International Journal of Pharmaceutical Drug Design (IJPDD)
Website: https://ijpdd.org/
ISSN: 2584-2897
Vol. 2, Issue 4, April, 2025
Page No.: 136-142

Review

Pharmacological Activities of Thiazolidinone Derivatives: A Concise Review

Raj Kumar Singh[1*], Shourya Pratap[2], Dr Amresh Gupta[3]

[1*] *Department of Pharmaceutical Chemistry, Institute of Pharmaceutical Sciences & Research (IPSR) Mahadev Campus, Sohramau, Unnao, Uttar Pradesh, 209859, India*

[2,3] *Assistant Professor, Institute of Pharmaceutical Sciences & Research (IPSR) Mahadev Campus, Sohramau, Unnao, Uttar Pradesh, 209859, India*

Corresponding Author:
Raj Kumar Singh

Email:
rajsinghs9201@gmail.com

DOI: *10.62896/ijpdd.2.4.10*

Conflict of interest: *NIL*

Abstract:

A broad class of heterocyclic chemicals known as thiazolidinones has shown promise in the creation of new medicinal drugs. The wide range of biological actions of thiazolidinone derivatives is demonstrated in this review, which summarises current understanding of their potential for use in medicine. We discuss their proven effectiveness in treating a variety of illnesses, such as antibacterial, antiviral, anticancer, and anti-inflammatory uses. The emphasis is on studying their molecular mechanisms of action and clarifying the structure-activity correlations that control their pharmacological effects. Along with discussing current developments in synthetic approaches, we also draw attention to the opportunities and difficulties involved in turning these chemicals into pharmaceuticals that are therapeutically viable. For researchers looking to investigate the possible therapeutic uses of thiazolidinone derivatives, this review attempts to offer a succinct yet thorough resource.Heterocyclic systems are found in many medications and physiologically significant compounds. A unique class of heterocyclic compounds with a wide range of biological activity is thiazolidinone. Numerous researchers have been interested in investigating this skeleton's numerous potentials against various activities because to the diversity in the biological response profile. The spectrum of actions is expanded when various functional groups are successfully added to the basic thiazolidinone ring. The most significant derivative of thiazolidinone is 4-thiazolidinone. It has a substituent in positions two, three, and five and a carbonyl group at position four. In order to determine the future prospects of thiazolidinone derivatives in the medical area, this study focusses on the different biological activities of these compounds from previous studies and review efforts.

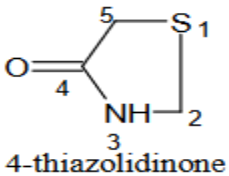
Keywords: Thiazolidinone, thiazolidine, anticancer, antitubercular, analgesic, anticonvulsant

Article History
Received: 12/03/2025
Accepted: 26/03/2025
Published: 10/04/2025

Introduction

A significant class of heterocyclic chemicals, thiazolidinones are thiazolidine derivatives that have been thoroughly investigated for their potential medical uses. Sulphur and nitrogen atoms are located at positions 1 and 3, respectively, while carbonyl groups are found at positions 2, 4, or 5 of thiazolidinones. Nonetheless, its derivatives are among the most researched compounds and offer a variety of medicinal

properties. The derivatives 1, 3-thiazolidin-4-ones, which contain nitrogen and sulphur atoms at positions 1 and 3, as well as a carbonyl group at position 4, have been the focus of much research in recent years.[1]



4-thiazolidinone

The molecular weight of the 4-thiazolidinones is typically 103.139g/mol, and they have a melting point of 42–44°C. The melting point is lowered when an alkyl group is attached to a nitrogen atom. Water dissolves 4-thiazolidinone without any aryl or higher alkyl groups acting as substituents. There have been reports of several geometrical and optical isomers of 4-thiazolidinone. Among the many therapeutic uses of the 4-thiazolidinone scaffold are anti tubercular, anti-inflammatory, anticonvulsant, antibacterial, antiviral, antipsychotic, and anticancer properties.

The global population is at risk due to the rising incidence of infectious diseases. It has been widely documented that the presence of arylazo, sulfamoylphenylazo, or phenylhydrazono moieties at various positions along the thiazolidinone ring has increased antimicrobial activity. These moieties also have intriguing properties such as antihistaminic agents, bacterial enzyme inhibitors, cox-1 inhibitors, and non-nucleoside inhibitors of HIV type 1 reverse transcriptase (HIVRT). Several publications highlighting their medical properties have been published in the literature. Anders et al. claim that 4-thiazolidinones may be regarded as phosphate bioisosteres and, as such, exhibit antibacterial activity by inhibiting the bacterial enzyme involved in the formation of the cell wall's peptidoglycan layer. Since mycobacterial cell wall formation depends on rhamnose, which is absent from humans, several thiazolidinone have recently been described as novel inhibitors of mycobacterial rhamnose enzymes. These inhibitors are supposed to be selective.[2]

A number of substituted thiazolidinones have been discovered to have hypnotic, hypolipidemic, antitubercular, anthelmintic, analgesic, anti-inflammatory, anticancer, and anti-diabetic properties. Some thiazolidinone compounds were also discovered to exhibit cardiovascular action. The variety of biological action prompts investigation into this heterocyclic compound's potential against a range of activities. This article provides a concise overview of the thiazolidinone scaffold's numerous biological and pharmacological properties. Thiazolidinone nuclei are found in the structures of medications such as etozoline, ralitoline, and epalrestat.

MECHANISM OF ACTION OF THIAZOLIDINONE COMPOUNDS

The diverse range of actions of thiazolidinone derivatives results in several mechanisms of action. By preventing fungus mycelia from growing, it can have antifungal effects. Thiazolidinone's anti-inflammatory effect is brought about via its suppression of COX-2. The synthesis of DNA in cancer cells can be inhibited by some thiazolidinone derivatives. Certain thiazolidinone derivatives have anti-HIV properties and function as non-nucleoside inhibitors of HIV type 1 reverse transcriptase.

BIOLOGICAL ACTIVITIES OF THIAZOLIDINONE DERIVATIVES; A REVIEW

Tumul Srivastava et al. synthesised 1-thia-azaspiro[4]alkan-3-ones and 1-thia-4,8-diazaspirodecan-3-one, which were screened against M. tuberculosis using the Microplate Alamar Blue Assay (MABA) on a High Throughput Screening machine at 25 µg/ml and lower concentrations using M. tuberculosis H37Ra as a stand-in for the virulent H37Rv strain. The MABA results have been shown to be similar to those of a standard system-based test. The common antitubercular medications ethambutol, ethionamide, para aminosalicyclic acid, isoniazid, and rifamycin were used as positive controls.[3]

Jaju and colleagues synthesised iso-nicotinylhydrazide derivatives and used the Almar-blue susceptibility test to screen for in-vitro antimycrobacterial activity against M. tuberculosisH37rv. As demonstrated by the fact that compounds lacking any substitution on the aromatic ring exhibited no action, they discovered that different substituents on the aromatic ring of 4-thiazolidinone significantly impacted the

International Journal of Pharmaceutical Drug Design (IJPDD)
Website: https://ijpdd.org/
ISSN: 2584-2897
Vol. 2, Issue 4, April, 2025
Page No.: 136-142

antitubercular activity. It was discovered that the aromatic ring substituted compound's hydroxyl and methoxyl groups (fig. 1) were more active.[4]

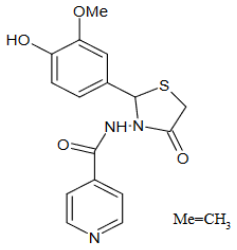


Fig.1, Thiazolidinone derivative 1

Growing Mycobacterium TB secretes protein tyrosine phosphatases A (MptpA) and B (MptpB) into the host cell, which selectively demonstrate a target for tuberculosis treatment.

Vintonyak et al. created a brand-new class of indoline-2-one-3-spirothiazolidinones as powerful and specific MptpB inhibitors. The phenyl substituent alteration on the thiazolidinone and 2-indolinone positions was examined. Moreover, halogen substitution boosts the activities.[5]

Babaoglu et al. sought to identify novel inhibitors of the enzymes in the biosynthesis pathway and demonstrated the activity of 4-thiazolidinone against M. tuberculosis by inhibiting dTDP-rhamnose production.[6]

Zitouni et al. reported synthesising derivatives of N-pyridyl-N'-thiazolylhydrazine. The compound below (fig. 2) exhibited strong antitubercular activity; its structure demonstrated that whereas 3-pyridyl and 4-pyridyl groups were detrimental to activity, 2-pyridyl and 2-hydroxyl-5-methoxyphenyl groups were necessary for antimycobacterial activity. [7]

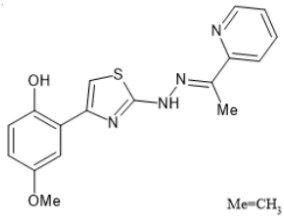


Fig.2, Thiazolidinone derivative 2

In the 2-[3-methyl-2,6-substituted-4-hydrazono] series Regarding acid-resistant mycobacteria, -1,3-thiazolidin-4-one (fig. 3) shown greater activity than mycobacteria of the human type strain, and only a small number of the synthesized compounds exhibited activity that was comparable to that of rifampicin.

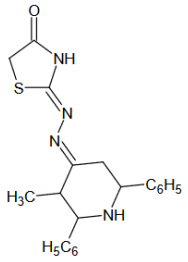


Fig.3, Thiazolidinone derivative 3

2. Anti-inflammatory and analgesic activity

A biological reaction to damaging stimuli, inflammation is associated with numerous pathophysiological disorders. Macrophages respond to inflammatory stimuli by releasing cellular defence chemicals and anti-inflammatory substances like nitric oxide. Since the COX enzyme catalyses the manufacture of PGs and thromboxan from arachidonic acid, aryalkanoic acids are the building blocks of the commonly used NSAIDs naproxen and ibuprofen. This medication's manner of action causes undesirable side effects. A new compound (fig.4) that was substituted with a chloro group at the second position of the phenyl ring demonstrated nearly equal anti-inflammatory activity to that of phenylbutazone at 50 mg/kg. Kumar et al. reported new quinazolinone derivatives with thiazolidinone at the second position to address the issues of anti-inflammatory and analgesic activity.[8]

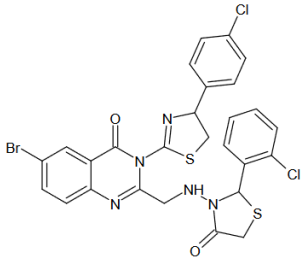


Fig.4, Thiazolidinone derivative 4

Biphenyl-4-carboxylic acid 5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl amide derivatives shown strong anti-inflammatory properties in a different investigation. Bromine substitution on both aromatic rings of compound (fig. 5) resulted in percentage inhibitions of 44.5 and 55.73. [9]

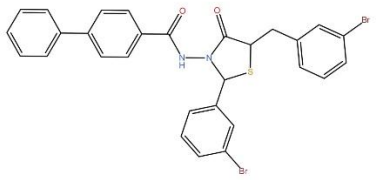


Fig.5, Thiazolidinone derivative 5

As an anti-inflammatory, Sparatore F. synthesised aromatic Schiff base and derivatives of 2, 3-disubstituted-1, 3-thiazolidine-4-one. While only moderate activity was seen in the writhing test in mice, both types of drugs demonstrated good levels of action against carrageenan-induced oedema in the rat hind paw.[10]

Ottana et al. looked into 3,3-(1,2-ethanediyl)-bis [2-aryl-4-thiazolidinone] derivatives, which had intriguing stereo-selective analgesic and anti-inflammatory properties. They also hypothesised that these compounds interact with the inducible COX-2 isoform. The 5-arylmethylidene moiety is absent from 3-[2-(4-methylphenyl)-2-oxo-1-phenylethyl] Its anti-inflammatory and analgesic properties were also improved by -2, 4-thiazolidinedione (fig. 8).[11]

The ability of 2-aryl-3-{5-[([1,3,4]thiadiazino[6,5-b]indol-3-ylamino)methyl] to reduce inflammation Thiadiazol-2-yl-1,3,4 Rat paw oedema produced by carrageenan was used to study -1,3-thiazolidin-4-one.[12]

Newbold investigated 2-[(butoxycarbonyl) methylene]-4-thiazolidinone's anti-inflammatory properties. It was discovered that the chemical had no effect on the majority of acute inflammatory models. It avoided the development of secondary lesions in the rat that received an adjuvant injection in the footpad and partially suppressed the oedema caused by carageenan.[13]

Amin and colleagues synthesised a number of spiro [(2H, 3H) quinazoline-2, 1'-cyclohexan]-4(1H)-one derivatives. These substances' analgesic, ulcerogenic, and anti-inflammatory properties were assessed. Compounds that have a 2-thiophene substitution at thiazolidinone's C-2 have demonstrated the strongest anti-inflammatory and significant analgesic effects.[14]

3. Anticonvulsant & antipsychotic activity

The ability of various series of 2-(arylimino)/(arylhydrazono)-3-aryl/(alkylaryl)/furfuryl/2-pyrimidyl/cycloalkyl/(3-(N-morpholin-4-yl-propyl) to cause seizures When administered at a dose of 100 mg/kg, 4-thiazolidinones have been shown to prevent seizures in albino mice of both sexes caused by pentylenetetrazol. The majority of the substances were found to be protective against seizures caused by pentylenetetrazol, with protection levels reaching 80%.[15]

Archana kumar has developed a novel thiadiazolyl and thiazolidinonyl quinazolin-4-(3H)- ones in 2002. The substances were tested for anticonvulsant properties and contrasted with the common medications sodium valproate, lamotrigine, and phenytoin sodium. 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 was the most active of the 30 compounds.[16]

Strong antipsychotic and anticonvulsant properties can be found in several derivatives of substituted thiazolidinonyl carbazol. Compounds with a thiazolidinone ring exhibited stronger antipsychotic and anticonvulsant properties than those with an azetidinone ring [17]. A number of 3-[(3-substituted-5-methyl-4-thiazolidinon-2 ylidene)hydrazono]-indolinone derivatives (fig.6) are assessed for their potential to decrease central nervous system activity.[18]

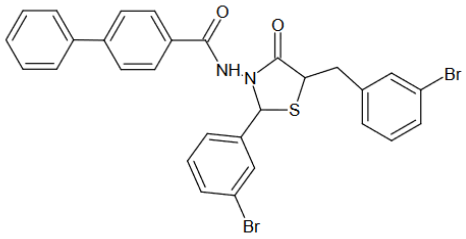


Fig.6, Thiazolidinone derivative 6

Structurally related to 3-[4-[4- (6-fluorobenzothien-3-yl)-1-piperazinyl]butyl]-2,5,5-trimethyl-4-thiazolidinone maleate, a series of piperazinyl butyl thiazolidinones were synthesised and tested in vitro for dopamine D2 and serotonin 5HT2 and 5HT1A receptor affinity. The compounds were also tested in vivo in animal models of possible antipsychotic activity and screened in models predictive of extra pyramidal side effect liability.[19]

4. Anticancer and anti proliferative activity

Through repeated library techniques, 10 cytoselective molecules have been discovered from 372 thiazolidinone analogues. With an IC50 ranging from 0.21 to 2.93 μM, these substances specifically destroyed the non-small cell lung cancer cell line H460 and its paclitaxel-resistant mutant H460taxR. At doses as high as 195 μM, they demonstrated significantly lower toxicity to normal human fibroblasts. Two hydrogen bond acceptors and three hydrophobic areas were suggested to be common properties in a pharmacophore derived from active compounds.[20]

Gududuru et al. investigated the potential cytotoxic effects of a number of 2-arylthiazolidine-4-carboxylic acid amides on prostate cancer. In PPC-1 cells, the compound exhibited 38-fold selectivity and an IC50 of 0.55 lM, making it the most potent and selective cytotoxic agent. The SAR analysis revealed that while potency rose with increasing chain length from C7 to C18, one additional carbon unit added to the alkyl chain resulted in a notable decrease in activity; hence, an alkyl chain with a C18 unit was ideal for thiazolidine analogue efficacy. While a derivative of a furanyl ring demonstrated comparable cytotoxicity, substituting an alkyl or cyclohexyl group for the phenyl ring decreased efficacy. A new series of 2-aryl-4-oxo-thiazolidin-3-yl amides was created by the same research team, and all of the produced compounds were tested against five human prostate cancer cell lines. According to their findings, adding an alkyl chain increased the antiproliferative activity whereas substituting an aryl group decreased the biological activity.[21]

Hafez et al. produced a number of substituted triazolo [4, 3] pyrimidin-6-sulfonamides with a thiazolidinone moiety integrated, and they documented their anticancer properties. The majority of the synthesised compounds were found to have moderate activity, and all 60 evaluated cell lines showed good growth inhibitory action. Indeed, it appears that the thienyl group at C-2 of thiazolidinone and the presence of 4-methylpiperazin/morpholine on C-5 are crucial for anticancer behaviour.[22]

The potential of several isatin-based thiazolidine conjugates (fig.7) as novel anticancer drugs has been studied due to their affinity for tyrosine kinases, cyclin-dependent kinases, and carbonic anhydrase isozymes. More activity was demonstrated by 1, 3-dihydroindol-2-one conjugates with 3, 5-diaryl-4, 5-dihydro pyrazolyne derivatives than by any of the thiazolidinone conjugates.[23]

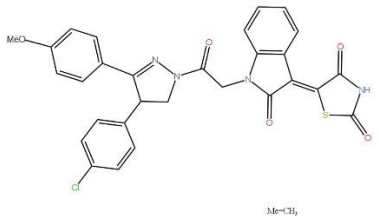


Fig.7, Thiazolidinone derivative 7

5. Antibacterial and antifungal activity

Thiazolidinones that have C-2 and N-3 substituted locations exhibit varying levels of antibacterial and antifungal activity. Multi-drug resistance microbial infections have become a major health concern due to their sharply increased incidence in recent decades. In order to increase the antibacterial and antifungal activity, nearly every location of 4-thiazolidinone has been investigated. Thiazolidinone derivatives' SAR investigations demonstrated that they work better against gram-negative bacteria than gram-positive ones. As a result, finding novel antimicrobial drugs will continue to be a significant and difficult endeavour for medicinal chemists.[24]

Liesen et al. reported 4-thiazolidinone derivatives made from ethyl (5-methyl-1-H-imidazole-4-carboxylate), and the compound's antibacterial and antifungal properties were assessed against a range of pathogens. According to the results, the investigated compounds have limited antibacterial and antifungal properties when compared to the common medications ketoconazole for antifungal activity and chloramphenicol and rifampicin for antibacterial activity.

Kocabalkanli and colleagues synthesised mannich bases of about 2, 5-disubstituted 4-thiazolidinones and assessed their antibacterial efficacy. They found that the least active compound contained a hydrogen atom in lieu of chlorine and a morpholine in place of pyrrolidine, while the most active compound had a methyl and a pyrrolidino methyl at the fifth position of the thiazolidinone (fig.8), as well as a p-chlorophenyl group on the oxadiazole.

International Journal of Pharmaceutical Drug Design (IJPDD)
Website: https://ijpdd.org/
ISSN: 2584-2897
Vol. 2, Issue 4, April, 2025
Page No.: 136-142

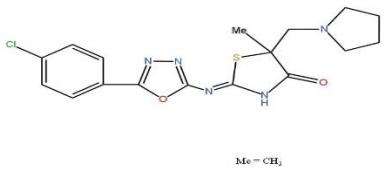


Fig.8, Thiazolidinone derivative 8

Additional 2-phenyl-3-(4,6-diarylpyrimidin-2-yl)thiazolidin-4-one analogues have been synthesised by Gopalakrishnan et al. and evaluated for antibacterial activity against Salmonella typhi, E. Coli, Pseudomonas aeruginosa, vibrio cholera, and Staphylococcus aureus. The standard medication used was ciprofloxacin. The findings showed that the p-(OCH3) and p-(CH3) groups at the phenyl ring connected to the pyrimidine ring have potent antibacterial properties.

6. Antiviral and cytotoxic activities

A series of 2-Substituted-3-[(coumarin-4-oxy) acetamido] thiazolidin-4-one has been synthesised by Omaima Mohamed AbdElhafez et al. The compounds' antiviral activity against Herpes simplex type 1 (HS-1) cultured on Vero African green monkey kidney cells was evaluated using cytotoxicity and antiviral assays. Every chemical showed some degree of cytotoxicity. Phenyl-2-(4-chloro)-3-[(coumarin-4-oxy) acetamido] At 0.12 mg/m, thiazolidin-4-one, which has the highest activity of any of the chemicals in this investigation, was able to lower the amount of plaques by 30%.

The antiviral activity of 1,3-thiazolidin-4-one derivatives produced by Ravichandran et al. against Herpes simplex virus-1, Herpes simplex virus-2, Influenza A subtype, and Influenza B was assessed (fig.9).

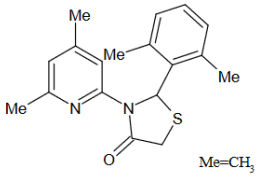


Fig.9, Thiazolidinone derivative 9

CONCLUSION

Clinically used medications do not include the strength of the 4-thiazolidinone nucleus. Other possible activities need to be investigated, even if the four main areas of therapeutic application are antibacterial, anti-inflammatory, antitubercular, and anticancer. Although the majority of the locations were investigated to enhance 4-thiazolidinone's antibacterial and antitubercular characteristics, none of the derivatives shown encouraging therapeutic action. The type and location of the substituents at the aryl moiety connected to the thiazolidinone ring determine the compounds' activity. Hence additional inquiry in this field may provide significant results. Regarding the potency and structure activity relationship (SAR) of the described compounds, no consensus has been reached. Therefore, more research in this area could be very fruitful. These findings emphasise the significance of the nucleus. However, since 4-thiazolidinone has a variety of derivatives, there is a lot of potential in this interesting molecule. According to the literature, 4-thiazolidinone offers a variety of possible uses, and researchers are interested in its simple synthesis methods. The report's primary relevance and justification centre on investigating the biological activity investigations of thiazolidinone derivatives, which will support the reviewers' work in the field.

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.

*****