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# Thiazolidinediones - Emerging Anticonvulsant with Other Pharmacological Activity Hetrocyclic Scaffold

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**Abstract:** Thiazolidinediones (TZDs) are five-membered heterocyclic having sulfur, nitrogen, and oxygen atoms in their cyclic ring structure has drawn attention because of its diverse pharmacologically activities connected with it. A lot of research work has been done on various thiazolidinone derivatives for synthetic schemes and biological activities of its novel derivatives. The thiazolidinediones is not only synthetically important scaffold but also possesses a wide range of promising biological activities i.e antimicrobial, anti-inflammatory, anticonvulsant, antimalarial, analgesic, anti-HIV and anticancer action. Some thiazolidinediones derivatives have better activity than standard drug and could become a new drug for the market in future.

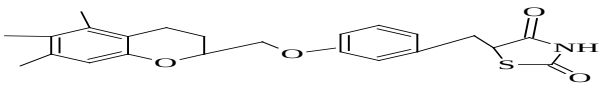
**Keywords:** TZDs, Five-membered Heterocyclic, Anticonvulsant, Anti-HIV, Anticancer Agent.

## 1. Introduction

Thiazolidinedione and its analogs are resourceful substrates and most promising nucleus which play an important role in the field of organic, medicinal chemistry as well as in life science. Thiazolidinedione and its derivatives are used in organic synthesis and they are used in evaluating novel product that possesses different biological activities [1]. In early 1982 a number of TZDs were intensively studied as antihyperglycemics agent where ciglitazone was the first representative and other derivatives like englitazone, troglitazone, and pioglitazone followed soon and established as a promising antihyperglycemics agent by improving sensitization of insulin receptors [2, 3]. Later on further studied TZD nucleus or as hybrid molecules when combined with other heterocyclic rings produce wide range of biological activities such as antimicrobial[4], antiviral[5], anti-arrhythmic [6], anti-inflammatory [7], analgesic[8], anti hyperlipidemic[9], anti-obesity [10], aldose reductase inhibition [11], anticancer[12], antidiabetic activity [13-15] etc. Plethora of information this review is complementary to earlier reviews and aims to review the highlighting on various biological activities of thiazolidinediones.

## 2. Anti-diabetic Activity

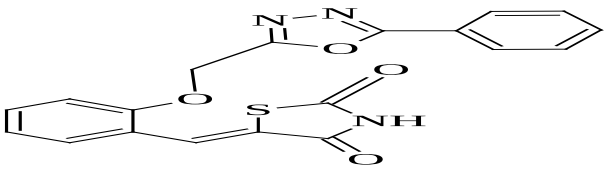
Jawale et al.(2012), synthesized aryl sulfonylurea thiazolidine-2, 4-diones derivatives and among all synthesized compound (1) showed significant hypoglycemic activity.[13]




1

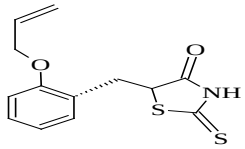
Nazreen et al. synthesized (2014), novel 1, 3, 4-oxadiazole and 2, 4-thiazolidinedione based bis-heterocycles and studied blood glucose lowering effect comparable with standard drug pioglitazone (4) and rosiglitazone (5). Compound (2) may be considered as a

potential candidate for the development of new antidiabetic agents. [14]



2

Zhou et al. (2015), synthesized 2-thioxo-4-thiazolidinone derivatives and evaluated them on antidiabetic activity in respect of peroxisome proliferator activated receptor γ binding activity comparable with rosiglitazone. Compound (3) and (4) has shown most promising anti-diabetic activity. [15]



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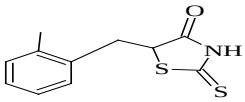
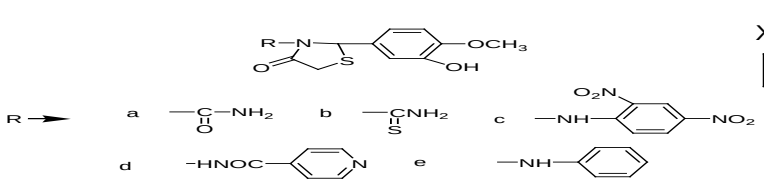


4

**3. Anticonvulsant Activity**

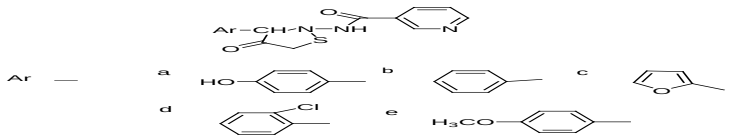
Senthilraja *et al*. (2012) synthesized a new series of 2, 3-disubstituted thiazolidin-4-ones were obtained by the condensation of appropriate amines with vanillin and mercapto acetic acid in the presence of DCC in anhydrous THF by microwave irradiation. The title compounds were investigated for their anticonvulsant activity. Among the test compounds, compound N-(2-(3-hydroxy-4-methoxyphenyl)-4-oxothiazolidin-3-yl) isonicotinamide emerged as most active compound of the series and it is moderately more potent than the reference standard diazepam. [16]



5

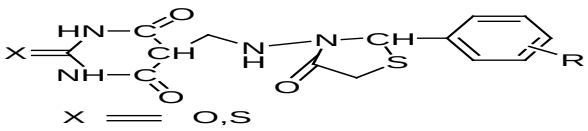
Preethi *et al.* (2012) synthesized and evaluate biological activity of some novel 4-thiazolidinone derivatives from pyridine-3-carbonyl hydrazine and benzaldehyde Schiff base and evaluated for anticonvulsant activity. In this all have anticonvulsant activity comparable with control. a and c shows higher activity as comparable to other derivatives. It also showed anti-tubercular, anti-bacterial and anti-fungal activity. [17]

4-Thiazolidinone and 2-Azetidinone Derivatives."



6

Agarwal *et al.* (2006) synthesized some potential ~~5~~-[(2-phenyl-4-oxo-thiazolidin-3-yl)amino]-2-oxo-thiobarbituric acids derivatives anticonvulsant activity. [18]

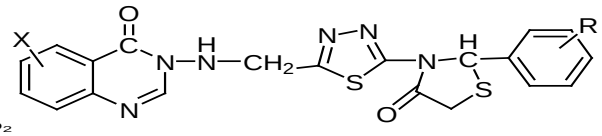


7

Archana *et al.* (2002) synthesized newer 3-({4-[2-alkylphenyl)-4- oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6monosubstituted quinazolin-4(3*H*) one derivatives have been synthesized by Wilson Cunico et al. and screened *in-vivo* for their anticonvulsant activity. [19]

R= $OCH_3$

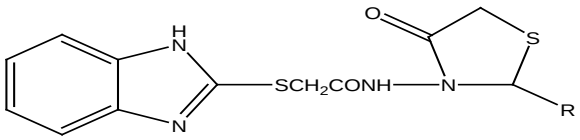
R= M-$OCH_3$, P-OH



8

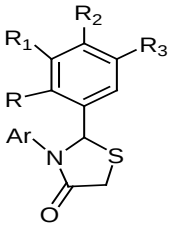
Shingalapur *et al.* (2010) synthesized a group of 4-thiazolidinones containing 2-mercapto benzimidazole

moiety and screened them for *in-vivo* anticonvulsant activity by Maximal Electroshock (MES) model. 4-Thiazolidinones containing 2-mercapto benzimidazole moiety were synthesized and reported for anticonvulsant, antidiabetic and DNA cleavage studies. [20]



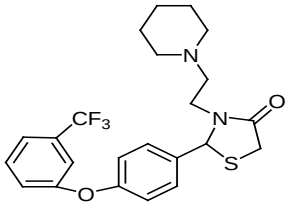
9

Dwivedi *et al.* (1972) anticonvulsant activity of 2,3-diaryl 1,3-thiazolidin-4-one reported.[21]



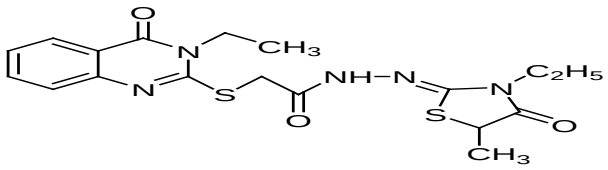
10

Terrett *et al.* (2004) synthesized some 4-thiazolidinones as 3(2piperidin1yl)ethyl)2(4(3(trifluoromethyl)Phenoxy)Phe yl)thiazolidin-4-one evaluated for anticonvulsant activity as sodium channel agonist demonstrated significant activity and give relief in pain associated with arthritis, headache and terminal cancer.[22]



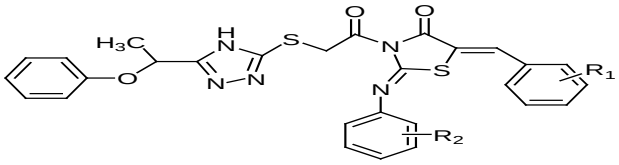
11

Gursoy *et al*. (2005) synthesized quinazoline based thiazolidinones(z)-2-(3-ethyl-4oxo3,4dihydroquinazoline-2-ylthio)-N-(3-ethyl-5-methyl-4-oxothiazolidin-2-ylidene)acetohydrazide reported to have anticonvulsant activity.[23]



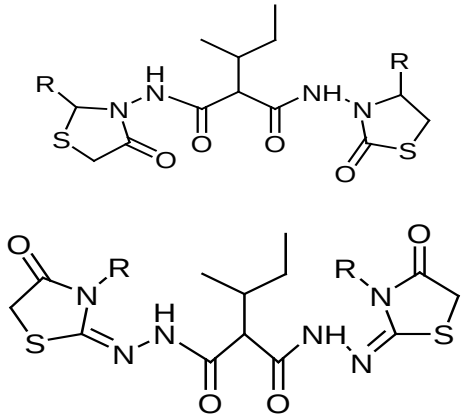
12

Shiradkar *et al.* (2007) synthesized a new series of clubbed thiazolidinone-triazoles (2Z,5Z)-5-benzylidene-3-(2-(5-(1-phenoxyethyl)-4H-1,3,4triazol-3-ylthio)acetyl)-2-phenyl imino) thiazolidin-4-one were synthesized and studied the effect of hydrophobic unit, hydrogen bonding domain and electron donor group on the compounds for anticonvulsant activity. Some of them exhibited excellent anticonvulsant activity. [24]



13

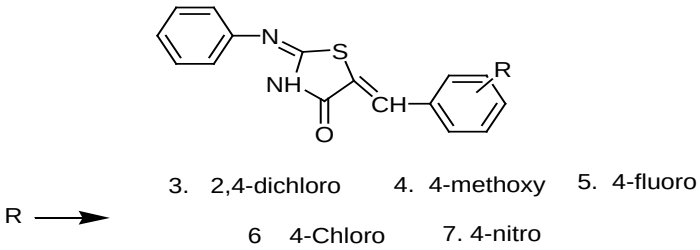
Shyam *et al.* (1972) reported the synthesis, characterization, and anticonvulsant evaluation of new N,N'-bis(arylidene)dihydrazide and bis*(4*-thiazolidinone) derivatives. Up to 90% protection was observed in the PTZ seizure.[25]



14

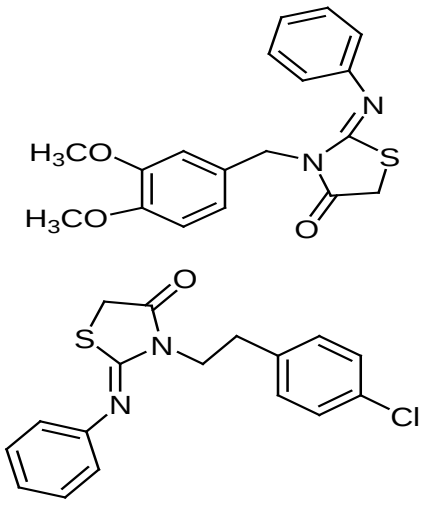
Singh *et al.* (2011) synthesized 5-benzylidene-2-(phenylimino) thiazolidin-4-ones were prepared and evaluate for their potential anticonvulsant activity by

determining their ability to provide protection against convulsion. In this 4th, 5th, 6th showed significant antiepileptic activity.3rd and 7th showed the less significant activity.[26]



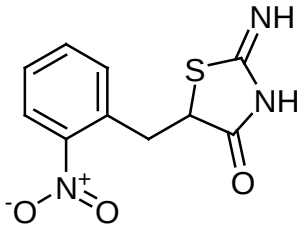

15

Parmar *et al.* (1972) reported the anticonvulsant activity of several series of 2( (arylimino)/(arylhydrazono)-3-aryl/(alkylaryl)/furfuryl/2pyrimidyl/cycloalkyl/(substituted amino)/(3-(N-morpholin-4-yl-propyl)-4-thiazolidinones has been studied against pentylenetetrazolin induced seizures in Albino mice of either sex at a dose of 100 mg/kg. Most of the compounds were found to exhibit protection against PTZ induced seizure and the degree of protection ranged up to 80%. [27]



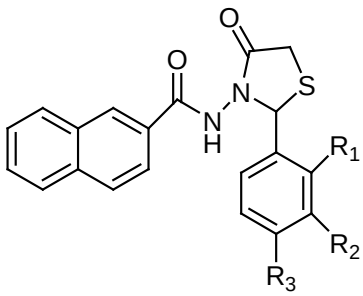

16

Velmurugan *et al.* (2012) synthesized a number of 2-imino-5-(Z)-arylmethylidene-1,3-thiazolan-4-one derivatives from thiourea and studied on anticonvulsant activity using maximal electroshock-induced seizure (MES) in mice. Out of the synthesized six compounds, compound [13] 5-(2-nitrobenzyl)-2-iminothiazolidin-4-one posses good anti-convulsant activity showing good response in flexion, extension, clonus and stupor but less activity compared to standard drug phenytoin. [28]



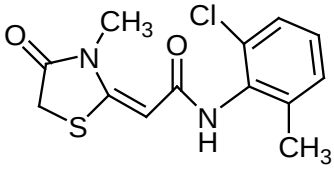

17

Indulatha *et al.* (2012) synthesized N-[4-oxo-2-(substituted phenyl)-thiazolidin-3-yl]-3-carboxamido-2H-chromen-2-one [14] derivatives and evaluated for their anticonvulsant activity. All the synthesized new derivatives were examined by the Maximal Electro Shock induced seizures (MES). All the compounds reduce the time of the tonic extensor phase. Compound N-[4-oxo-2-(o-nitro phenyl)-thiazolidin-3-yl]-3- carboxamido-2H-chromen-2-one derivatives.[29]




18

Yenamandra *et al.* (2006) reported that (E)-N-(2-chloro-6-methylphenyl)-2-(3-methyl-4-oxothiozolidin-2-ylidene) acetamide has anticonvulsant activity.[30]

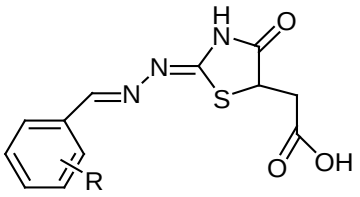


19

## 4. Antimicrobial activity

Kavitha *et al.* (2006) synthesized some novel bioactive venlafaxine analogs such as 2,3-disubstituted 1,3-thiazolidin-4-ones it showed inhibitory activity on pathogenic strains such as Bacillus subtilis, Escherichia coli, Pseudomonas fluorescens, Xanthomonas campestris pvs, Xanthomonas oryzae, Aspergillus niger, Aspergillus flavus,Fusarium oxysporum, Trichoderma species, and Fusarium monaliforme species.[31]

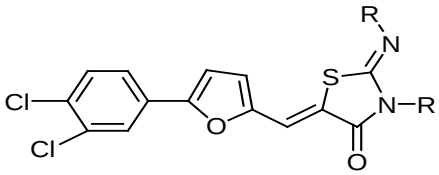
R = 2-fluoro, 4-fluoro, 4-dimethylamino, 2,4-dimethoxy, 2,4-dichloro,3,5-di-tert-butyl-4hydroxy.



20

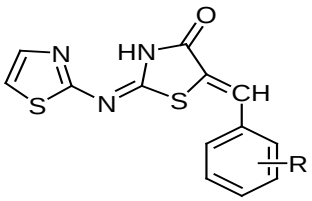
Bhoot *et al.* (2006) synthesized 2-(p-tolylimino)-3-(4-tolyl)-5-[5-(3,4-dichlorophenyl)-2-furylidene]-4-thiazolidinone and derivatives as an antimicrobial agents. Compounds were screened *in vitro* for their antimicrobial activity towards variety of bacterial strains such as B. mega, S.aureus, *E. coli*, *P.* vulgaris and fungi such as Aspergillus niger.[32]

R=phenyl,2methoxyphenyl,2methylphenyl,3methylphenyl 4-nitrophenyl substituents.



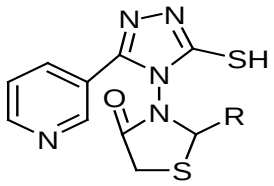
21

Vicini *et al.* (2006) reported synthesis of 2-thiazolylimino-5-arylidene-4-thiazolidinones as antimicrobial agent.[33]



22

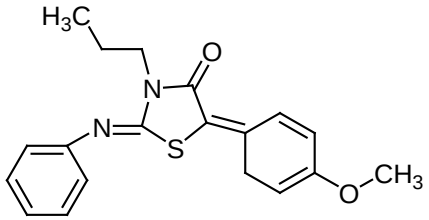
Dave *et al.* (2007) synthesized 3-(3-mercapto-5-pyridin-3-yl-[1,2,4-]-triazole-4-yl)-2-aryl-1,3-thiazolidin-4-ones and reported for antimicrobial activity. [34] R=aryl



23

## 5. Anti-inflammatory activity

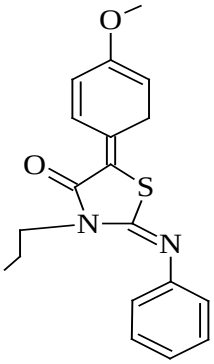
Ram *et al.* (1998) synthesized various derivatives of thiazolidinones from 2-chloro phenothiazines and screened that compound for anti-inflammatory activity against carageneenan induced oedema in albino rats. All Thiazolidinones derivatives have shown promising anti-inflammatory activity. Out of these compound (2Z,5E)-5-(4-methoxycyclohexa-2,4-dienylidene)-2-(phenylimino)-3-propylthiazolidin-4-one.[35]



24

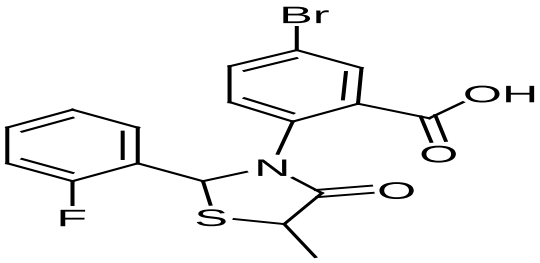
Ottana *et al.* (2005) described the anti-inflammatory activity of 5- arylidene-2-imino-4-thiazolidinones. All derivatives exhibited significant activity in models of acute inflammation such as carrageenan-induced paw and pleurisy edema in rats. In particular, 5-(4-

methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone displayed high levels of carrageenan induced paw edemainhibition, comparable to those of indomethacin.[36]



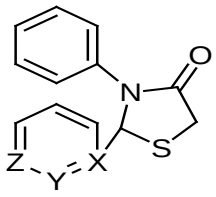
25

Kumar *et al.* (1999) synthesized some new anthranilic acid derivatives, 2-substituted-3-(4-bromo -2 - carboxyphenyl) - 5 - methyl - 4 - thiazolidinones and evaluated them for anti-inflammatory activity against carrageenan-induced edema in albino rats. The most active member of the series, 3-(4-bromo-2-carboxyphenyl)- 2-(fluorophenyl)-5-methyl-thiazolidinone.



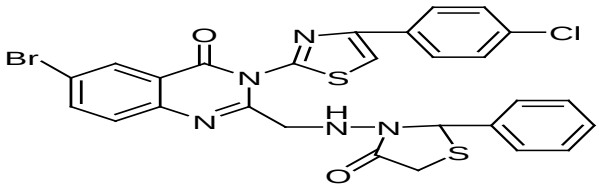
26

Vazzana *et al.* (2004) synthesized aromatic Schiff bases and 2,3-disubstituted-1,3-thiazolidin-4-one derivatives as anti-inflammatory agents. Both types of compounds displayed good level of activity against carrageenan induced edema in rat hind paw, while only moderate activity was observed in the writhing test in mice.



27

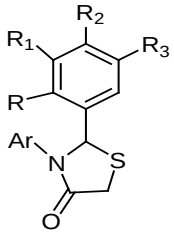
Kumar *et al.* (2007) synthesized 3-[4'-(p-chlorophenyl)-thiazol-2-yl]-2-[(substitutedazetidinone/thiazolidinone)-aminomethyl]-6-bromoquinazolin-4-ones. Some of the compounds have shown satisfactory anti-inflammatory activity.



28

**6. Antibacterial activity**

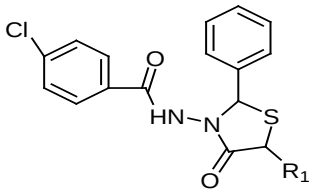
Sayyed *et al.* (2006) synthesize 2,3-diaryl-1,3-thiazolidin-4-one derivatives having a 2,6-dichlorophenyl, or 1,2,4-triazole ring at N-3 and variously substituted 3-iodo- or 3-bromo-phenyl rings at C-2have been synthesized and tested as antibacterial agents. The results of the *in vitro* tests showed that some of them have effective antibacterial activity. We have shown that a high level of activity was associated with the presence of a 3-iodo or 3-bromo- substituted phenyl ring at C-2. Moreover, we found that an increase in antibacterial activity was dependent on the presence of a 2,3-dichlorophenyl group at N-3.



29

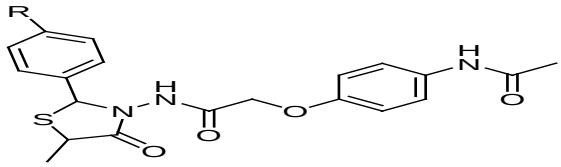
Solanki *et al.* (1994) synthesized a series of 4-chloro-N-(4-oxo-2,5-diphenylthiazolidin-3-yl)benzamide.

Compounds with $R_1$=p-$CH_2C_6H_5$, -m-$C_6H_4Cl$, $C_6H_4OCH_3$, $C_6H_4OCH_3$, $C_6H_4OC_2H_5$, -2-$C_{10}H_7$ were sceened for antitubercular activity against H37RV strain of Mycobacterium tuberculosis. The activity was compared with standard isonicotinic acid hydrazide with R=-p-$C_6H_4OC_2H_5$ showed activity at 30 µg/ml whereas the other revealed low inhibitory effect



30

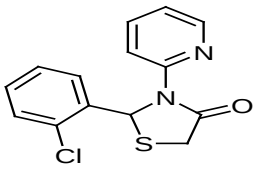
Haresh Oza *et al.* (1998) reported the series of 2-aryl-3-p-acetamidophenoxyacetamido-5- methyl-4-thiazolidinones. Primary screening of the compounds for antitubercular activity have been conducted at 12.5 µg/ml against Mycobacterium tuberculosis H37RV in BACTEC 12B medium using BACTEC 460 radiometric system. It can be concluded that compounds exhibited various degree of activity (0 to 35%).



31

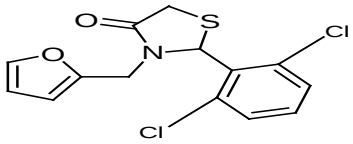
## 7. Anti HIV Activity

Sriram *et al.* (2005) synthesized several 1,3, thiazolidinone-4-one bearing various substituted diaryl ring at C-2 and N-3 position, by utilizing microwave irradiation and evaluated for their anti HIV and anti YFV activities. The result of the in vitro anti HIV evaluation showed that 2-(2-chlorophenyl)- 3-pyridin-2-yl-1,3-thiazolidin-4-one proved to be an effective inhibitors of HIV-1 replication.



32

Rawal *et al.* (2005) synthesized various series of 2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones as selective HIV-RT Inhibitors. In this 2-(2,6- Dichlorophenyl)-3-(furan-2-yl) methyl-thiazolidin-4-one was found to be the most promising of the series.



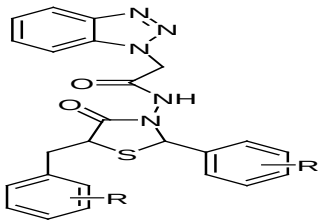
33

Monforte *et al.* (2001) the anti-HIV activity of several series of 2,3-diaryl 1,3thiazolidin-4-ones has been studied which are reported as a new family of antiviral agents acting as NNRTIs with minimal cytotoxicity.

34

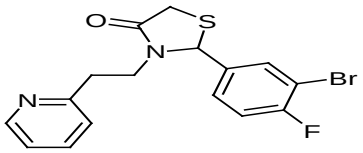
## 8. Analgesic Activity

Asate *et al.* (2006) prepared various series of 5-arylidene-2-aryl-3-(benzotriazoloacetamidyl)-1,3-thiazolid-4-ones and screened that compound for analgesic activity. The activity was performed on Albino rats by Eddy and Limbic method at an oral dose of 25 mg/kg body weight. The compound with R=2-Br, 3-Br, 4-Br, are found to have 141.93, 142.85 and 141.26% analgesic activity respectively.



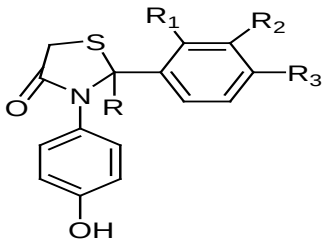
35

Burley *et al.* (2007) synthesized a series of new N-type (calcium channel blockers derived from the 'hit' structures 2-(3-bromo-4-fluorophenyl)-3-(2-pyridin-2-ylethyl) thiazolidin-4-one and its 2-[4-(4-bromophenyl)pyridin-3-yl]-3-isobutyl analogue. According to SAR (Structure Activity Relationship) this compound identified as the most potent compounds in this series. These compounds show promise as lead structures in the quest for clinically effective N type blockers in the treatment of pain.



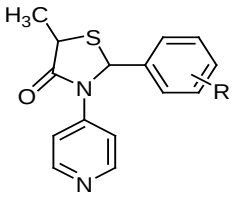
36

Taranalli et al. (2009) synthesized thiazolidine-4-one derivatives and evaluated for anti-inflammatory, 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.



37

Nagalakshmi et al. (2011) synthesized, Characterized and Antiproliferative Activity of Some Novel 2-(substitutedphenyl)-5-methyl-3-(pyridin4yl)1,3thiazolidin-4-ones. This exhibited significant antitumor and antiproliferative activity against DAL and L929 cells in vitro and Structural variation to obtain more potent, selective and less toxic antitumor agents.R=4-Cl, 4-F, 2-F, 4-$NO_2$

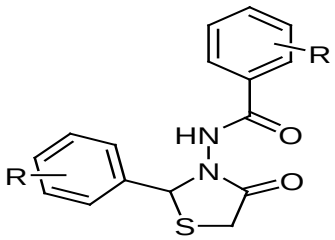


38

## 9. Anthelmintic Activity

Kumar et al. (2002) Synthesized a series of 2-aryl-3-substituted benzamido-1,3-thiazolidin-4- ones and all these compounds evaluated for anthelmintic activity against Pheritima posthuma and Eudrilus sp. by Garg's method. The results shows that the compound N-[2-(2-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]benzamide is a very potent and active against both the sepsis. All other compounds show moderate to good anthelmintic activity.

R=4-N-($CH_3$)



39

## 10. Conclusion

The survey of the literature revealed that, thiazolidinone is a versatile lead molecule for designing potential bioactive agents, and its derivatives were reported to possess broad-spectrum ant diabetic, antiviral, antimicrobial, cytotoxic, anti-inflammatory, anxiety, analgesic, anti-histaminic,

anti-diuretic activities. Further we can conclude that many other derivatives of thiazolidinone can be synthesized which will be expected to show potent pharmacological activities and can be industrial importance. This review is an endeavor to highlight the progress in the pharmacological activity of the Thiazolidinones [Figure-1].

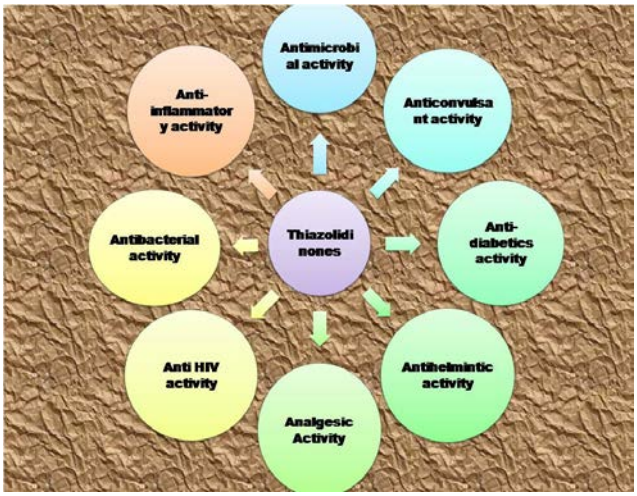



**Figure-1**

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