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A Brief Review on Biological Activities of Thiazolidinone Derivatives

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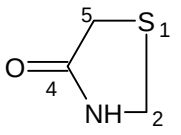
ABSTRACT

A large number of drugs and biologically relevant molecules contain heterocyclic system. Thiazolidinone is the special class of heterocyclic compounds with a broad spectrum of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. Successful introduction of different functional group into the basic thiazolidinone ring increases the spectrum of activities.4-thiazolidinone is a most important derivative of thiazolidinone. It have carbonyl group at 4th position & substituent in 2, 3& 5th position.This review focuses on various biological activities of thiazolidinone derivatives from earlier research & review works and find out the future perspective of thiazolidinone derivatives in the field of medicine.

INTRODUCTION

Thiazolidinones are thiazolidine derivatives which belongs to the important group of heterocyclic compounds have been extensively studied for their applications in medicine. Thiazolidinones have a sulfur atom at position 1and nitrogen at position 3 and a carbonyl group at position 2, 4 or 5.However its derivatives belongs to the most frequently studied moieties and have a wide range of therapeutic activities, from the derivatives 1, 3-thiazolidin-4-ones have an atom of sulfur and nitrogen at position 1&3, and carbonyl group at 4th position was subjected to extensive study in recent years. [1]



4-thiazolidinone

The 4-thiazolidinones are usually solid and have a molecular weight of103.139g/mol and melting point of about 42-44°c, attachment of an alkyl group to nitrogen atom decreases the melting point. The 4-thiazolidinone that does not have any aryl or higher alkyl groups as substituent are soluble in water. Various optical and geometrical isomers are reported on 4-thiazolidinone. The 4-thiazolidinone scaffold has widely featured in a number of therapeutic activities like antitubercular, anti-inflammatory, anticonvulsant, antimicrobial, antiviral antipsychotic and anticancer activities.

The increased prevalence of infectious diseases threatens the world population. It has been extensively reported that presence of arylazo, sulfamoylphenylazo or phenylhydrazono moieties at different position of the thiazolidinone ring enhanced antimicrobial activity and also, they have interesting activity like cox-1 inhibitors, inhibitor of bacterial enzyme, non nucleoside inhibitors of HIV type1 reverse transcriptase (HIVRT) and antihistaminic agents. Numerous reports have appeared in the literature that highlights their medicinal activities. According to Anders *et al*. 4-thiazolidinones may be considered as phosphate bioisosteres and therefore, inhibit the bacterial enzyme, which is involved in the biosynthesis of peptidoglycan layer of the cell wall thereby showing antibacterial action. Some thiazolidinone has been recently reported as novel inhibitors of mycobacterial rhamnose enzymes and is to be selective as rhamnose, which is not found in humans, has been shown to be essential for mycobacterial cell wall synthesis. [2]

Several substituted thiazolidinone have been found to be possessed antitubercular, anthelmintic, analgesic, anti-inflammatory, anticancer, ant diabetic, hypnotic, hypolipidemic activity. Cardiovascular activity was also found to be exhibited by some thiazolidinone derivatives. This diversity in the biological activity leads to explore this heterocyclic compound to its multiple potential against several activities. Present article is a brief account of various biological and pharmacological activities of thiazolidinone scaffold. The drugs like Etozoline, Ralitoline and Epalrestat have thiazolidinone nucleus in their structure.

MECHANISM OF ACTION OF THIAZOLIDINONE COMPOUNDS

Thiazolidinone derivatives have several mechanism of action due to the wide range of activities. It can act as antifungal agent by inhibiting the mycelia growth of fungi. The anti-inflammatory action of thiazolidinone is occurring by the COX-2 inhibition. Some thiazolidinone derivative can inhibit the DNA synthesis in the cancer cell. Certain thiazolidinone derivative act as non nucleoside inhibitor of HIV type1 reverse transcriptase and possess anti-HIV activity[25].

BIOLOGICAL ACTIVITIES OF THIAZOLIDINONE DERIVATIVES; A REVIEW

Tumul srivastava *et al*. synthesized compounds 1-thia-azaspiro[4]alkan-3-ones and 1-thia-4,8-diazaspirodecan-3-one are screened against *M.tuberculosis* using Microplate Alamar Blue Assay(MABA) on High Through put Screening machine at 25 µg/ml and lower concentration using M.*tuberculosis* H37Ra as a surrogate for the virulent H37Rv strain. The results of MABA have been found comparable to standard system based assay. The standard antitubercular drugs rifamycin, isoniazid, para aminosalicyclic acid, ethambutol and ethionamide were taken as positive controls. [3]

Jaju and co-workers had synthesized iso-nicotinylhydrazide derivatives and screened there in-vitro antimycrobacterial activity against *M.tuberculosis*H37rv using alamar-blue susceptibility test. They found that the antitubercular activity was considerably affected by various substituent on the aromatic ring of 4-thiazolidinone and it was proved by the fact that compounds which does not having any substitution on aromatic ring did not have any activity. The hydroxyl and methoxyl group on aromatic ring substituted compound (fig.1) was found to be more active. [4]

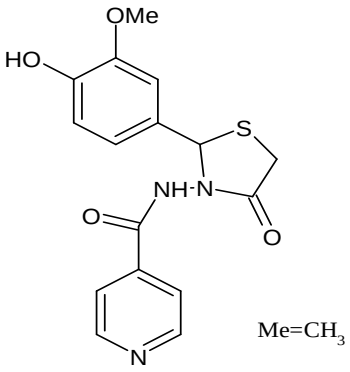


Fig.1, Thiazolidinone derivative 1

Protein tyrosine phosphatases A (MptpA) and B (MptpB) secreted into the host cell by growing *Mycobacterium tuberculosis* potently to be active selectively showed a target for the treatment of tuberculosis.

Vintonyak *et al*. designed a novel series of indoline-2-one-3-spirothiazolidinones as new potent and selective inhibitors of MptpB. They studied the modification on phenyl substituent on the thiazolidinone and 2-indolinone position. Halogen substitution also increases the activities. [5]

Babaoglu *et al*. reported the activity of 4-thiazolidinone against M.tuberculosis by inhibition of dTDP-rhamnose synthesis in an attempt to find new inhibitors of the enzymes in the biosynthetic pathway. [6]

Zitouni *et al*. reported the synthesis of N-pyridyl -N'-thiazolylhydrazine derivatives. Compound below (fig.2) showed high antitubercular action, its structure revealed that 2-pyridyl and 2-hydroxyl-5-methoxyphenyl group are essential for antimycobacterial activity while 3-pyridyl, 4-pyridyl group were unfavourable for activity. [7]

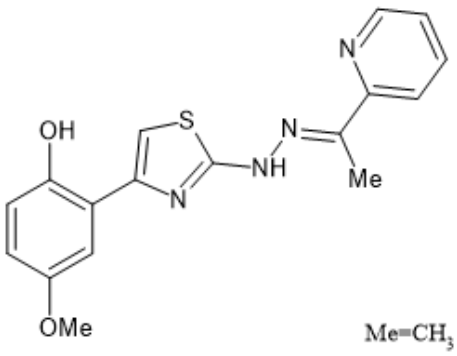


Fig.2, Thiazolidinone derivative 2

Series of 2-[3-methyl-2,6-substituted-4-hydrazono]-1,3-thiazolidin-4-one (fig.3) with respect to acid resistant mycobacteria showed to have more activity with respect to mycobacteria of the human type strain and few of the synthesized compounds showed comparable activity with rifampicin.

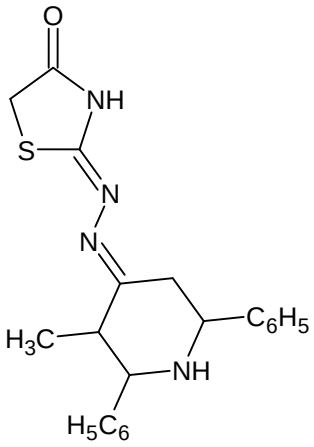


Fig.3, Thiazolidinone derivative 3

2. Anti-inflammatory and analgesic activity

Inflammation is a biological response to the harmful stimuli and is linked with many pathophysiological conditions. In response to inflammatory stimuli, macrophages release anti-inflammatory agents like nitric oxide, and cellular defence molecules. Arylalkanoic acids constitute the basis for the widely used NSAIDs naproxen and ibuprofen, which inhibit the COX enzyme that catalyzes the biosynthesis of PGs and thromboxan from arachidonic acid. The mode of action of this drugs results in unwanted side effects. To overcome the problems anti-inflammatory and analgesic activity of new quinazolinone derivatives having thiazolidinone at 2nd position was reported by kumar *etal*. New compound (fig.4) which was substituted with chloro group at 2nd position of phenyl ring, showed almost equal anti-inflammatory activity to that of phenylbutazone at 50mg/kg. [8]

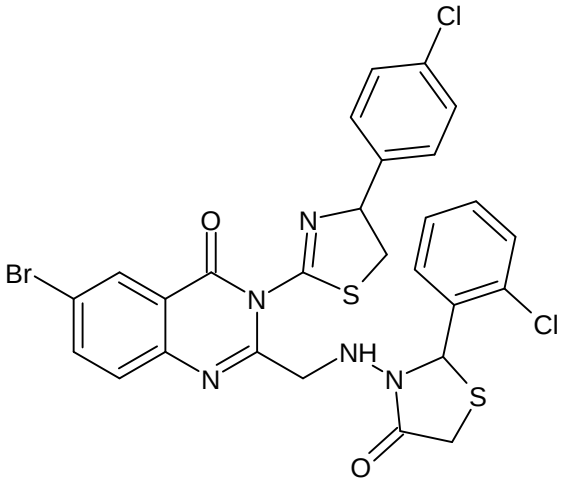


Fig.4, Thiazolidinone derivative 4

In another study biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amide derivatives exhibited significant anti-inflammatory activity. Compound (fig .5) with a substitution of bromine on both the aromatic ring showed percentage inhibition of 44.5 and 55.73. [9]

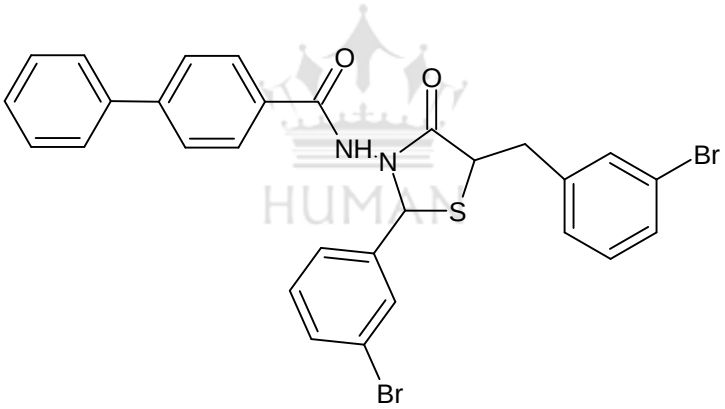


Fig.5, Thiazolidinone derivative 5

Sparatore F. has synthesized aromatic Schiff base and 2, 3-disubstituted-1, 3-thiazolidine-4-one derivatives as anti-inflammatory agent. 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. [10]

Ottana *et al*. investigated 3,3-(1,2-ethanediyl)-bis [2-aryl-4-thiazolidinone] derivativeswhich shows interesting stereo selective anti-inflammatory/ analgesic activities and suggested that these derivatives interact with inducible COX-2 isoform. Absence of 5-arylmethylidene moiety in 3-[2-(4-methylphenyl)-2-oxo-1-phenylethyl]-2, 4-thiazolidinedione (fig.8) enhanced its anti-inflammatory activity and decreased the analgesic activity. [11]

The anti-inflammatory properties of 2- aryl-3-{5-[([1,3,4]thiadiazino[6,5-b]indol-3-ylamino)methyl]-1,3,4-thiadiazol-2-yl}-1,3-thiazolidin-4-one were studied using carrageenan induced rat's paw edema method. [12]

Newbold, studied the anti-inflammatory activity of2-[(butoxycarbonyl) methylene]-4-thiazolidinone. The compound was found to devoid of activity against most models of acute inflammation. It partially inhibited carageenan induced edema in the rat and prevented completely the development of secondary lesions in the rat injected with adjuvant in the footpad. [13]

Amin *et al*. prepared several spiro[(2H, 3H) quinazoline-2, 1'-cyclohexan]-4(1H)-one derivatives. These compounds were evaluated for their antiinflammatory, ulcerogenic and analgesic activities. Compound with 2-thiophene substitution at C-2 of thiazolidinone has shown most active anti-inflammatory activity and considerable analgesic activity. [14]

3. Anticonvulsant & antipsychotic activity

The anticonvulsant activity of several series of 2-(arylimino)/(arylhydrazono)-3-aryl/(alkylaryl)/furfuryl/2-pyrimidyl/cycloalkyl/(3-(N-morpholin-4-yl-propyl)-4-thiazolidinones has been studied against pentylenetetrazol induced seizure in albino mice of either sex at a dose of 100 mg/ kg. Most of the compounds were found to exhibit protection against pentylenetetrazol- induced seizures, and the degree of protection ranged up to 80%. [15]

Archana kumar has synthesized a newer thiadiazolyl and thiazolidinonyl quinazolin-4-(3H)-ones in 2002. The compounds were screened for their anticonvulsant activity and were compared with the standard drugs, phenytoin sodium, lamotrigine, sodium valproate. Out of the 30 compounds the most active compound was 3-({4-[2-(m-methoxy-hydroxyphenyl)-4-oxo-1, 3-thiazolidin- 3-yl]-1, 3,4-thiadiazol-2-yl} methylamino)-2-methyl-6-bromoquinaxolin-4(3H)-one. [16]

A number of substituted thiazolidinonyl carbazol derivatives are potent antipsychotic and anticonvulsant agent. Compound shaving thiazolidinone ring showed more potent antipsychotics as well as anticonvulsant activities as compared to compounds having azetidinone ring[17]. Series of 3-[(3-substituted-5-methyl-4-thiazolidinon-2 ylidene) hydrazono]-indolinonederivatives (fig.6) are evaluate for CNS depressant activity. [18]

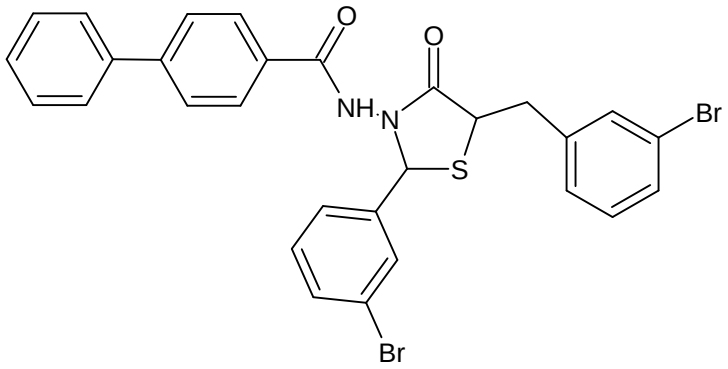


Fig.6, Thiazolidinone derivative 6

A series of piperazinyl butyl thiazolidinones structurally related to 3-[4-[4- (6-fluorobenzothien-3-yl)-1-piperazinyl]butyl]-2,5,5-trimethyl-4-thiazolidinone maleate were prepared and evaluated in vitro for dopamine D2 and serotonin $5HT_2$ and $5HT_1A$ receptor affinity. The compounds were examined in-vivo in animal models of potential antipsychotic activity and screened in models predictive of extra pyramidal side effect liability. [19]

4. Anticancer and anti proliferative activity

Ten cytoselective compounds have been identified from 372 thiazolidinone analogues by applying iterative library approaches. These compounds selectively killed both non-small cell lung cancer cell line H460 and its paclitaxel-resistant variant H460taxR at an IC_{50} between 0.21 and 2.93µM while showing much less toxicity to normal human fibroblasts at concentrations up to 195 µM. A pharmacophore derived from active molecules suggested that two hydrogen bond acceptors and three hydrophobic regions were common features.[20]

Gududuru *et al.* tested a series of 2-arylthiazolidine-4-carboxylic acid amides for possible cytotoxic activity in prostate cancer. Compound was found to be most potent and selective cytotoxic agent with IC_{50} of 0.55 lM and 38-fold selectivity in PPC-1 cells. The SAR study showed that as the chain length increased fromC_7 to C_{18}, the potency also increased but further increase in the alkyl chain by one carbon unit caused a significant loss of activity; so alkyl chain with C_{18} unit was optimal for effectiveness of thiazolidine analogues. Replacement of the phenyl ring with an alkyl or cyclohexyl group reduced the potency while replacement with furanyl ring derivative showed equivalent cytotoxicity. The same research group designed new series of 2-aryl-4-oxo-thiazolidin-3-yl amides and all synthesized compounds were evaluated against five human prostate cancer cell lines. They reported that

increase in the alkyl chain enhanced the antiproliferative activity while replacement of the alkyl chain with aryl group reduced the biological activity. [21]

Hafez *etal*. synthesized a series of substituted triazolo [4, 3] pyrimidin-6-sulfonamide with an incorporated thiazolidinone moiety and reported for their antitumor activity. Most of the synthesized compounds were found moderate in activity and compound displayed a good growth inhibitory activity on all tested60 cell lines. In fact, the presence of 4-methylpiperazin/morpholine on C-5and thienyl group at C-2 of thiazolidinone seems to be very important for anticancer activity. [22]

A number of isatin-based thiazolidines conjugates (fig.7) have been investigated as anticancer activity, their affinity to tyrosine kinases, cyclin-dependent kinases and carbonic anhydrase isozymes suggested their potential as novel anticancer agents. None of the thiazolidinone conjugates showed greater activity than 1, 3-dihydroindol-2-one conjugates with 3, 5-diaryl-4, 5-dihydro pyrazolyne derivatives.[23]

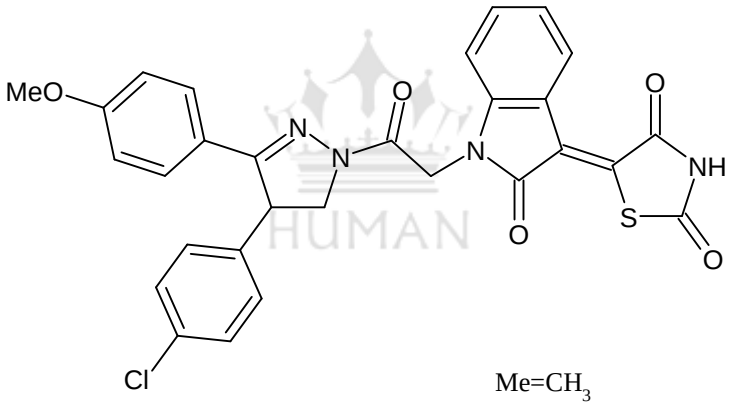


Fig.7, Thiazolidinone derivative 7

5. Antibacterial and antifungal activity

Thiazolidinones with C-2 and N-3 substituted positions possess diverse degrees of inhibition against bacteria and fungi. The dramatically rising prevalence of multi-drug resistant microbial infections in the past few decades has become a serious health problem. Approximately all the positions of 4-thiazolidinone have been explored to improve the antibacterial and antifungal activity. The SAR studies of thiazolidinone derivatives showed that they are more effective on gram-negative bacteria as compared to gram-positive bacteria. The search for new antimicrobial agents will consequently remain as an important and challenging task for medicinal chemists. [24]

Liesen *et al*. reported 4-thiazolidinone derivatives obtained from ethyl (5-methyl-1-H-imidazole-4-carboxylate) and the compound were evaluated against variety of pathogens for their antibacterial and antifungal activity. The results showed that the tested compounds possessed weak antibacterial and antifungal activities compared to standard drugs chloramphenicol and rifampicin for antibacterial activity and ketoconazole for antifungal activity.

Kocabalkanli *etal*. synthesized mannich bases of some 2, 5-disubstituted 4-thiazolidinones and evaluated their antimicrobial activity. They reported that the most active compound had a p-chlorophenyl group on the oxadiazole, a methyl and a pyrrolidino methyl at the 5thposition of the thiazolidinone (fig.8), while the least active one has a hydrogen atom in place of chlorine and a morpholine in place of pyrrolidine.

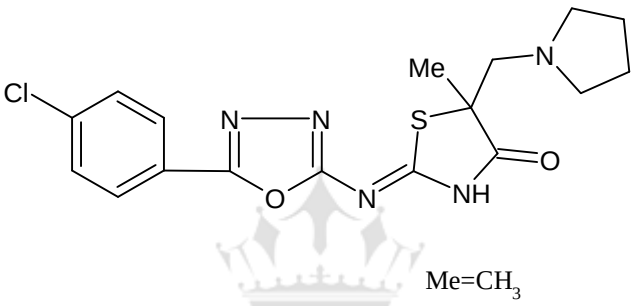


Fig.8, Thiazolidinone derivative 8

Further analogous of 2- phenyl-3-(4,6-diarylpyrimidin-2-yl)thiazolidin-4-ones have been synthesized by Gopalakrishnan *et al*. and tested for their antibacterial activity against *staphylococcus aureus, vibrio cholera, salmonella typhi, E.Coli*, and *Pseudomonas aeruginosa*. Ciprofloxacin was used as standard drug. Results revealed that p-(OCH3) and p-(CH3) groups at phenyl ring attached to the pyrimidine ring exerted strong antibacterial activity.

6. Antiviral and cytotoxic activities

Omaima Mohamed AbdElhafez *etal*. have synthesized a series of 2-Substituted-3-[(coumarin-4-oxy) acetamido] thiazolidin-4-one. Antiviral and cytotoxicity assays were carried out and the compounds were tested for antiviral activity against *Herpes simplex* type1 (HS-1) grown on Vero African green monkey kidney cells. Each compound exhibited some cytotoxicity. Compound 2-(4-chloro phenyl)-3-[(coumarin-4-oxy) acetamido] thiazolidin-4-

one has the highest activity among all the compounds in this study and was able to reduce the number of plaques by 30% at a concentration of 0.12mg/m.

Ravichandran *et al*. were prepared 1,3-thiazolidin-4-one derivatives and their antiviral activity against *Herpes simplex* virus-1,*Herpes simplex* virus-2, Influenza A subtype and Influenza B was evaluated (fig.9).

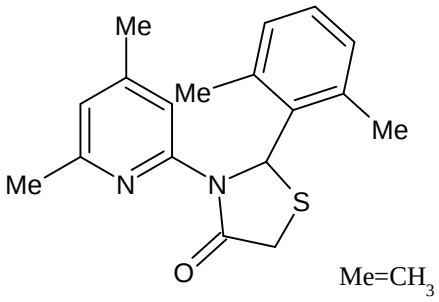


Fig.9, Thiazolidinone derivative 9

The summarized biological activities of thiazolidinone derivatives is given in the table.1 below,

Table.1

S.no.	Compound name	Biological activity
1.	Iso-nicotinyl hydrazide derivative of thiazolidinone	Antitubercular activity
2.	Quinazolinone derivative of thiazolidinone	Anti inflammatory activity
3.	3-[(3-substituted-5-methyl-4-thiazolidinon-2-ylidine) hydrazono]-indolinone derivative	CNS depressant activity
4.	Isatin- based thiazolidine conjugates	Anticancer activity
5.	2-p-chlorophenyl oxadiazole derivative of thiazolidinone	Antimicrobial activity
6.	1,3-thiazolidin-4-one derivative	Antiviral activity

CONCLUSION

The potency of 4-thiazolidinone nucleus is cleared from the clinically used drugs. Though the antibacterial, anti-inflammatory, antitubercular and anticancer are the four major areas of clinical use, other potential activities are still to be explored. Most of the positions were explored to improve the antibacterial and antitubercular profile of 4-thiazolidinone but still

none of the derivatives showed promising therapeutic activity. The activity of the compounds depends upon the nature and position of the substituents at the aryl moiety attached with thiazolidinone ring. Hence further investigation in this direction may yield fruitful results. No concerted conclusion has emerged regarding structure activity relationship (SAR) and potency of the reported derivatives. Hence further study in this direction may be quite rewarding. From these observations, the importance of the nucleus is highlighted. But there is much scope in this promising moiety as a number of different derivatives are available for 4-thiazolidinone. The literature revealed that 4-thiazolidinone has diverse potential activities, and the easy routes for synthesis have taken attention of the researchers. The main significance and rationale of the work, focuses on exploring the biological activity studies of thiazolidinone derivatives which will help the reviewers to perform the research within the field.

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REFERENCES

1. Jain A K, Vaidya A, Ravichandran V, Kashaw S, Agrawal R. Recent developments and biological activities of thiazolidinones. *Bioorg. Med. Chem*. 2012; p.01-17.
2. Patil P A, Patel T K, Pawar S P. Chemistry and biological activities of 4-thiazolidinones. *World. J. Pharm*. Vol (4); Issue 5.2015; p.1780-1790.
3. Srivastava T, Gaikwad A K, Sinha S, Katti S B. Synthesis and biological evaluation of 4-thiazolidinone derivatives as potential antimycobacterial agents, Tetrahedron, 2005; p.120-130.
4. Jaju S, Palkar M, Maddiv S, Ronad P K, Satyanarayana D. *Arch. Pharm. Chem. Life. Sic*. 2009; p.342-723.
5. Vintonyak V K, Warburg K, Kruse H. Grimme S. Hubel K. *Angew. Chem*. 2010; p.122-134.
6. Babaoglu K, Page M A, Jones V C, Mcneil M R, Dong C, Naismith J H. *Bioorg. Med. Chem. Lett*. 2003; p.13-32.
7. Zitouni G, Kaplancikli Z A, Ozdemir A. *Eur. J. Med. Chem*. 2010; p.45-85.
8. Kumar A, Rajput C S, Bhati S K. *Bioorg. Med. Chem*. 2007; p.15-25.
9. Deep A, Jain S, Sharma P C. *Acta poloniae pharmaceutica drug Res*. 2010; p.67-83.
10. Vazzana I, Terranova E, Mattioli F, Sparatora F. Aromatic Schiff bases and 2, 3-disubstituted-3, 1-thiazolidin-4-one derivative as anti- inflammatory agents, Arkivoc, 2004; p.364-374.
11. Ottana R, Maccari R, Barreca M L, Bruno G, Rotondo A, Rossi A, Chiricosta G. *Bioorg. Med. Chem*. 2005; p.13-42.
12. Bhati S K, Kumar A. *Eur. J. Med. Chem*. 2008; p.43-58.
13. Newbould B B. *British J. Pharmacology*. 1965; p.246-321.
14. Amin K M, Kamel M M, Anwar M. Khedr A, Syamy N. *Eur. J. Med. Chem*. 2010; p.45-60.
15. Ottana R, Maccari R, Barreca M L *etal*. *Bioorg. Med. Chem*. 2007; p.243-425.
16. Kumar A, Srivastava V K. Synthesis of newer thiadiazolyl and thiazolidinonyl quinazolin-4(3H)-ones as potential anticonvulsant agent, *Eur. J. Med. Chem*. 2002; p.873-882.
17. Kaur H, Kumar S, Vishwakarma P, Sharma M, Saxena K. *Eur. J. Med. Chem*. 2010; p.45-67.

18. Karall N, Gursoy A, Terzioglu N, Ozkurml S, Ozer H, Ekinci A C. *Arch. Pharm. Med. Chem*. 1998; p.331-354.
19. Asati K C, Srivastava S K, Srivastava S D. *Ind .J. Chem*. 2006; p.526-531.
20. Hongyu Zetal. Design, synthesis, cytoselective toxicity, structure activity relationships, and pharmacophore of thiazolidinone derivatives targeting drug resistant lung cancer cells. *Ind .J. Med. Chem*. 2008; p.1242-1253.
21. Gududuru V, Hurh H. Dalton J T, Miller D. *Bioorg. Med. Chem. Lett*. 2004; p.14-23.
22. Hafez H N, El-Gazzar A. *Bioorg .Med .Chem*. 2009; p.764-769.
23. Havrylyuk H, Abu-Hashem A A. *Arch. Pharm. Chem. Life. Sic*. 2011; p.344-514.
24. Omar K, Geronikaki A, Zoumpoulakis P, Camoutsis C *etal*. *Bioorg. Med. Chem*. 2010; p.18-26.
25. Manjal S K, Kaur R *etal*. Synthetic and medicinal perspective of thiazolidinones : A review. *Bioorganic chemistry*.75(2017); p.406-423.