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# THE EMERGING ROLE OF THIAZOLIDINONE IN MEDICINAL CHEMISTRY: A REVIEW OF RECENT DEVELOPMENTS (2018-2024)

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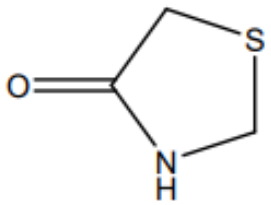
## ABSTRACT

Thiazolidinones, which have a wide range of biological functions, have become a promising scaffold in medicinal chemistry. A thorough summary of the most current advancements in the field of thiazolidinone-based medicinal chemistry from 2018 to 2024 is what this review attempts to deliver. In order to emphasise the prospective uses of thiazolidinone derivatives as antibacterial, antiviral, anti-inflammatory, anticancer, and neuroprotective medicines, we go over their synthesis, structural changes, and biological assessments. The review also looks at the pharmacokinetic characteristics, molecular docking studies, and structure-activity connections of drugs based on thiazolidinone. We also go over the difficulties and prospects for thiazolidinone-based drug discovery, highlighting the necessity of more study to completely realise the therapeutic potential of this adaptable scaffold. This review highlights the potential of thiazolidinone-based medicinal chemistry to aid in the creation of new therapeutic medicines while offering a timely update on the field's current status.

**KEYWORDS:** thiazolidinones, antibacterial agents, molecular modeling, docking studies, structure-activity relationship.

## 1. INTRODUCTION

In recent decades, medicinal chemistry has focused a great deal of attention on thiazolidinones, a class of five-membered heterocyclic molecules. Following their initial recognition for their antibacterial and antifungal qualities, thiazolidinones have been discovered to possess a wide range of biological activities, such as neuroprotective, antiviral, anti-inflammatory, and anticancer functions.[1] Because of the thiazolidinone scaffold's adaptability and simplicity in synthesis and modification, medicinal chemists are drawn to it in their pursuit of new therapeutic medicines. A planar, five-membered ring with three carbon atoms, a nitrogen atom, and a sulphur atom is what defines the thiazolidinone ring system. A large variety of thiazolidinone derivatives with a range of biological activities can be synthesised because to its special structure, which permits the inclusion of many functional groups.[2] Due to thiazolidinones' ease of synthesis and modification, a variety of methods for their manufacture have been developed, including conventional and microwave-assisted synthesis as well as green chemical techniques. Research on thiazolidinones, with an emphasis on their possible medicinal uses, has significantly increased over the last ten years. According to recent research, thiazolidinones have the potential to be effective antibacterial agents that can combat a variety of bacteria, viruses, and fungi.[3] Thiazolidinones are appealing possibilities for the therapy of a number of illnesses since they have also been demonstrated to have anti-inflammatory, anticancer, and neuroprotective properties.[4] The objective of this review is to present a thorough summary of the most important developments, difficulties, and prospects for the future in the quickly developing field of



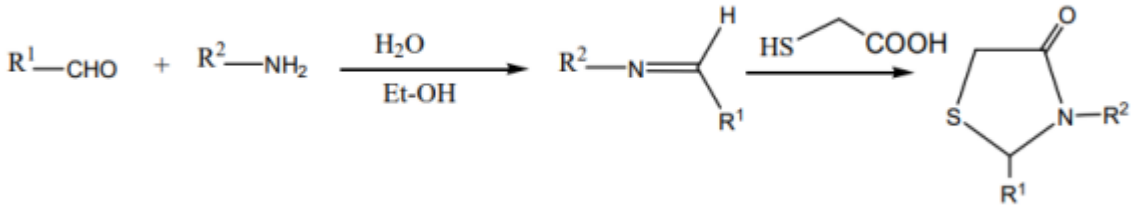

4-Thiazolidinone

thiazolidinone-based medicinal chemistry during the 2018–2024 research period[5] Since they have been discovered to be helpful intermediates for the synthesis of numerous heterocyclic compounds, thiazolidinone derivatives are the focus of much attention. Designing, synthesising, and producing compounds that are useful as human therapeutic agents is one of the primary goals of organic and medicinal chemistry.[6] Chemical libraries based on favoured structures are now accessible thanks to advancements in combinatorial chemistry

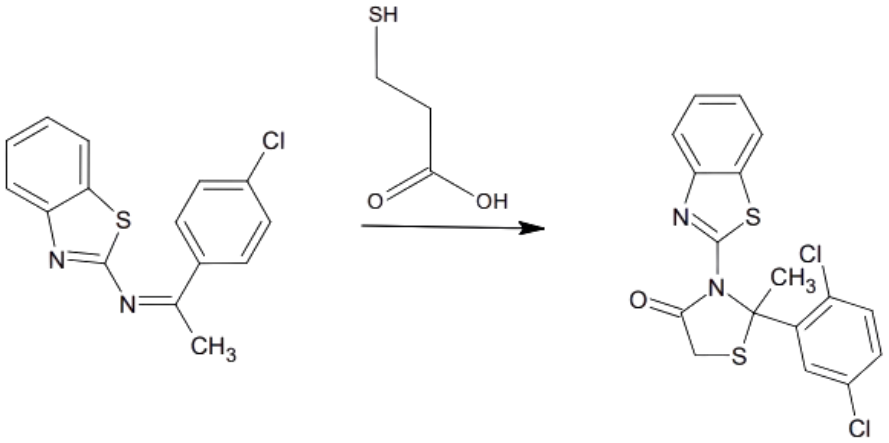
over the last ten years.[7] Although substitution can occur at positions 2, 3, and 5 in the moiety, the group bonded to the carbon atom at the 2-position exerts the biggest influence on structure and characteristics. The moiety's carbonyl group is extremely non-reactive. Thaiazole's tetrahydro derivative is called thiazolidine, whereas thiazolidine's oxo derivative is called thizolidinone. When an alkyl group is attached to the nitrogen, the melting point of the 3-unsubstituted thiazolidinone is lowered. Normally, these compounds are solids that melt down with decomposition.Water solubility is moderate for thiazolidinones without aryl or higher alkyl substituents. 4-Derivatives of thiazolidinone have antibacterial, anticonvulsant, antifungal, antithyroid, antitubercular, and antidiabetic properties.[8]

## 2. 2.SYNTHESIS OF THIAZOLIDINONES DERIVATIVES

2.1 The primary synthesis procedures for 1,3-thiazolidin-4-ones involve the utilisation of three components: an amine, a carbonyl molecule, and a mercapto acid.[9] The disclosed classical synthesis can be carried out in one pot using a three-component condensation or in two steps. The formation of an imine is the initial stage of the reactions, where the carbonyl of the aldehyde or ketone is attacked by the amine's nitrogen. This is followed by an intramolecular cyclisation when the water is removed.[10]




2.2 The synthesis of thiazolidinone from Schiff's bases using microwave assistance and thiolactic acid. In order to compare the yields, the products were made using both conventional and microwave synthesis techniques. According to their findings, the yield percentage of the microwave-irradiated synthesis was higher than that of the conventional synthesis.[11]

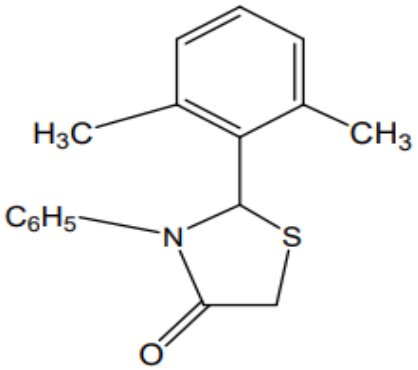



## 3. BIOLOGICAL ACTIVITY OF 4-THIAZOLIDINONES

Since the thiazolidinones ring has been added to a vast array of known biologically active compounds, either as a substituent group or in substitution of another ring, researchers have produced a number of molecules with this moiety. Many papers in the literature describe the various biological roles of thiazolidinone derivatives, some of which are discussed in this review.

### 3.1 Cytotoxic activity

Monforte et al.[12] have synthesised multiple series of derivatives of 2, 3-diaryl-1, 3-thiazolidin-4-one.The chemical (I) was discovered to be the most effective of them all and was described as a novel class of antiviral drugs that functioned as NNRTIs with little cytotoxicity. The compound's cytotoxic action was discovered to increase when an aryl group is substituted at the nitrogen atom.

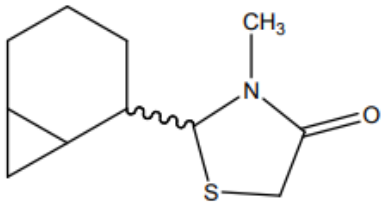



2-(2,6-dimethylphenyl)-3-phenylthiazolidin-4-one

**(I)**

2-adamantyl-substituted thiazolidin-4- one derivatives has synthesized and evaluated its activity against HIV-1 (IIIB) and HIV-2(ROD) in CEM cell cultures, by taking Nevirapine as

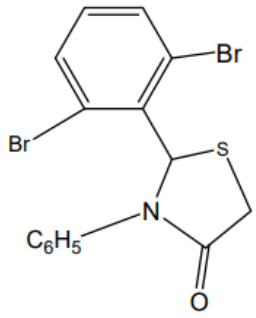
reference compound by Balzarini et al.[13] Among them compound (II) was found to be more potent.Substitution by admantyl at second position was found to shown increased in cytotoxic activity.




2-(bicyclo[4.1.0]heptan-2-yl)-3-methylthiazolidin-4-one

**(II)**

Rawal et al.[14] has synthesized 2-(2,6-dibromophenyl)-3-heteroaryl-1,3-thiazolidin-4-onederivatives.Among the various derivatives compound (III) shows the potent activity. Due to substitution of aryl group at nitro atom shows increased in cytotoxic activity.

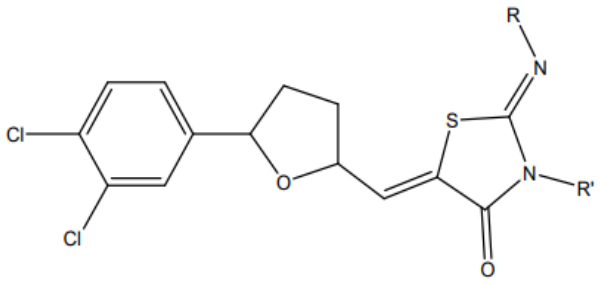



2-(2,6-dibromophenyl)-3-phenylthiazolidin-4-one

**(III)**

### 3.2Antimicrobial activity

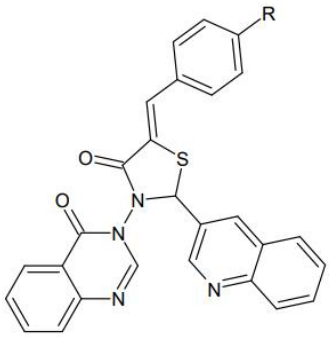
5-(3, 4-dichlorophenyl)-2 furylidene] 2-(ptolylimino)-3-(4-tolyl)-5-[ Bhoot and colleagues.[15] synthesised 4-thiazolidinone derivatives (IV) as antimicrobial agents, and then The antimicrobial efficacy of the compounds against a range of bacterial strains, including B. mega, S. aureus, E. coli, and P. vulgaris, as well as fungi, including A. niger, was evaluated in vitro at a concentration of 40µg. Compounds containing phenyl and 2-methoxyphenyl, 2-dimethylphenyl, 3-methylphenyl, and 4-nitrophenyl substituents exhibited remarkable inhibition; of these derivatives, IVa, IVb, IVc, and IVd demonstrated the strongest efficacy against the bacterial strains.




**(IV)**

| Compound | R | R' |
|---|---|---|
| Iva | C6H5 | C6H5OCH |
| IVb | C6H5 | C6H5CH(CH3)2 |
| IVc | C6H5 | C6H5CH3 |
| IVd | C6H5 | C6H5NO2 |

Desai et al.[16] synthesised a series of 2-(2-chloroquinolin-3-yl)-5-((aryl)benzylidene) in 2013. Among the newly synthesised compounds, some shown excellent antibacterial action against Candida albicans, A. niger, and A. clavatus, while others demonstrated exceptionally good antifungal activity against E. coli, S. aureus, P. aeruginosa, and S. pyogenus. Compounds 3a and 3b both demonstrated great efficacy against bacterial and fungal species.

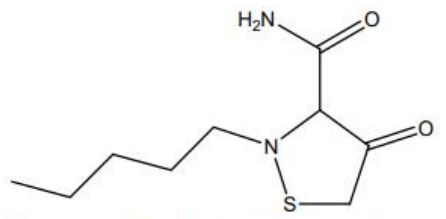



3 a, R= -2-OH

3 b, R=-4-$CH_3$

### 3.3 Anti-Cancer Activity

A series of 2-amyl-4-oxothiazolidin-3-yl amides were synthesised by Gududuru et al.[17] and their ability to inhibit prostate cancer cells was assessed. A few strong compounds that were more selectively effective in killing prostate cancer cells than serine amide phosphates were found; the most potent of these was compound (V), which was found to increase anticancer activity by substituting a long alkyl chain at the nitrogen atom.

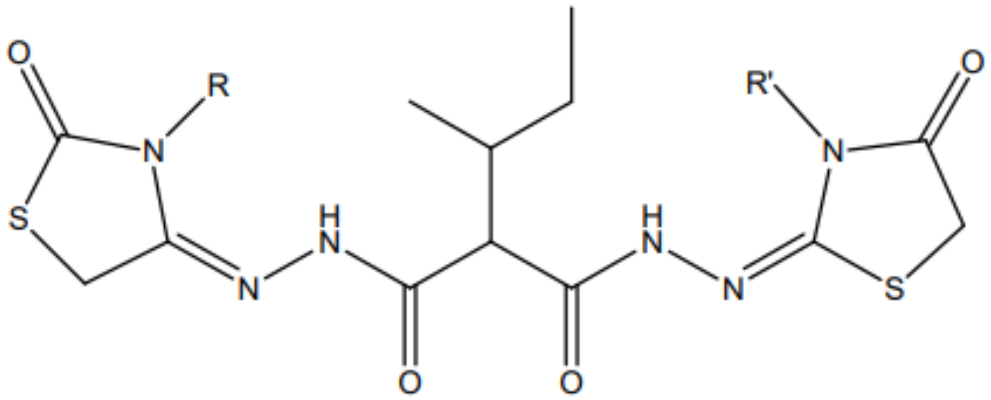



4-oxo-2-pentylisothiazolidine-3-carboxamide

**(V)**

### 3.4 Anticonvulsant activity

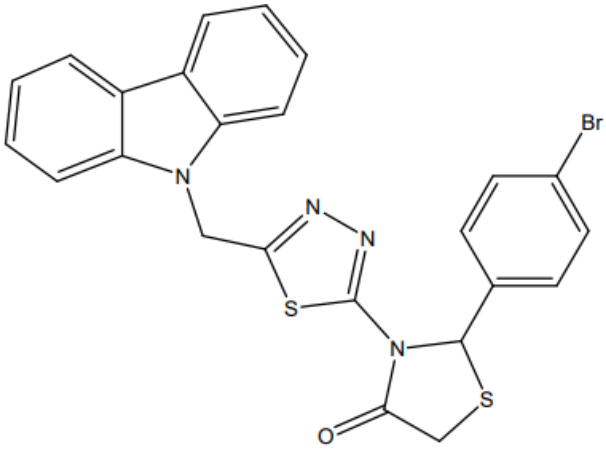
Bis (4-thiazolidinone) (VI) derivatives were synthesized, described and assessed for their anticonvulsant efficacy by Ulusoy et al.[18] Compound VIa and VIb derivatives exhibit 90% protection against seizures caused by pentylenetetrazole. It is discovered that substitution by alkyl and phenyl groups exhibits strong action.




**(VI)**

| Compound | R | R' |
|---|---|---|
| Via | C6H5CH3 | CH3 |
| VIb | C2H5 | OCH3 |

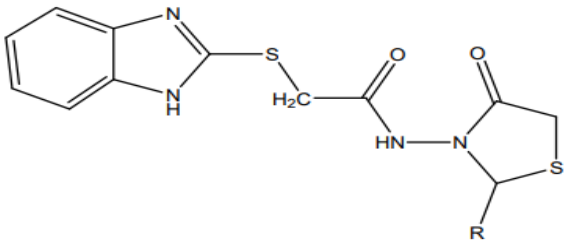
Kaur et al.[19] created a new substituted thiadiazolylazetidinonyl and tested it for anticonvulsant properties. It was determined that of the several derivatives, (VII) exhibited the most promising anti-convulsant efficacy.



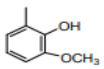
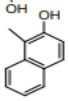

3-(5-((9*H*-carbazol-9-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-(4-bromophenyl)thiazolidin-4-one

**(VII)**

Shingalapur et al.[20] synthesised a class of 4-thiazolidinones with a 2-mercapto benzimidazole moiety (VIII) and used the Maximal Electroshock (MES) model to screen them for in-vivo anticonvulsant efficacy. With strong anticonvulsant effects, the compounds VIIIa, VIIIb, VIIIc, and VIIId were found.



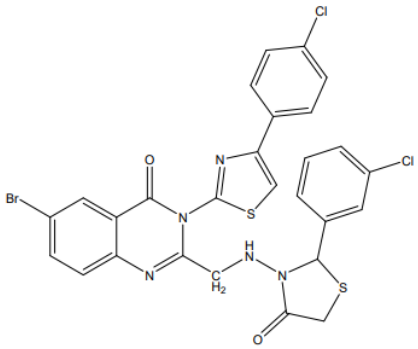

**(VIII)**

| Compounds | R |
|---|---|
| VIIIa |  |
| VIIIb |  |
| VIIIc |  |
| VIIId |  |

### 3.5 Anti-Inflammatory Activity

Kumar et al.[21] has synthesized N-Chloroacetyl-5-bromoanthranilic acid, 3-[4'-(pchlorophenyl) thiazol-2'-yl] -2-chloro methyl-6-bromo quinazolin-4-one, 3-[4'-(p-chloro phenyl) - thiazol-2'-yl]-2-hydrazino methyl-6-bromo quinazolin-4-one, 3-[4'-(p-chloro phenyl) - thiazol-2'-yl] -2 substituted benzylidene amino methyl-6-bromo quinazolin-4-ones,2 - [(4'-oxo-3'-chloro-2'-phenyl azetidin-1'-yl) amino methyl]-3-[4'-(p-chloro phenyl) thiazol-2"-yl]-6-bromo quinazolin4-ones (12–19) and 2-(4'-oxo-2'-phenyl-thiazolidin-3"-yl-

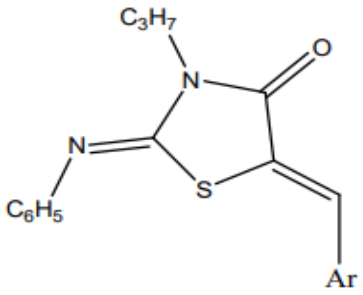
amino methyl)-3-[4"-(p-chloro phenyl) - thiazol-2"-yl] -6-bromo quinazolin-4-ones.Among them (IX) showed maximum antiinflammatory activity.



2-(4'-oxo-2'-(o-chlorophenyl)-thiazolidin-3'-ylaminomethyl)-3'-[4"-(p-chlorophenly)-thiazol-2"-yl]-6-bromoquinazolin-4-one

**(IX)**

Using carrageenan-induced paw and pleurisy oedema in rats, Ottana et al.[22] synthesised 5-arylidene-2-imino-4-thiazolidinone derivatives and tested their anti-inflammatory properties using indomethacin as a standard medication.

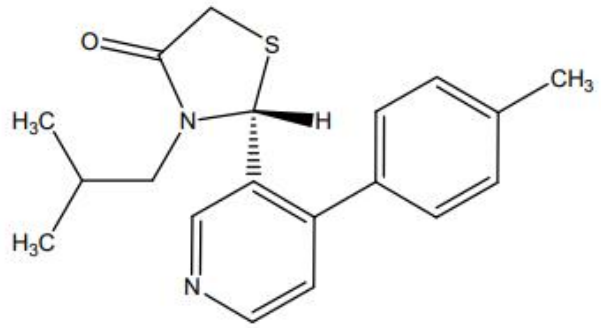


**(X)**

| Compound | Ar |
|---|---|
| **Xa** | 3-$CH_3OPh$ |
| **Xb** | 4-$CH_3SPh$ |
| **Xc** | 4-$CH_3SO_2Ph$ |
| **Xd** | 4-$CH_3OPh$ |
| **Xe** | 4-ClPh |
| **Xf** | 3,4 –$(CH_3O)_2Ph$ |

### 3.6 Analgesic activity

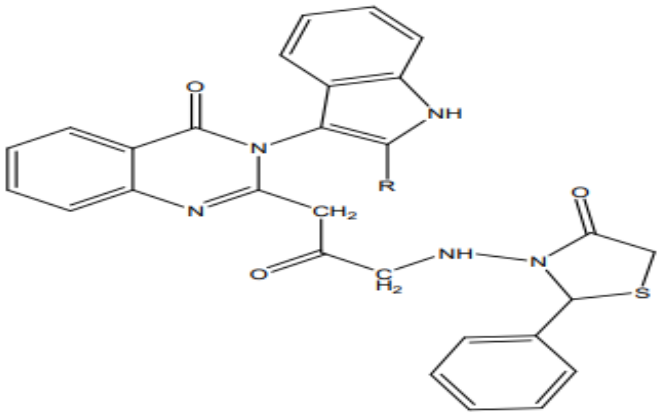
Burley et al.[23] has synthesized a series of new N-type (Cav2.2) calcium channel blockers derived from the 'hit' structures 2-(3-bromo-4-fluorophenyl)-3- (2-pyridin-2-ylethyl) thiazolidin4-one 9 and its 2-[4-(4-bromophenyl)pyridin-3-yl]-3-isobutyl analogue. By SAR (Structure Activity Relationship) compound (XI) have been identified as the most potent compounds in this series. These compounds show promise as lead structures in the quest for clinically effective Ntype blockers in the treatment of pain.



(*R*)-3-isobutyl-2-(4-*p*-tolylpyridin-3-yl)thiazolidin-4-one

**(XI)**

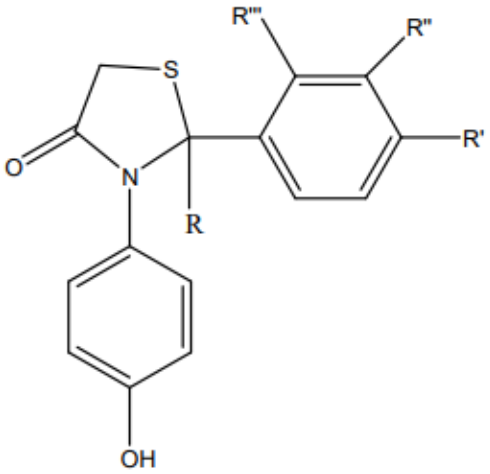
Kumar et al.[24] have produced 2-(substituted phenyl methylene imino) amino acetyl methylene-3-(2'-substitutedindol-3'-yl).-halosubstituted-4 (3H) quinazolinones and 2-(substituted phenyl amino methylene acetyl-4'-oxo-1'-thiazolidinyl-3-(2''-substituted indol-3''-yl) 4(3H) quinazolinone respectively. We observed that compound (XII) was the most effective.



**(XII)**

| Compound | X | R | R' |
|---|---|---|---|
| **XIIa** | H | $CH_3$ | 2-$OCH_3$ |
| **XIIb** | H | $CH_3$ | 2-Cl |
| **XIIc** | 6-I | H | 2-$OCH_3$ |
| **XIId** | 6-I | H | 4-Cl |
| **XIIe** | 6-Br | $CH_3$ | 2-OCH3 |
| **XIIf** | 6-Br | $CH_3$ | $N(CH3)_2$ |
| **XIIg** | 6-Br | $CH_3$ | 2-Cl |

Taranalli et al.[25] has synthesized thiazolidine-4-one derivatives and evaluated for antiinflammatory, analgesic and anti-ulcer activity by carrageenan-induced paw edema test, acetic acid induced writhing method and pylorus ligation ulcer model respectively. All the compounds showed significant anti-inflammatory, analgesic and anti-ulcer activity at 100 mg/kg b.w.

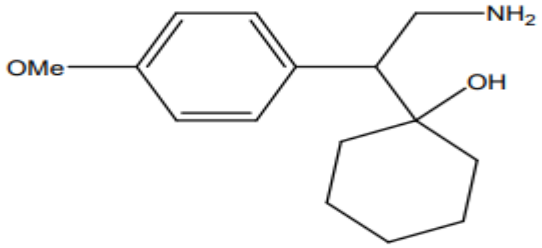



**(XIII)**

| Compound | R | R' | R'' | R''' |
|---|---|---|---|---|
| **XIIIa** | H | H | H | H |
| **XIIIb** | H | $OCH_3$ | H | H |
| **XIIIc** | H | $CH_3$ | H | H |
| **XIIId** | H | $CH_3$ | $CH_3$ | $NH_2$ |

### 3.7 Future aspect of thiazolidinone

A wide range of the pharmacological activity linked to the moiety has been introduced by some of the many thaizolidinone derivatives with biologically active scaffolds. To obtain the desired characteristic, thiazolidinone is coupled with various rings. Among these is Venlafaxine (XIV), a member of the SNRI class of antidepressants that differs significantly from other antidepressants due to its distinct morphologic and structural characteristics. Several substituted aromatic and heterocyclic aldehydes can be used to create 2,3-disubstituted-1,3-thiazolidin-4-ones by employing venlafaxine as a crucial intermediary 1-[2-amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol.[26]

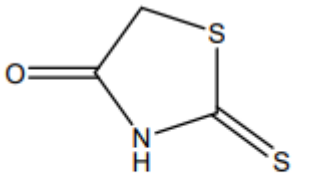



1-[2-amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol

**XIV**

HIV integrase may be inhibited by 2-thioxo-4-thiazolidinone (rhodanine) derivatives (XV). Rhodacyanine dyes are one example of how these structures have been shown to confer antitumor effects. A crucial structural scaffold for the inhibitory action of integrase is the

moiety. These compounds are good starting points for the creation of antiviral and anticancer medications.[27]



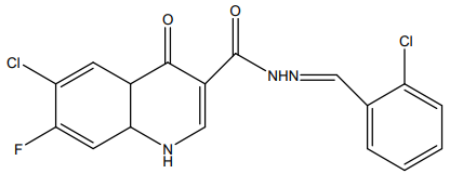
2-thioxo-4-thiazolidinone

**XV**

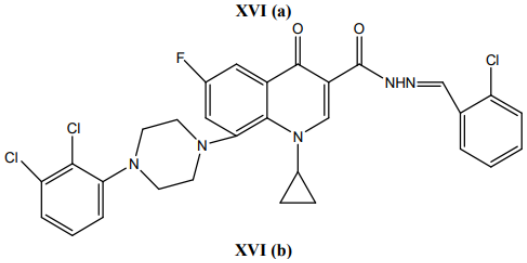
### 3.8 Pyridine Based 4-Thiazolidinones

To obtain the appropriate therapeutic activity, it has become more common in recent years to couple distinct heterocyclic nuclei. Derivatives of 4-thiazolidinone that include pyridine and 2-amino-6-nitrobenzothiazole moieties are very useful for exhibiting antibacterial and antifungal qualities.[28]

2-substituted phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-(2,3-dichlorophenylpiperazin1-yl] as a seriesPatel and Patel synthesised 4-oxo-1,4 dihydroquinoline carbamido-1,3-thiazolidin-4-ones derivatives (XVI) and tested them for antibacterial activity. Compounds XVI (a), XVI (b), and XVI (c) exhibit strong activity with substitution of 2-Cl, 2-Cl, and 4-Cl, respectively.[29]

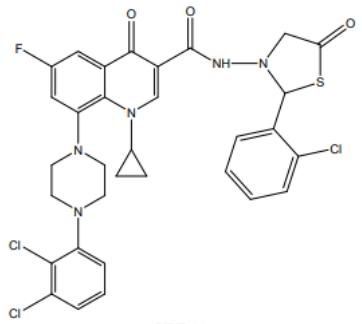


**XVI (a)**

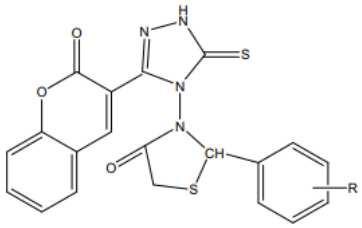


**XVI (b)**

2-(substituted phenyl) in succession-3-[3-(2-oxo-2H-chromen-3-yl)-5-thioxo-1,5-dihydro-H1,2,4-triazol-4-yl]-1,3-thiazolidin-4-ones (XVII) were produced and their antibacterial qualities assessed. The most successful of the series, compound XVII (a) demonstrated 92% growth inhibition against S. aureus, while compounds XVII (b), XVII (c), and XVII (d) shown 85% inhibitory action against Candida albicans.[30]



XVI (c)

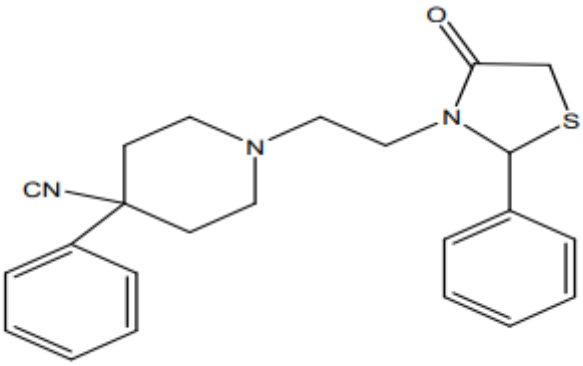


XVII a) R=H
b) R=N($CH_3$)$_2$
C) R=4-Cl
D) R=2-Cl

## 4. 4.Some Other Aspects

### 4.1 Antidiarrhoeal Activity

Mazzoni et al. produced a number of 1,3-thiazolidin-4-one derivatives and tested them for antidiarrheal properties.2-phenyl-3-{2-[(4-phenyl-4 cyano)piperidino]ethyl}-1,3-thiazolidin-4-one (XVIII) was the most active compound.[31]

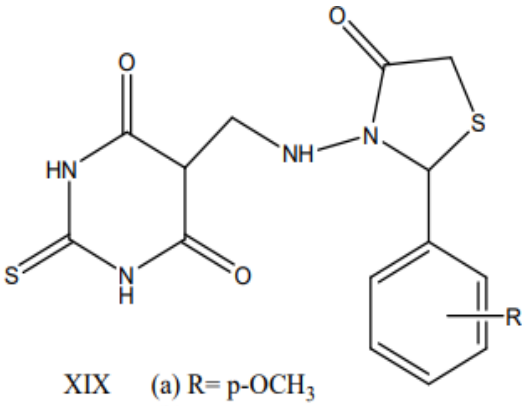


XVIII

Oxo-thiobarbituric acid Fused Derivatives.

Agarwal et al. produced A variety of 5-[(2-phenyl-4-oxothiazolidin-3-yl)amino] derivatives 4-({4-[2-alkylphenyl)-4-oxo-1,3-thiazolidin-3-yl] and 2-oxo-thiobarbituric acids.[32] -2-ylmethylamino-1, 3, 4-thiadiazol For acute toxicity tests, Archana et al. synthesised derivatives of 2-methyl-6-monosubstituted-quinazolin-4 (3H)-one and tested them in vivo for anticonvulsant action at a dose of 30 mg/kg[33] In contrast to other substituted derivatives,

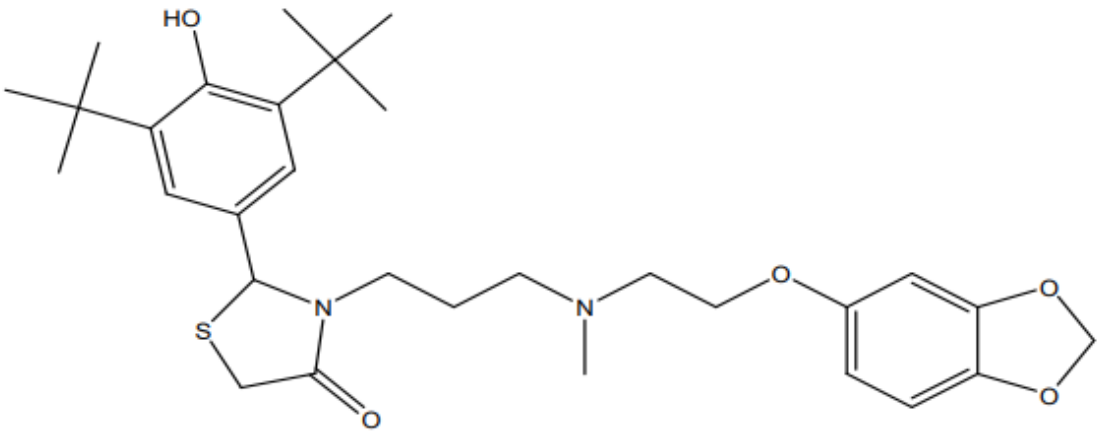
they found that p-methoxyphenyl and m-methoxy phydroxyphenyl substituted in thiazolidinone moieties had a stronger response. The strongest chemicals were identified as XIX (a), XIX (b), and XIX (c).



XIX (a) R= p-$OCH_3$
(b)R = m-$OCH_3$,
(c) p-OH

### 4.2 Antioxidant Activity

Kato et al. synthesised a series of 2-(3, 5-di-tert-butyl-4-hydroxyphenyl)-3-(aminopropyl) thiazolidinones to investigate new calcium antagonists with strong anti-schemic properties. These substances were created so that a single molecule might have both antioxidant and Ca2+ antagonistic properties. These include 2-(3, 5-di-tert-butyl-4-hydroxyphenyl)-3-[3-[N-methyl-N-[2-[3, 4-(methylenedioxy)phenoxy] ethyl]amino] propyl]In vitro, it was discovered that -1, 3-thiazolidin-4-one (I) was extremely powerful and had a balanced mix of these activities [34]

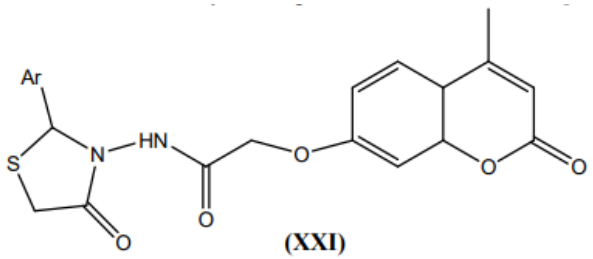


2-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-[3-[N-methyl-N-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one

**XX**

### 4.3 Coumarine derivatives and thiazolidinone

Milan et al. synthesised a number of N-(2-aryl-4-oxo-thiazolidine-3-yl)-2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-acetamides (XXI) derivatives and used the phosphomolybdenum technique to assess its antioxidant properties. Ascorbic acid was found to have inferior antioxidant activity to three of the 1, 3-thiazolidine-4-ones, XXI (a), XXI (b), and XXI (c).[35]




**(XXI)**

**Ar**
**a)**2,3-dihydroxyphenyl
**b)**2,4-dihydroxyphenyl
**c)**2,5-dihydroxyphenyl

## 5. CONCLUSION

According to the literature review, 4-thiazolidinone has a wide range of biological activities and has caught the interest of chemists, pharmacologists, and researchers in the field of medicinal chemistry. In addition, several of the novel biological properties linked to thaizolidinone have been investigated, including its anticonvulsant, antioxidant, and FSH (follical stimulating hormone) agonistic properties. Given the current situation, 4-thiazolidinone has a high biological potential for usage as a crucial scaffold in medicinal chemistry.

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