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RECENT DEVELOPMENTS AND BIOLOGICAL ACTIVITIES OF THIAZOLIDINONE DERIVATIVES: A BRIEF REVIEW

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Abstract

Since they have a wide range of pharmacological actions against many targets, 4-thiazolidinones, which are thiazolidine derivatives with a carbonyl group at 4th position, have been regarded as a moiety of choice. 4-Thiazolidinones have a wide range of biological effects, including those against cancer, bacteria, viruses, mycobacteria, HIV, analgesia, inflammation, antioxidants, anticonvulsants, diabetes, malaria, hypertension, arrhythmia, and protozoa. Numerous researchers have been drawn to this skeleton to investigate its potential against a variety of activities due to the diversity in the biological response profile. Sincere review of the chemistry, synthesis, spectrum investigations, and uses of 4-thiazolidinone is attempted in the current work.

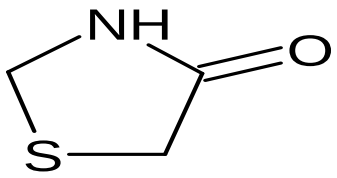
Key words: Thiazolidinone, chemistry of 4-thiazolidinone, Biological activity.

1) INTRODUCTION

The thiazolidine derivatives, or thiazolidinones, are a significant class of heterocyclic compounds with sulphur and nitrogen arranged in a five-member ring. There has been a lot of interest in the chemistry of 4-thiazolidinone derivatives[1], which is a key component in many synthetic pharmaceuticals with a wide range of biological activities, including anti-inflammatory, anticonvulsant, anti-fungal, anti-thyroid, antitubercular, and antidiabetic properties[2]. Because it produces several derivatives with a wide range of biological activity,

the nucleus is also referred to as the "wonder nucleus." The emphasis of the current review is on the many pharmacological traits connected to substituted thiazolidinones and structurally related thiazolidines[3].

2. STRUCTURE & PROPERTIES OF THIAZOLIDINONE



Molecular formula : C_3H_5NOS

Molecular weight : 103.143

Synonyms : 1, 3-thiazolidin-4-one

Physical properties

Description : Colourless solid

Melting point : 194° C

Boiling point : 294.52° C

Density : 1.278 g/cm^3

Molar refractivity : 25.476 cm^3

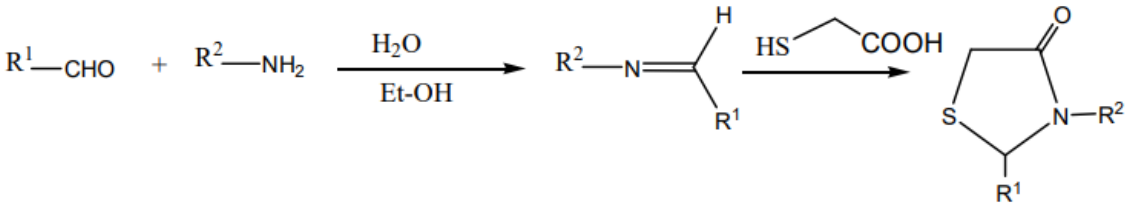
Solubility : Soluble in ethanol, acetone; insoluble in water

Stability : Stable under normal temperature and condition

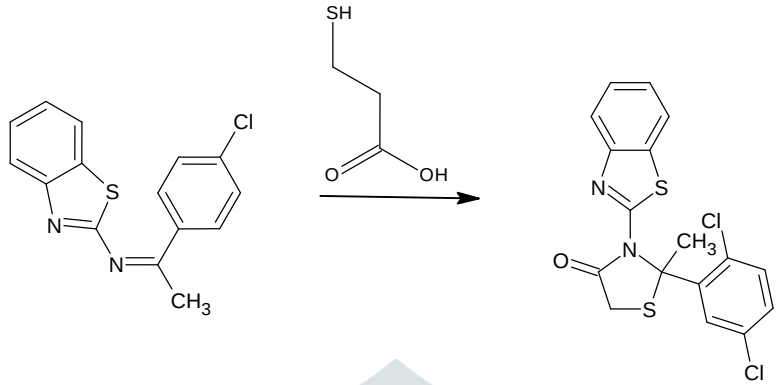
3) SYNTHESIS OF THIAZOLIDINONES DERIVATIVES

Numerous techniques have been documented for creating 4-thiazolidinones.

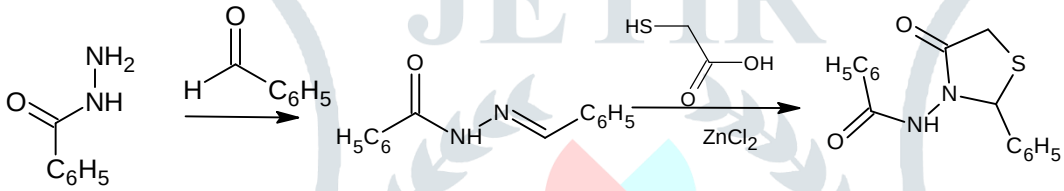
- An amine, a carbonyl molecule, and a mercapto acid are the three ingredients used in the main synthesis processes for 1,3-thiazolidin-4-ones[4]. Either a two-step method or a one-pot three-component condensation can be used for the reported classical synthesis. The first step in the reactions is the creation of an imine (the nitrogen of the amine attacks the carbonyl of the aldehyde or ketone), which is then attacked by the produced sulphur nucleophile, followed by intramolecular cyclization on the removal of water[5].



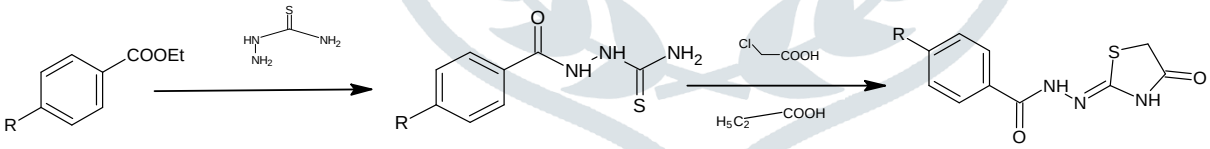
- The use of thiolactic acid in the microwave-assisted synthesis of thiazolidinone from the Schiff's bases. Both traditional and microwave methods of synthesis were used to make the products, and the yields were compared. They came to the conclusion that the conventional synthesis' percent yield could not compare to that of the microwave-irradiated synthesis[6].



- When acid hydrazide is combined with aromatic aldehydes, the resulting hydrazones undergo a second reaction with thioglycolic acid in methanol to produce 2-substituted 4-thiazolidinones[7].



- An aromatic ester and thiosemicarbazide[8] were combined to create hydrazine carbothioamide, which was then readily heterocyclized by chloroacetic acid and sodium acetate to produce thiazolidin-4-one[9].



4) BIOLOGICAL ACTIVITY OF 4-THIAZOLIDINONES

Researchers have created a number of compounds containing this moiety because the thiazolidinones ring has been introduced into a huge variety of known biologically active compounds, either as a substitutuent group or as a replacement of another ring. The literature is replete with publications documenting the many biological functions of thiazolidinone derivatives, some of which are covered in this review.

4.1. Antimicrobial activity

Different levels of inhibition against bacteria and fungus are present in thiazolidinones with substituted positions at C-2 and N-3. Multi-drug resistance microbial infections have rapidly increased in frequency during the past few decades, resulting in a significant health risk. Nearly every position of the 4-thiazolidinone has been investigated in an effort to increase its antibacterial and antifungal activities.

Thiazolidinone derivatives' SAR analyses revealed that they are more efficient against gram-negative bacteria than gram-positive bacteria. Therefore, finding novel antimicrobial drugs will continue to be a difficult and vital work for medicinal chemists. According to Liesen et al., 4-thiazolidinone compounds made from ethyl (5 methyl-1-H-imidazole-4-carboxylate)[10] The entire produced chemicals were tested for their antibacterial and antifungal activities against a variety of diseases(Fig.1). The results showed that the investigated compounds displayed poor antibacterial and antifungal activities compared to conventional medications chloramphenicol and rifampicin for antibacterial activity and ketoconazole for antifungal activity.

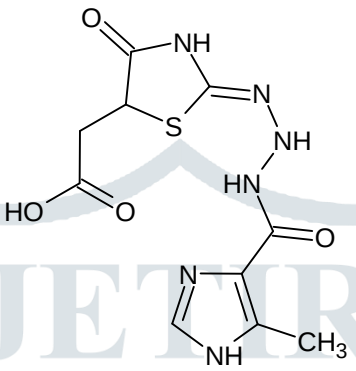


Fig.1

Various 5-substituted 5-(N,N-disubstituted amino methyl) -2-[(4-carbethoxymethylthiazol 2-yl)imino] -4-thiazolidinones (Fig. 2) synthesise by Altintas et al[11]. Using the disc diffusion method, derivatives were tested for their in vitro antibacterial activity against the following bacteria: Staphylococcus aureus ATCC 6538, Staphylococcus epidermidis ATCC 12228, Escherichia coli ATCC 8739, Klebsiella pneumoniae ATCC 4352, Pseudomonas aeruginosa ATCC 1539, Salmonella typhi, Shigella flexneri.

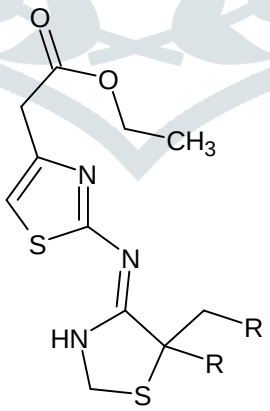
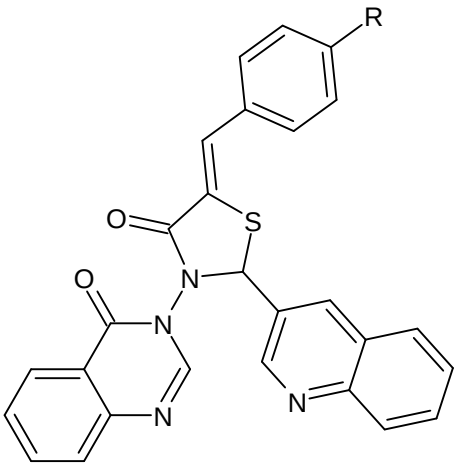


Fig.2

A series of 2-(2-chloroquinolin-3-yl)-5-((aryl)benzylidene) was created by Desai et al[12]in 2013. 3(4H)-(4-oxo-2-phenylquinazolin-3-yl)thiazolidin-4-ones against E. coli, S. aureus, P. aeruginosa, and S. pyogenus, some of the recently synthesised compounds showed promising antibacterial activity against C. albicans, A. niger, and A. clavatus, some showed extremely good antifungal activity. Both 3a and 3b compounds were highly effective against bacterial and fungal species.



3 a, R= -2-OH

3 b, R=-4-CH_3

Fig.3a,3b

According to Singh et al study's of substituted thiazolyl-thiazolidinyl benzothiazoles, none of the compounds with a 2-substituted 4-thiazolidinone ring had any antibacterial action, yet they were all highly effective insecticides[13]. Its insecticidal action was improved by a phenyl ring electron-withdrawing group, such as p-OCH3 (Fig.4). S. aureus and E. coli were resistant to the antibacterial effects of a compound that included the azetidinone moiety rather than the thiazolidinone moiety. Azetidinones were shown to have higher antibacterial activity than thiazolidinones, according to 25 thiazolidinone derivatives made from chalcones of 4-hydroxycoumarin (Fig.5). This is because compounds with the methoxy group had stronger antibacterial activity overall.

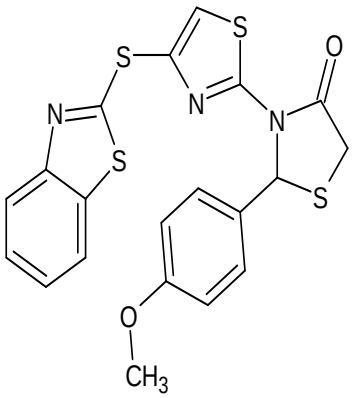


Fig.5

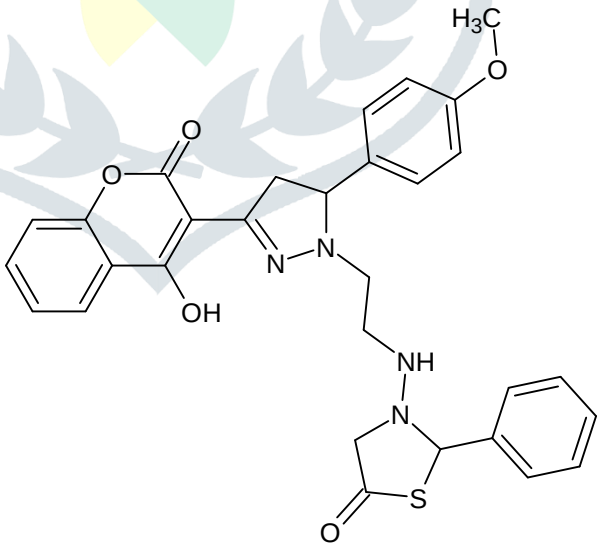


Fig.4

The 5-arylidene moiety of 2-(thiazol-2-ylimino) thiazolidin-4-one plays a significant role in improving its antibacterial activities[14](Fig.6). When compared to arylidene derivatives substituted with hydrophilic hydroxyl, methoxy, or nitro groups, the antibacterial activity of substitution with a chloro group at the second, third, or fourth position on the benzene ring was improved (p-Cl substitution is most active). A number of 5-arylidene-4-thioxo-thiazolidine-2-one derivatives have recently had their cytotoxic and

antibacterial properties assessed. All of the bacteria tested did not respond to thiazolidine-2,4-dione; however, the antimicrobial activity was boosted when the carbonyl group was replaced with thio carbonyl. The results of this investigation showed that the bioisosteric substitution of thiocarbonyl for carbonyl in the thiazolidine ring increased the antibacterial activity[15]. The 5-arylidene-4-thioxo-thiazolidine-2-ones discovered may serve as helpful starting points for further lead optimization due to their antibacterial characteristics, particularly against multidrug-resistant strains of clinical isolates. Within this series, the derivative 5-(2,3,5 trichloro benzylidene)-4-thioxo-thiazolidine-2-one (fig 7) shown a higher inhibitory capability.

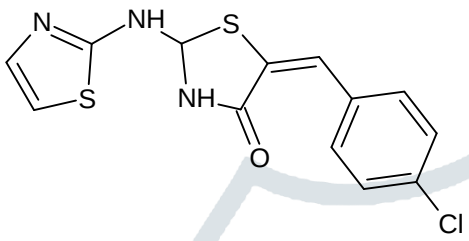


Fig.6

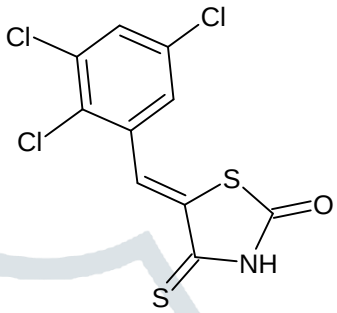
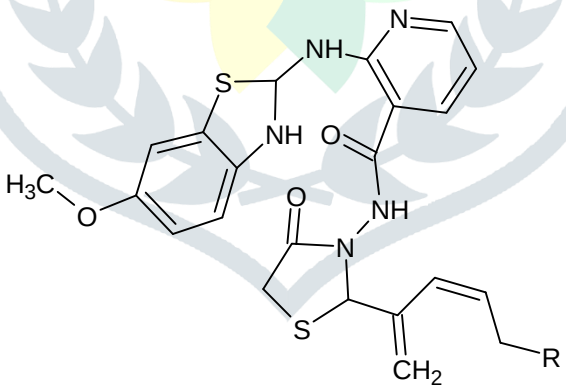


Fig.7

In 2010, Patel and Shaikh created Schiff's bases and 4-thiazolidinones using 2-chloropyridine 3-carboxylic acid and 2-amino-6-methoxybenzothiazole[16].They then tested the compounds for antibacterial efficacy. It was discovered that the compounds (fig 8) with the Cl, NO2 group, and furan nucleus were more active than the other synthetically created substances.



R=2-Cl,4-Cl,2-NO_2,3-NO_2

Fig.8

4.2 Antiviral/anti-HIV activity

Numerous series of 2,3-diaryl-1,3-thiazolidin-4-ones (Fig.9) have been examined for their anti-HIV efficacy. They have been described as a new class of NNRTI-acting antiviral medicines with low cytotoxicity[17]

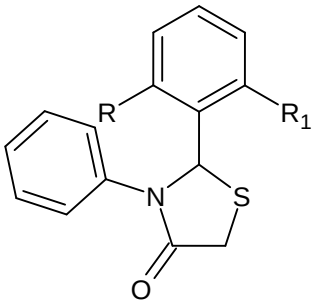


Fig.9

In order to investigate the structural prerequisites of thiazolidinone derivatives for anti-HIV activity, Ravichandran et al. (2009) employed the 3D-QSAR approach[18].They emerged with the conclusion that the 3, 2, and 6 substituted aromatic rings of thiazolidinones (Fig 10) are significant for anti-HIV activity.

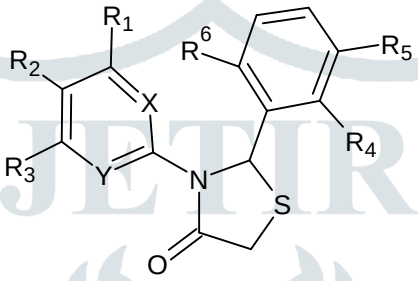


Fig.10

Using Nevirapine as a reference drug, 2-adamantyl-substituted thiazolidin-4-ones[19] (Fig. 11) were created and tested in CEM cell cultures for their effectiveness against HIV-1 (IIIB) and HIV-2(ROD).

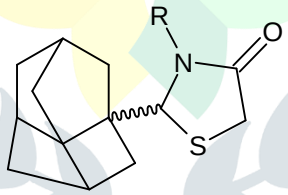


Fig.11

In order to produce 2-(aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones that are specifically HIV-RT inhibitors, Rawal et al. The most active compound discovered was compound[20] (Fig.12).

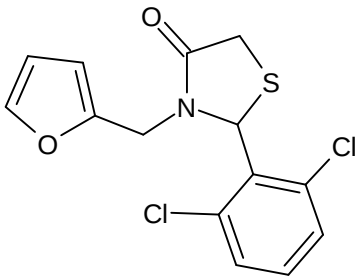


Fig.12

A number of 2,3-diaryl-1,3-thiazolidin-4-ones were created and tested for their anti-HIV activity by Barreca et al. in 2001[21]. By adding two chlorine atoms to the phenyl ring's 2 and 6 positions, as well as a 2 -

pyridinyl substituent to the thiazolidinone ring's N-3 atom, the anti-HIV activity was significantly increased. In actuality, the most encouraging activity was shown by the 6 methylpyridin-2-yl derivatives 13 a and 13 b.

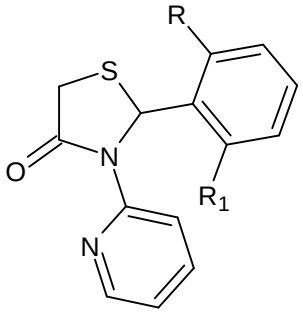


Fig.13 a, R & R_1 = F

b,R &R_1 = Cl

4.3 Antitubercular activity

A number of 4-thiazolidinone compounds were created and their potential for inhibiting mycobacterial growth was tested by Srivastava et al. in 2005[22]. Most active compound was found to be compound(Fig 14).

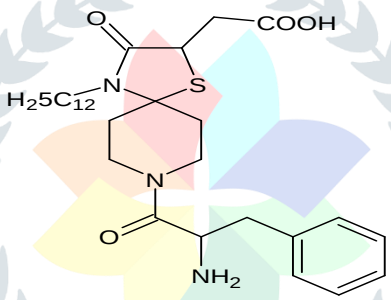


Fig.14

A target for the therapy of tuberculosis was revealed when protein tyrosine phosphatases .A (MptpA) and B (MptpB) released into the host cell by Mycobacterium tuberculosis grew potently to be active selectively. As a brand-new class of powerful and specific MptpB inhibitors, Vintonyak et al [23]created a novel series of indolin-2-one-3-spirothiazolidinones. They looked at the phenyl modification on the thiazolidinone and 2-indolinone locations. According to the SAR investigations, analogues of thiazolidinone containing mono or dialkyl substituents were shown to be less powerful than those bearing two fluorine atoms or a fluorine and a chlorine atom in the meta and para positions of the phenyl ring. When sulfonamide, trifluoromethoxy, or methoxy groups were added, the inhibitory effect was lost. Compound (Fig 15) was discovered to have strong activity against the M. tuberculosis protein tyrosine phosphatase B enzyme (IC50 1.1 lM). In an effort to discover new inhibitors of the enzymes in the vital rhamnose biosynthetic pathway, Babaoglu et al[24] revealed the action of 1,3-thiazolidin-4-ones (Fig 16) against M. tuberculosis by inhibiting dTDP-rhamnose production. 2,3,5-Trisubstituted-4-thiazolidinones were compiled into a virtual library. The 6-hydroxyl; dTDP-6-deoxy-D-xylo-4-hexulose 3,5- epimerase (RmlC) from Mycobacterium tuberculosis was then docked with the synthetic drugs.

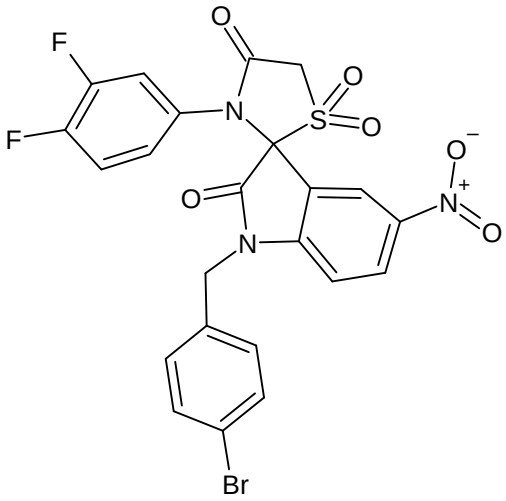


Fig. 16

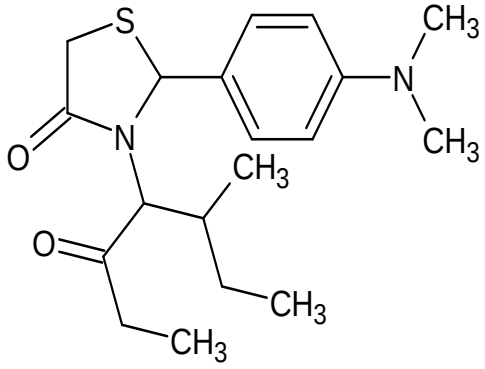


Fig.15

4.4 Anticancer activity.

By using repeated library techniques, ten cyto selective molecules have been found among thiazolidinone analogues (Fig. 17). With an IC 50 range between 0.21 and 2.93 M, these substances selectively killed the non-small cell lung cancer cell line H460 and its paclitaxel-resistant mutant H460taxR while posing significantly less damage to healthy human fibroblasts at doses up to 195 M. Two hydrogen bond acceptors and three hydrophobic areas were suggested to be common characteristics by a pharmacophore built from active compounds[25].

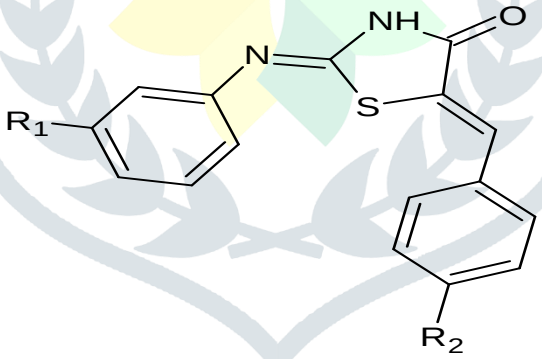


Fig.17

Mushtaque et al., 2019 developed a variety of 4-thiazolidinone analogues and tested them against a hepatocellular carcinoma cell line for anticancer activity (HepG2). The most cytotoxic substance was discovered to be compound (Fig 18) (IC50 = 75 M), while other compounds showed only moderate to low action[26](85-530 M).

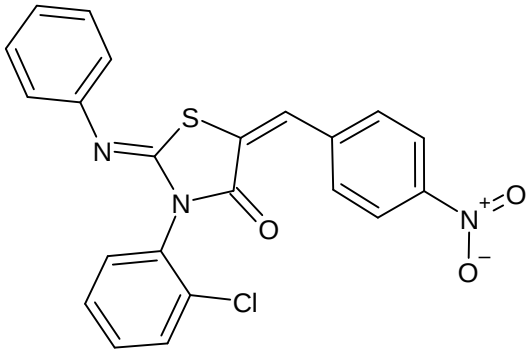


Fig.18

Holota et al., 2019 created a number of 2-(5-aminomethylene-4-oxo-2-thioxothiazolidin-3-yl)-3-phenylpropionic acid ethyl esters(Fig 19) and tested them for in vitro anticancer activity in accordance with the National Cancer Institute Developmental Therapeutic Program procedure[27]. The average GI50 value for compound 39 was 2.57 M, showing inhibition against all 59 human carcinoma cell lines.

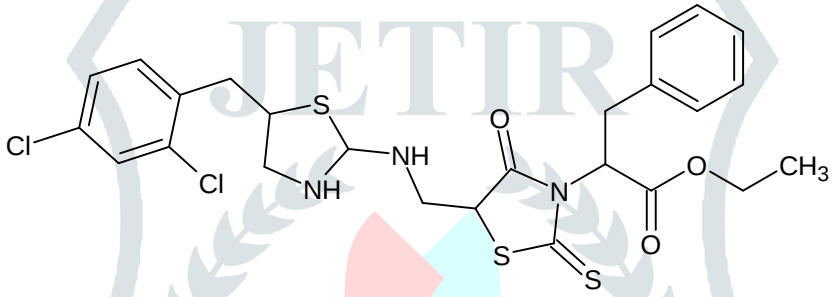


Fig.19

2-Imino-1,3-thiazolidin-4-ones (Fig .20) were synthesised by Kulabaş et al. in 2017 and their antiviral and anticancer properties were examined. None of the substances shown any obvious antiviral action[28]. The NIH3T3 cell line was used to test the cytotoxic property, while the K562, MCF-7, HT-29, SJSA1, A549, PC-3, and HeLa cell lines were used to test the anticancer activity. At a 10 M dose, the chemical showed a 35.82% reduction in cell proliferation in the HeLa cell line, and it was determined to be harmless.

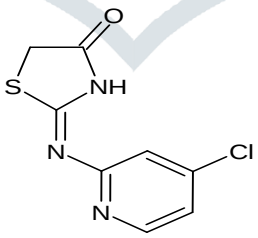


Fig.20

By using the MTT test, Wang et al. (2011) examined the cytotoxic effects of a variety of new 4-thiazolidinone and indolin-2-one hybrid derivatives against four human cancer cell lines[29]. Against one or more cancer cell lines, the majority of the synthesised compounds exhibited moderate to good cytotoxic effects. Against all four human cancer cell lines, compound (Fig 21) exhibited strong antitumor activity.

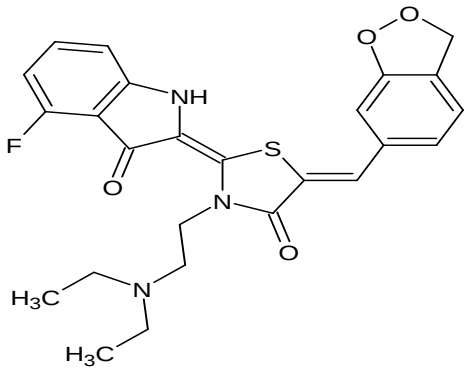


Fig.21

In order to test their potential for EGFR and HER-2 kinase inhibitory action, Lv et al. (2010) developed two series of thiazolidinone derivatives[30]. As a possible anticancer drug, compound (Fig. 22)has particularly shown notable EGFR and HER-2 kinase inhibitory activity as well as inhibitory efficacy in tumour growth inhibition.

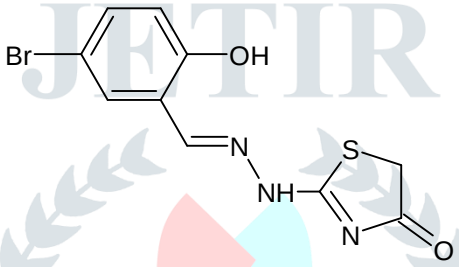


Fig.22

By using the MTT assay, compound (Fig.23) was tested against the HT-29, H460, and MDA-MB-231 human cancer cell lines. The IC50 values for each were 0.025, 0.075, and 0.77 lM, respectively. The SAR investigation revealed that replacement with a smaller electron-withdrawing fluorine atom at the indolin-2-one ring's position 5 and with a 3- (diethylamino) propyl group at the 4-thiazolidinone ring's position 3 had a beneficial impact on boosting antitumor activity. Thiazolidinone derivatives' ability to degrade DNA was reported by Gouda et al [31]. The DNA in the calf thymus was completely degraded in just a small number of the manufactured derivatives.

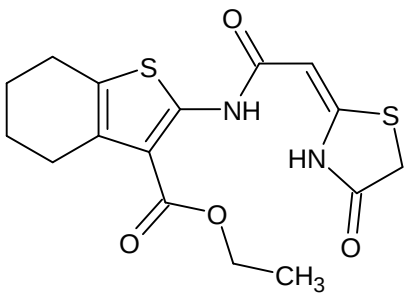


Fig.23

The anticancer activity of several isatin-based thiazolidine conjugates (Fig.24) has been studied[32], and their affinity for tyrosine kinase, cyclin-dependent kinases, and carbonic anhydrase isozymes suggested that they

may be useful as novel anticancer drugs. None of the thiazolidinone conjugates shown more activity than the conjugates of 1,3-dihydroindol-2-one with derivatives of 3,5-diaryl-4,5-dihydropyrazolyne.

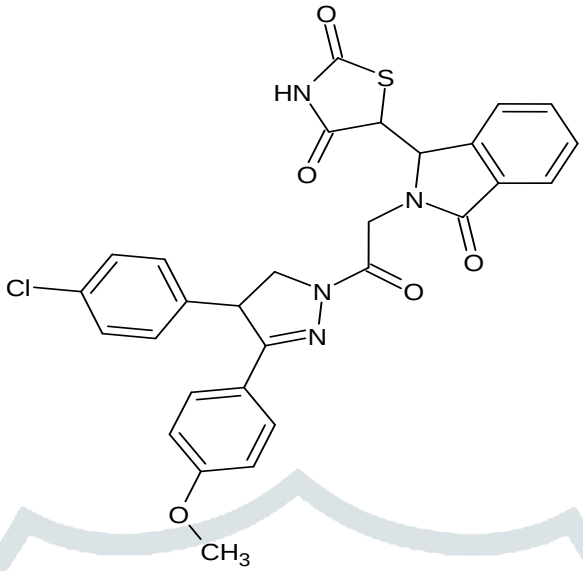


Fig.24

4.5 Antiinflammtory and analgesic activity

By monitoring the pro-inflammatory cytokine (TNF- and IL-6) production by lipopolysaccharides in THP-1 cells, Shinde et al., 2019 produced 3-(4,6-dichloro-1,3,5-triazin-2-yl)-2-phenylthiazolidin-4-one derivatives and tested them for their anti-inflammatory effect[33]. The halogenated derivatives showed better anti-inflammatory efficacy, while compound (Fig.25) showed the highest activity, inhibiting TNF- and IL-6 by 72 and 79%, respectively.

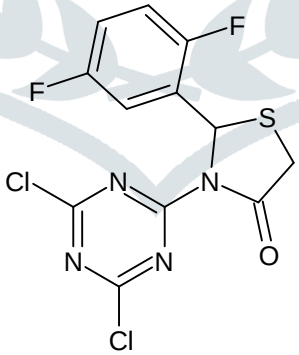


Fig.25

A series of 2-(substituted)-5-[(N-benzotriazolomethyl)-1,3,4-thiadiazolyl]-4-thiazolidinone was created by Singh et al. in 2011 and tested for analgesic efficacy. The analgesic efficacy of compounds 26a, 26b, and 26c was excellent[34].

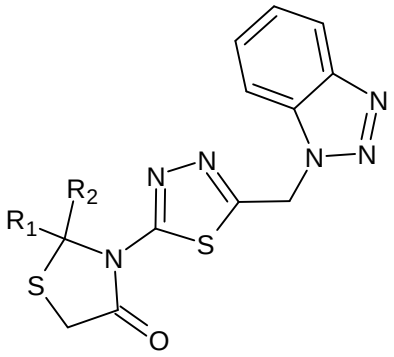


Fig.26 a , R_1 =H, R_2=C_6H_5

26 b , R_1=C_6H_5,R_2=4-Br-C_6H_4

26 c,R_1=H,R_2=-4-Cl-C_6H_4

In 2010, Deep et al. produced new 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amides of biphenyl-4-carboxylic acid and tested them for their ability to reduce inflammation[35]. Compounds 27a and 24b containing electron-withdrawing substituents were generally found to be more active than the other compounds, suggesting that these groups may interact with receptor sites.

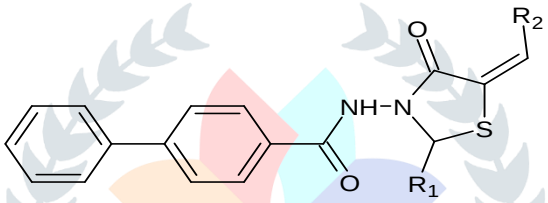


Fig.27 a,R_1=3-Br-C_6H_4,R_2=3-Br-C_6H_4

27 b,R_1=4-F-C_6H_4,R_2=3-NO_2-C_6H_4

Ottana et al. looked into derivatives of -(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinone] (Fig.28), which displayed intriguing stereoselective anti-inflammatory and analgesic properties and suggested that these compounds might interact preferentially with inducible COX-2 isoform[36] 90 Its anti-inflammatory action was increased and its analgesic efficacy was diminished when the 5-arylmethylidene moiety was absent from 3-[2-(4-methylphenyl)-2-oxo-l-phenylethyl]-2,4-thiazolidinedione(Fig.29). The anti-inflammatory effect was either reduced or eliminated by bulkiness at the NH group of the 2,4-thiazolidinedione ring.

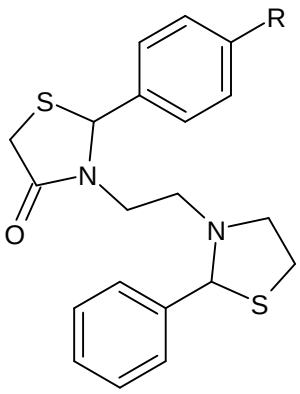


Fig.28

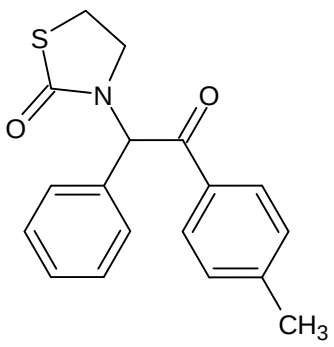


Fig.29

The anti-inflammatory effects of 2-aryl-3-[([1,3,4]thiadiazino[6,5-b]indol-3-ylamino]methyl] Carrageenan-induced rat paw edoema was used to study 1,3,4-thiadiazol-2-yl, 1,3-thiazolidin-4-one (Fig.30) in this study. The anti-inflammatory and analgesic effects of azetidinones are more effective than those of their comparable thiazolidinone molecules, according to Bhati and Kumar[37].

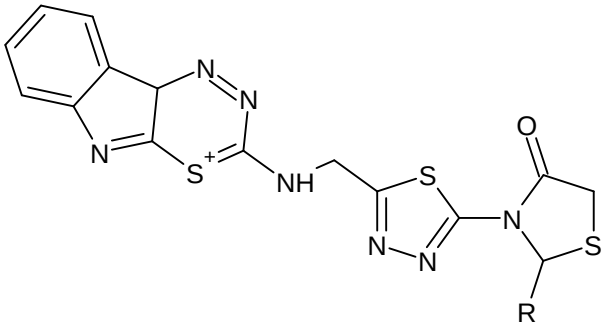


Fig.30

4.6 Anticonvulsant and antidepressant activity

Shiradkar et al. have created a brand-new set of clubbed thiazolidinone-barbituric acid (Fig.31) and thiazolidinone-triazole derivatives (Fig.32) in order to research the effects of a hydrophobic unit, hydrogen bonding domain, and electron-donor group on the compounds' anticonvulsant action,[38]. According to their research, the existence of the -OH function at the 4-position of the phenyl ring is necessary for anticonvulsant activity, and its removal or substitution by the -Cl, CH3, or -NO2 moieties is what causes a loss of activity. The activity was eliminated as a result of the hydrogen bonding domain (HBD) being missing after the hydroxyl group responsible for it was replaced.It was discovered that compounds with p-methoxyphenyl (Fig.33) substitution at the C-2 of the thiazolidinone ring were more active than standard medication sodium phenytoin in a series of thiazolidinonyl 2-oxo/thiobarbituric acidderivatives.

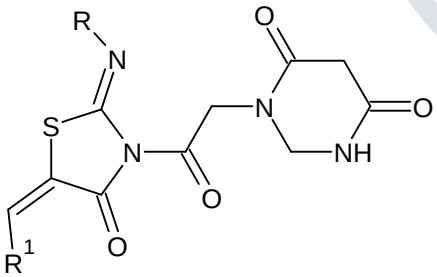


Fig.31

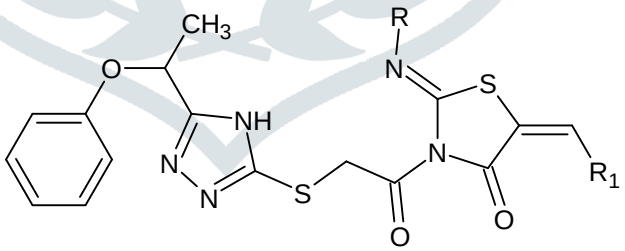


Fig.32

R, R^1 =-2-OHC_6H_4,-2-OH-C6H4

R,R^1=-2-OHC_6H_4,-2-OHC_6H_4

R, R^1=-2-OHC_6H_4,-4-CH_3C_6H

R,R^1=-2-OHC_6H_4,-4-$CH_3C_6H_4$

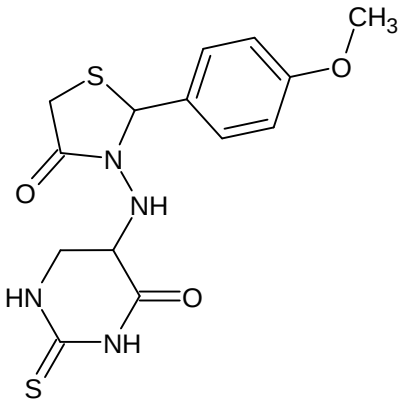


Fig.33

In a study by Akula et al., they created derivatives of 3-[1H-benzimidazole-2-yl-amino]-2-phenyl-1,3-thiazolidin-4-one, and the compound with 4-chloro (Fig.34) on the phenyl ring shown the most promising depressive activity of all the compounds studied[39].

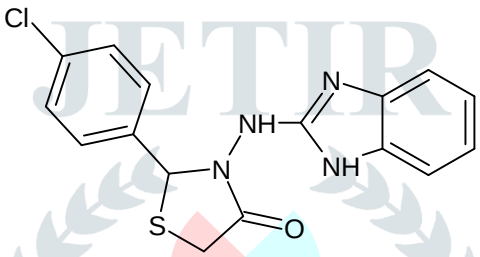


Fig.34

Thiazolidinone-barbituric acid and Thiazolidinone-triazole compounds clubbed together have recently been discovered to have anticonvulsant properties. The anticonvulsant action of the substance varied depending on which phenylthiazolidinonyl amino moieties were substituted at the barbituric acid's position five.

4.7 . Antidiabetic activity

In order to determine their antidiabetic potential, Rajalakshmi et al., 2020 produced oxazinyl thiazolidinone compounds and tested them for -amylase inhibition and -glucosidase inhibitory activities[40] It was discovered that compounds Fig.35a (chloro-substituted) and Fig.35 b (bromo-substituted) were more potent than the common medication acarbose.

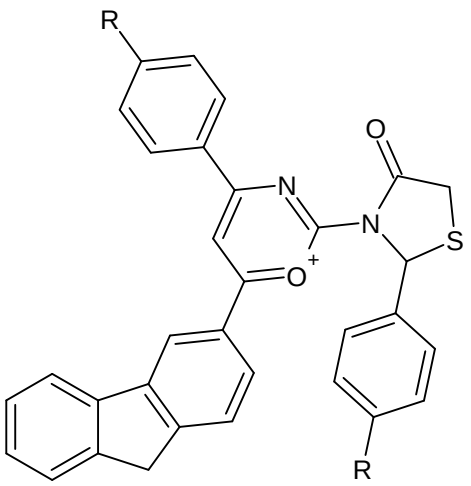


Fig.35 a,b R=Br,Cl

In a series of benzylidene-2,4-thiazolidinediones, compound (Fig.36) with 5-(2-(3,5-bis(trifluoromethyl) benzyloxy)-5bromo benzylidene) at C-5 to the TZD ring was more effective in inhibiting PTP1B. Many thiazolidine-2,4-dione derivatives with carboxylic ester moieties at N-3 and benzyl and heteroaryl substituents at C-5 have also been tested for their anti-hyperglycemic action. The most promising anti-hyperglycemic activity was revealed to be compound(Fig.37)

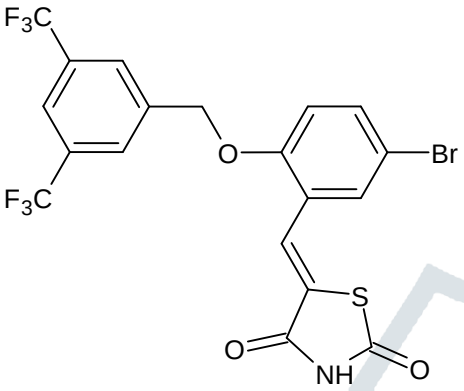


Fig.36

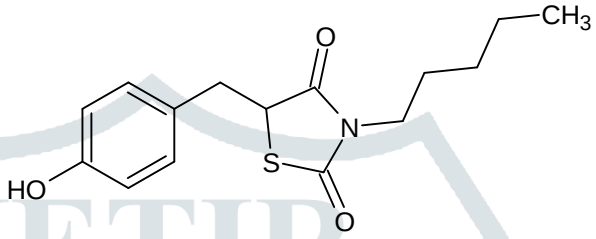


Fig.37

The thiazolidin-4-ones were created by Kishore et al. (2009) and given to Swiss albino mice with streptozotocin-induced diabetes[41]. The amount of fasting blood glucose was significantly reduced by both compound (Fig.38) and compound(Fig.39).

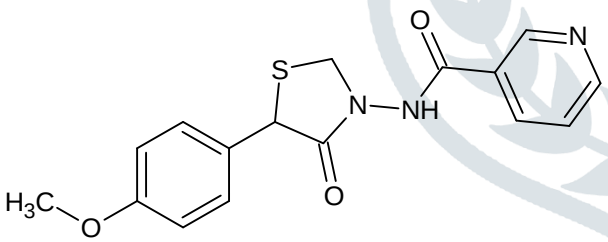


Fig.38

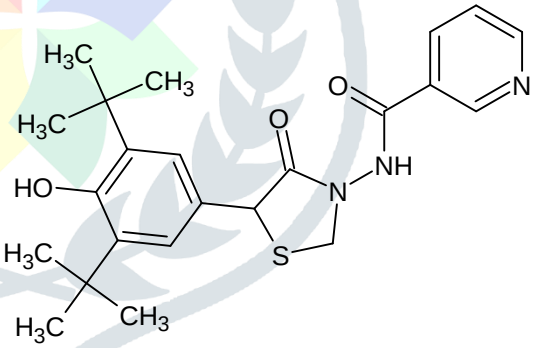


Fig.39

4-thiazolidinones were tested for their hypolipidemic and hypoglycemic effects in Swiss albino mice by Nampurath et al. in 2008[42] It was discovered that compounds (Fig.40) and (Fig.41) had effective hypolipidemic and glucose-lowering properties.

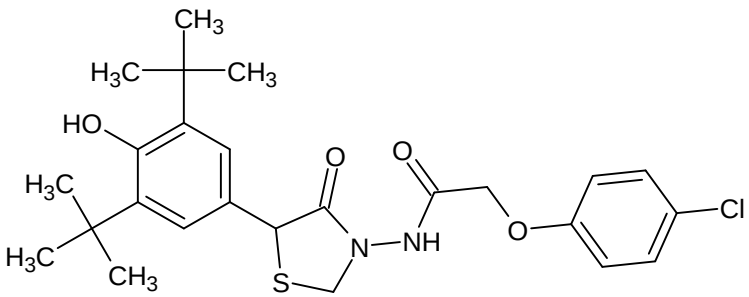


Fig.40

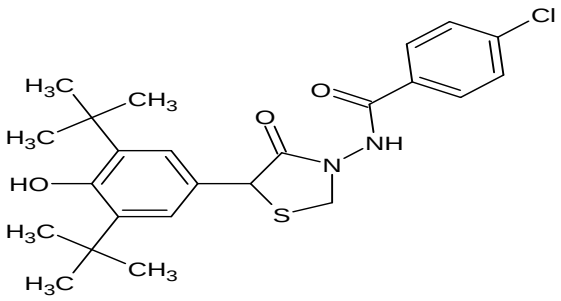


Fig.41

4.8 Antiparkinsonian activity

Gomathy et al. (2012) synthesised a number of 2-(naphthalen-1-yl)-N-[2-substituted (4-oxothiazolidin-3-yl)]acetamide derivatives and assessed the antiparkinson potential of these compounds using rat models with 6-hydroxydopamine lesioning[43]. The most active substance was compound (Fig.42), which had a 3-nitro phenyl group.

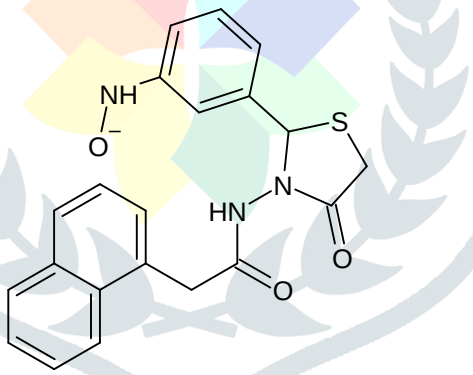
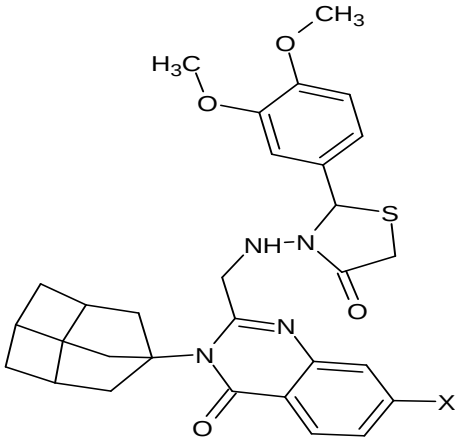


Fig.42

In order to assess the compounds' antiparkinsonian potential, Kumar et al. (2012) synthesised 3-admantadinyl-2-[((substituted phenyl)-4-oxo-thiazolidin-3-yl)methylamino]-quinazolin-4(3H)-ones[44].. Compounds (Fig.43) were discovered to be effective antiparkinsonian agents because they include a 3,4-dimethoxyphenyl group at position 2 of the thiazolidinone ring.



X=H,Br

Fig.43

5. CONCLUSION

Drugs that are therapeutically used have lost the 4-thiazolidinone nucleus' efficacy. Although the four main clinical applications of PTP1B inhibitors-antibacterial, antitubercular, antiviral, and antidiabetic—are still being investigated, there may be more potential targets. Despite the fact that the majority of locations were investigated in an effort to enhance the 4-thiazolidinone's antibacterial and antitubercular profile, none of the derivatives demonstrated antitubercular activity that was particularly promising. However, only a small number of derivatives with C-2 and N-3 substituted positions and the presence of electron-withdrawing substitution on aromatic ring on C-2 position of 4-thiazolinone present varying degrees of inhibition against Gram-positive and Gram-negative bacteria showing inhibition as good as to the standard drugs used. The kind of substituents positioned at the aryl moiety connected to the thiazolidinone ring determines the compounds' activity. Consequently, more research in this area could be worthwhile. SAR and the potency of the described compounds have not been the subject of any coordinated analysis. As a result, conducting more research in this area could be quite fruitful. The significance of the nucleus is brought to light by these observations. However, this interesting moiety has a lot of potential because 4-thiazolidinone has a variety of molecular targets. According to the literature, 4-thiazolidinone has a wide range of biological potential, and because it is simple to make, researchers have been interested in it.

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