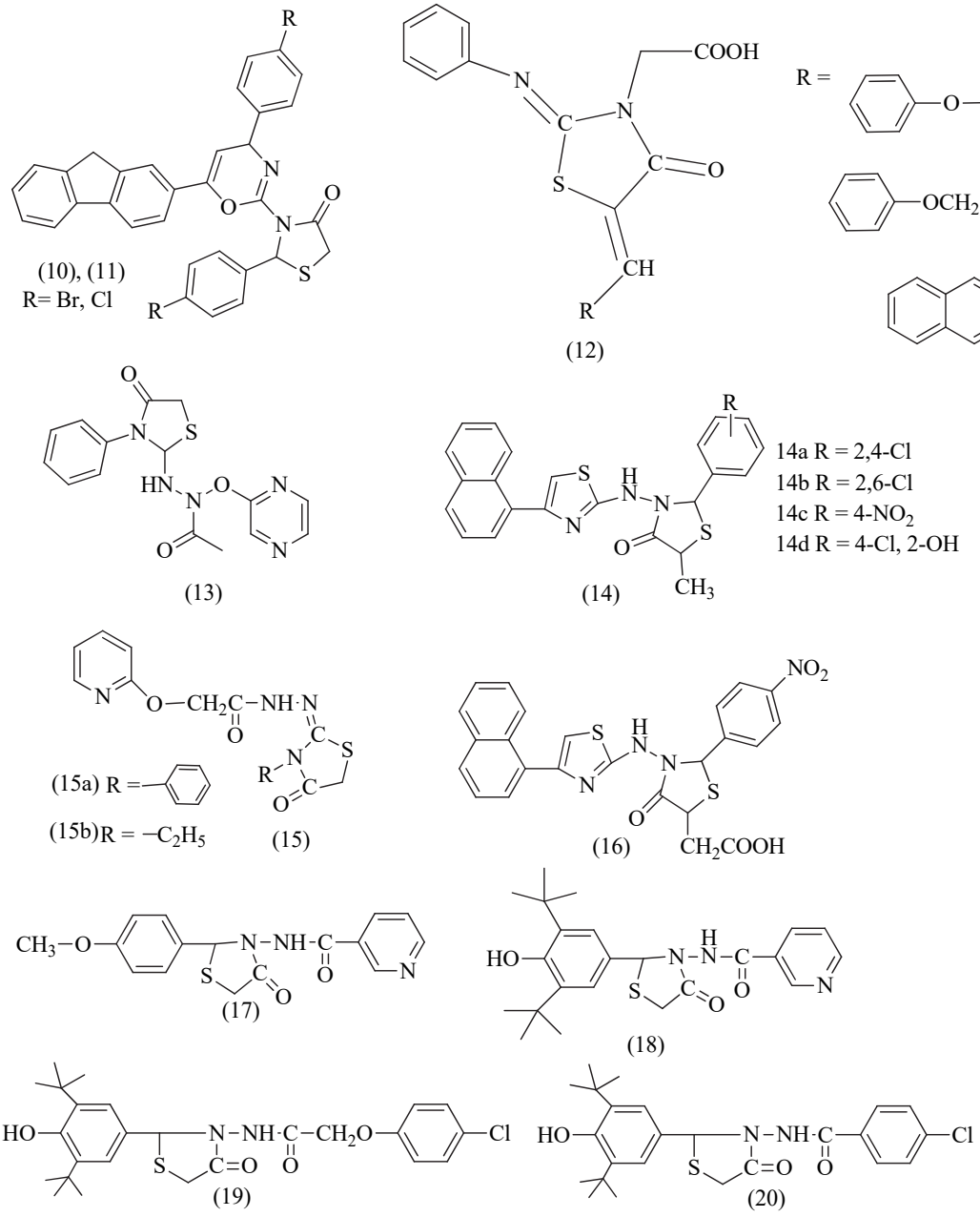


Fig. 2. 4-thiazolidinone derivatives possessing antidiabetic activity

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]

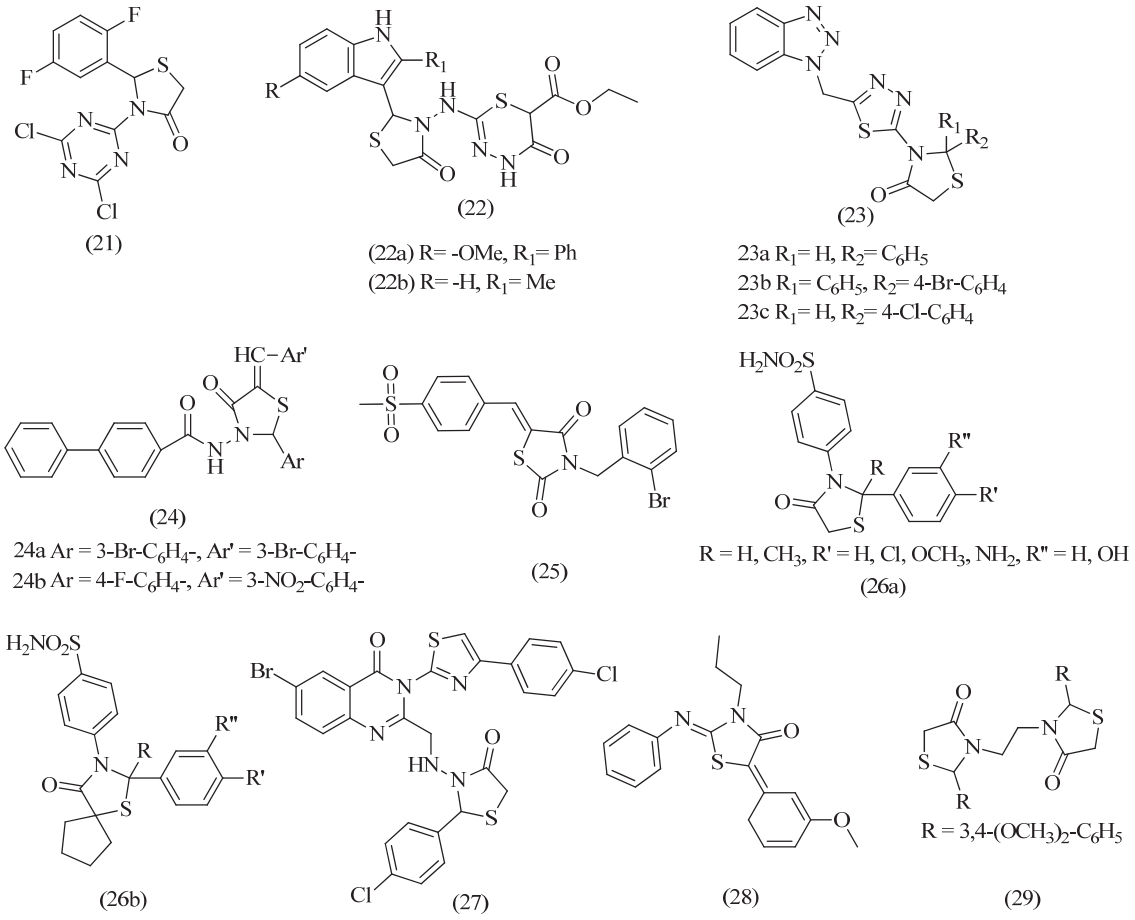


Fig. 3. 4-thiazolidinone derivatives possessing analgesic and anti-inflammatory activity

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.[30]

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.[31]

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.[32]

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, OCH_3, NO_2 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.[33]

Kumar *et al.,* 2007, synthesized a series of 3-[4'(*p*-chlorophenyl) thiazol-2'-yl]-2-[(substituted azetidinone/thiazolidinone)-aminomethy]-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.[19]

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.[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.[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]

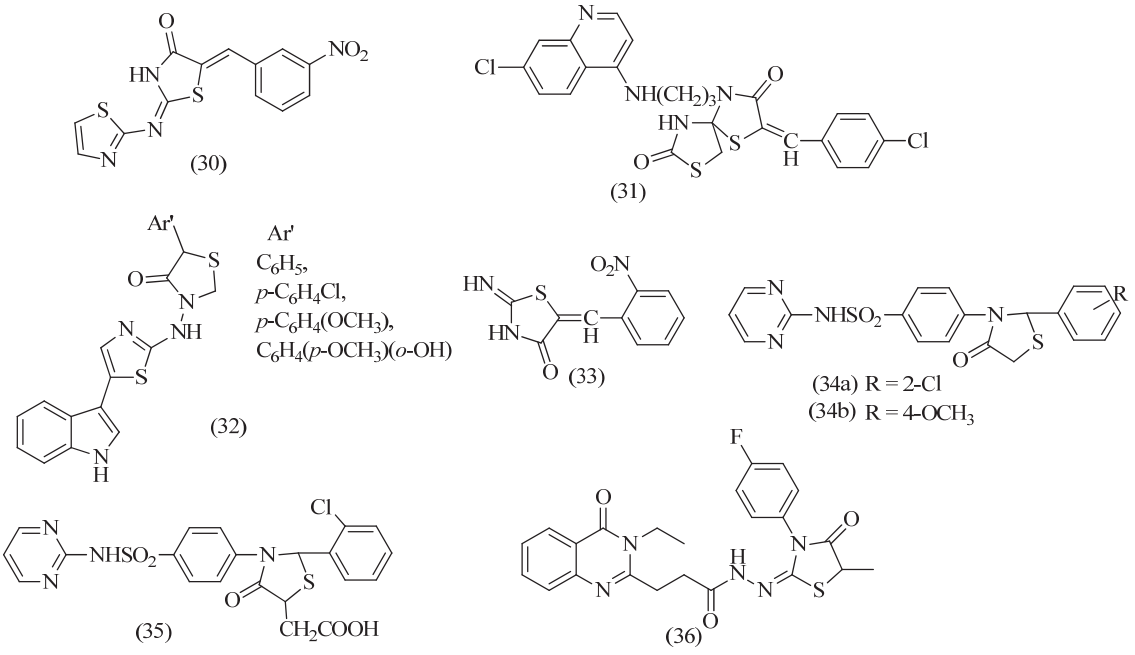


Fig. 4. 4-thiazolidinone derivatives possessing anticonvulsant activity.

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.[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.[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.[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** (IC_{50}= 2.67 mM) and **37b** (IC_{50}= 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 (IC_{50}= 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 GI_{50} 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** (IC_{50}= 18.35 μM) and **40b** (IC_{50}= 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 $H460_{taxR}$ while showing much less toxicity to normal human fibroblasts.[49]

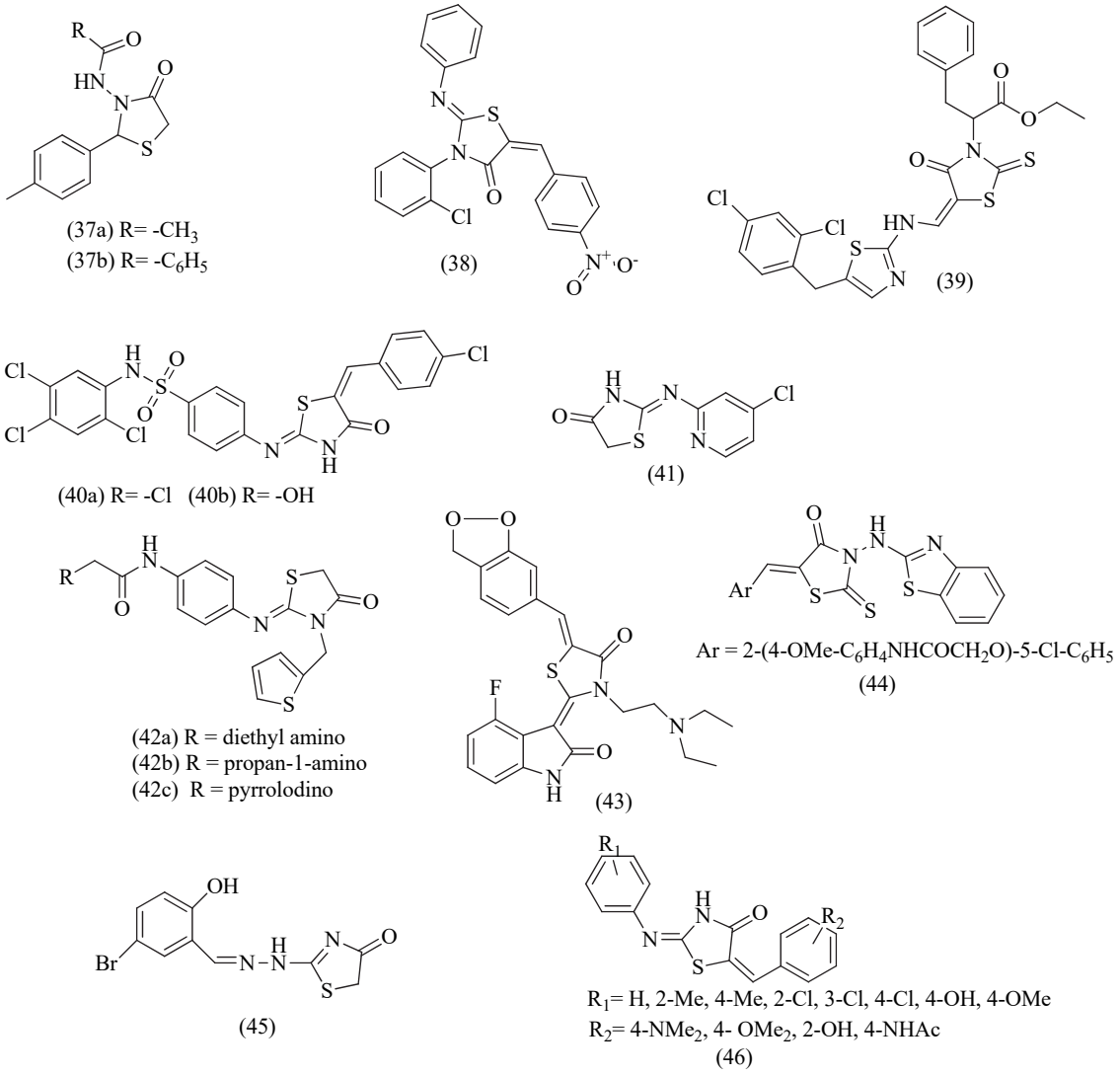


Fig. 5. 4-thiazolidinone derivatives possessing anticancer/antitumor activity.

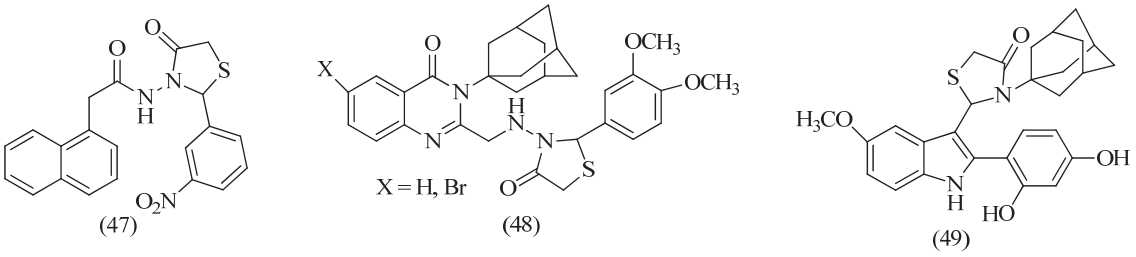
3.5. Antiparkinsonian activity

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-admantadinyl-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]



(47) (48) (49)

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. pyogenus*. 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, NO_2 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.[22]

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 aryloxy-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-carbethoxymethylthiazol-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. gypseum, 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]

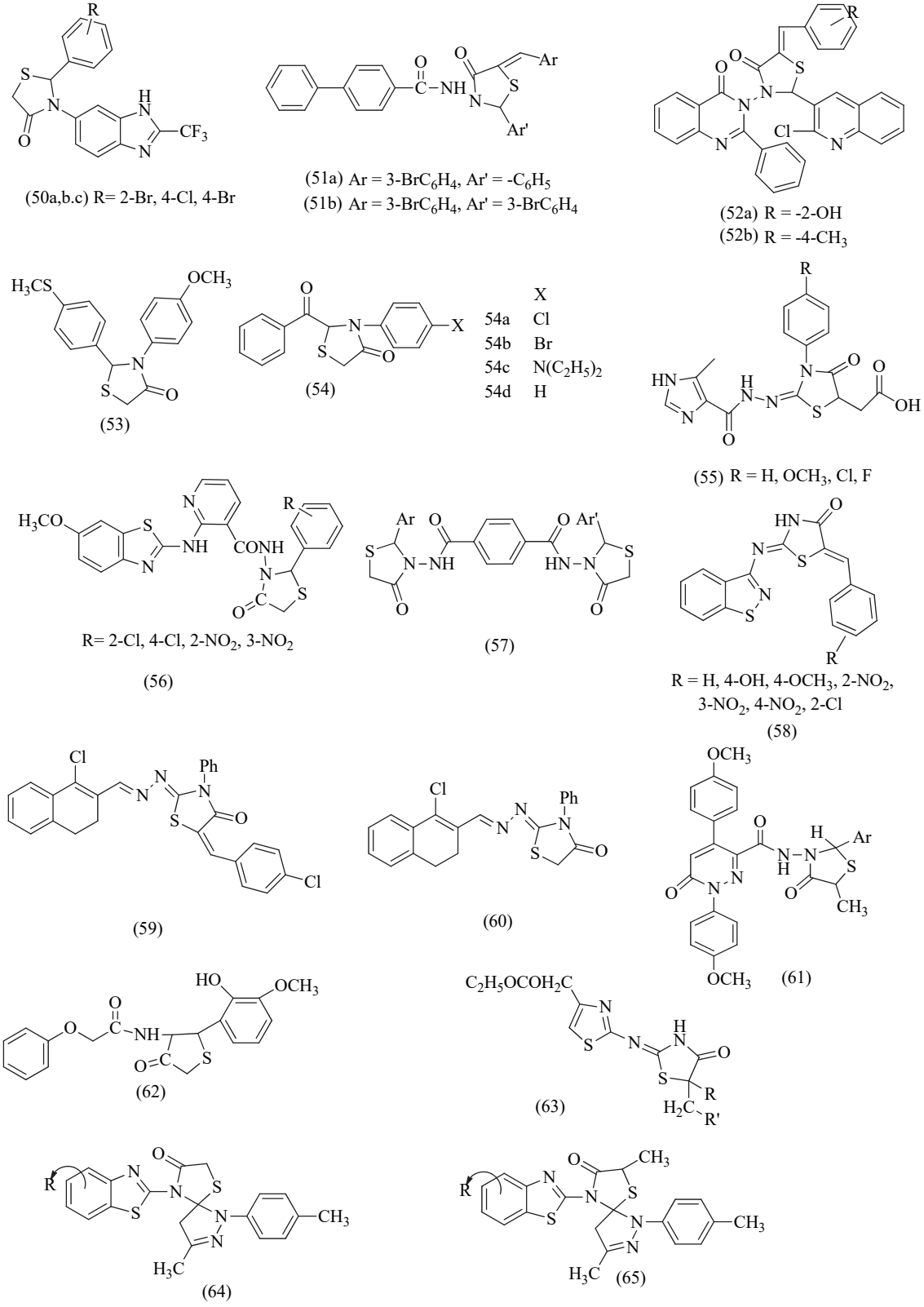


Fig. 7. 4-thiazolidinone derivatives possessing antimicrobial activity

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).[6]

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.[64]

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.[65]

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.[66]

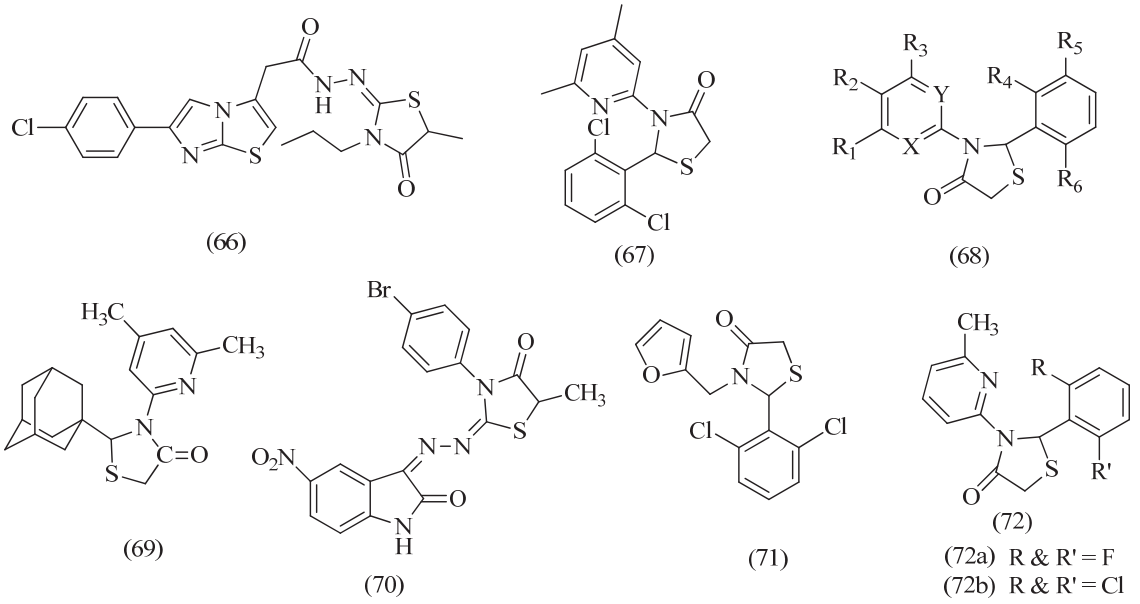


Fig. 8. 4-thiazolidinone derivatives possessing antiviral activity

Terzioglu *et al*., 2006, synthesized a series of 5-nitro-3-[(5-nonsubstituted/methyl-4-thiazolidinone-2-ylidene)hydrazono]-1*H*-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.[67]

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]

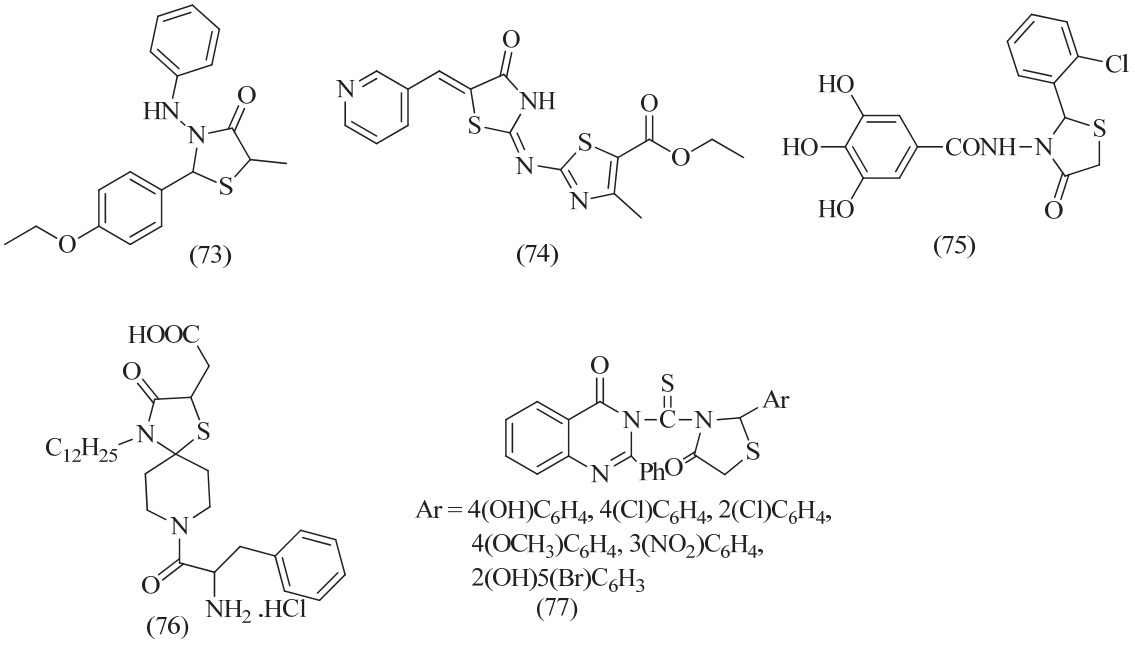


Fig. 9. 4-thiazolidinone derivatives possessing antitubercular activity

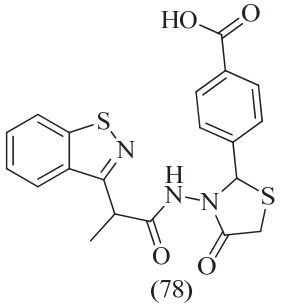
Ilango and Kumar, 2010, synthesized a series of novel 2-aryl *N*-(3,4,5-trihydroxy benzamido)-4-thiazolidinone derivatives by reacting various Schiff's bases of galloyl hydrazide with thioglycolic acid in presence of dioxane and screened for antitubercular activity. The compound **75** showed MIC values 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.[73]

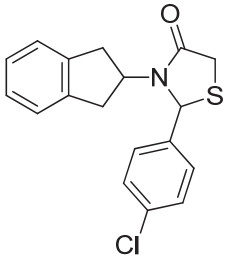
3.9. Miscellaneous activities

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.[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_{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.



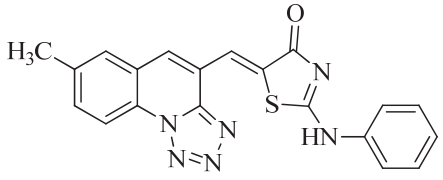
(78)

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_{50} 6.75 μM against hCAI and 7.55 μM against hCAII.[74]



(79)

Adhikari *et al*., 2012, synthesized a series of 5-{[(6-substituted-2-hydroxy quinolin-3-yl)methylidene]/5-[(7-substitutedtetrazolo[1,5-a]quinoline-4-yl)methylidene]}-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).[75]



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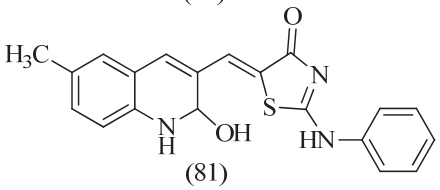
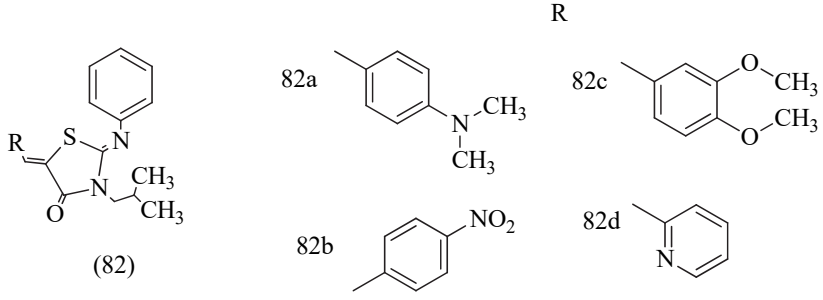


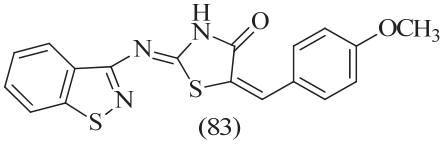
(81)

Mushtaque *et al*., 2012, synthesized a series of thiazolidinone derivatives **82** and screened them for *in vitro* antiamoebic activity against HM1: IMSS strain of *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]



(82)

Panico *et al*., 2011, investigated 2-benzo[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]

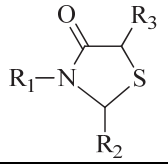


(83)

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 aryl or benzylidene
Antitumor/anticancer	unsubstituted, substituted aryl	substituted aryl,, *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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