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Chemical properties, synthetic methods and biological activities of thiazolidinone derivatives

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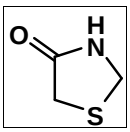
Abstract
Several thiazolidinone derivatives have been possessed considerable biological activities such as antibacterial, antitubercular, anthelmintic, anti-inflammatory, anticonvulsant, hypnotic, cardiovascular, anticancer, antifungal, antiviral, antihistaminic, and other anticipated biological activities. Nowadays world scientists are worried and trying to develop and discover new synthetic methodologies for synthesizing new thiazolidinone compounds with useful diverse biological activities.

Keywords: thiazolidinone derivatives, biological activities, synthesis

Introduction
Thiazolidinone moiety possesses several biological activities and it is an essential precursor for antimicrobial agents even many other useful applications [1, 2]. In recent years, a great increase in research of preparations, reactions, and the physiological activities of these compounds. The 4-thiazolidinone is a useful moiety for a variety of heterocyclic products including drugs [3, 4], dyes, and intermediates such as thiazol yellow, thioflavin T., thidiazuron [5], the uses of this class of chemicals (4-thiazolidinone derivatives) are as herbicides [6], insecticides [7, 8], etc. The thiazolidinones moiety is also associated with a broad spectrum of biological activities including antibacterial [9, 10], antifungal, anti-inflammatory, hypnotic, anticonvulsant, antitubercular, antiviral, antihistaminic, anthelmintic, cardiovascular, and anticancer. Several 4-thiazolidinones derivatives were investigated for their inhibitory effects on the oxidation of the substrates of the tricarboxylic cycle and β-hydroxybutyrate by rat brain homogenates for respiratory activity [11]. These observations served as the extension of investigation in the field of synthesis of 4-thiazolidione derivatives in the hope of discovering compounds with good pharmacological properties. The research activity is yet to find in this vast and interesting area of study; much more needs to be done and achieved. The synthesis and chemistry of 4-thiazolidinones using nonconventional, environment-friendly procedures are investigated.

Chemistry of 4-thiazolidinone
The4-thiazolidinone (1) is a derivative of thiazolidine (2) with a carbonyl group at the 4th position which belongs to an important group of heterocyclic compounds.



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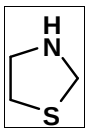


(2)

The methylene carbon atom at the fifth position of 4-thiazolidinone possesses nucleophilic activity and attacks an electrophilic center. The reaction product loses water, forming a 5-unsaturated derivative of the 4-thiazolidinone. The reaction occurs in the presence of a base and the anion of the 4-thiazolidinone is the attacking species [12]. The ease of formation of the anion and hence the degree of the nucleophilic activity is dependent not only on the electron-withdrawing effect of the adjacent carbonyl group but also on the presence of other electron-withdrawing groups such as those attached to the second carbon atom [13]. The electron attraction of sulfur of 2-thione group is greater than that of the oxygen of a 2-carbonyl group. The nucleophilic activity of 5-methylene carbon atom of 2-aryl-4-thiazolidinone or 2-arylimino-4-thiazolidinone should be influenced by the nature of the substituents attached to

the aryl group.The mobility of the hydrogen atoms in the methylene group depends much upon the electro-negativity and co-planarity of substitution on the exocyclic nitrogen. The aldehydes, react only on one 4-thiazolidinone moiety to give the corresponding 5-unsaturated products. The condensation of aldehydes with 2-alkylor-aryl-4-thiazolidinones does not occur due to acetic acid and sodium acetate, possibly because of the decreased reactivity of the methylene group. The reactivity is increased due to the presence of imino or thioxo groups at the second position at 4-thiazolidinone. Three components substituted aromatic amines, substituted aromatic aldehydes, and a mercapto acid are used to synthesize 4-thiazolidinone derivatives. These processes can be conducted in two ways, one step and two-step reactions [14, 15]. The analogs of 4-thiazolidinone moiety were synthesized by various conventional methods like condensation with aldehydes, with nitrous acid and nitroso compounds, with diazonium salts, with diphenyl fomnamidim, with orthoesters, with sodium, substituted benzoyl chlorides with various 2-thiono-4-thiazolidinones, phthalic anhydride undergoes condensation at 5th position of various 2-substituted imino-4-thiazolidinones in acetic anhydride and triethylamine.

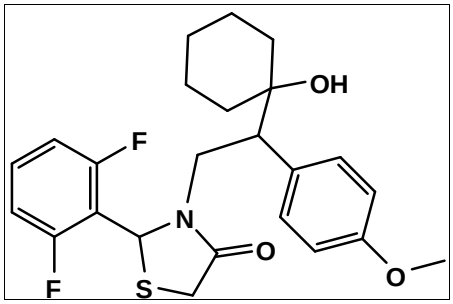
Several microwave-assisted condensation reactions such as aldol and Knoevenagel etc. have been accomplished using relatively benign reagents such as ammonium acetate. The conventional preparation of imines, amines, nitroalkenes, and *N*-sulfonylimines involves the azeotropic removal of water from the condensation reaction intermediates that are usually catalyzed by toluene sulphonic acid, titanium (IV) chloride. The aldol condensation was the first reaction of this type to be investigated. The reaction was performed with rhodanine and benzaldehyde or acetaldehyde, using sulfuric acid as the condensing agent [16-20].

Biological activities of thiazolidinones

Several thiazolidinone analogs have been reported to show considerable biological activities as antibacterial, antifungal, anti-inflammatory, anticonvulsant, hypnotic, antitubercular, anthelmintic, cardiovascular, anticancer, antiviral, and antihistaminic. The details of some important activities of thiazolidinones were reported.

Antibacterial activity

Somethiazolidinones were more active than thiazoles against some common bacteria [21]. Some thiazolidinone derivatives were tested against *Bacillus subtilis* and *Escherichia coli,* some compounds were exhibited more activity than reference drugs. This significant inhibitory activity can be attributed to fluorine atoms and has been observed in thiazolidinone derivatives with different positions, 2-(2, 6-Difluoro-phenyl)-3-[2-(1-hydroxycyclohexyl)-2-(4-methoxyphenyl)-ethyl]-4-thiazolidinone (3) [22]. Several 4-thiazolidinones, Pyrazin-2-yloxy)-acetic acid [3-(4-ethoxy-phenyl)-4-oxothiazolidin-2-ylidene]-hydrazide (4) were synthesized and used for their antibacterial studies against different strains like *S. aureus, B. subtilis, S. typhi, and E. coli* of bacteria and were found to have significant antibacterial activity. The presence of thiazolidinone ring was essential for antibacterial activity [23]. The functional groups of organic molecules' relationship with thiazolidinone proved the importance of basic precursor (thiazolidine).



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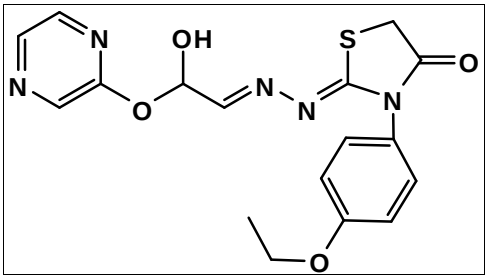
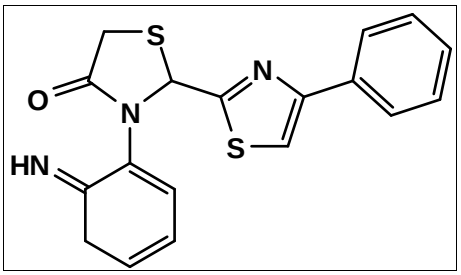


(**4**)

This antimicrobial activity attracted the attention and synthesized novel 4-thiazolidinone derivatives of 6-chloro-1-oxo-2, 3a, 8, 9-tetrahydro-1*H*-thiazolo [3, 2-a] quinoline-7-carboxaldehyde and evaluated as antimicrobial activity [24]. Several 4-thiazolidinone derivatives were screened *in vitro* against different bacterial strains *E. coli B. subtilis and B. megaterium* [25]. Some derivatives of 4-thiazolidinone were prepared and reported considerable biological activity [26].

Antifungal activity

The antifungal activities against *A. niger* at different concentrations of few compounds of 2-thioxo-4-thiazolidinone have been studied [27] and significant antifungal activity has been reported [28] against *B. allii* and *A. tenius* of 4-oxo-2-thionothiazolidine derivatives. Various 2-[(methylphenyl) imino]-3-hydroxy-phenyl-thiazolidin-4-ones and other 4-thiazolidinone analogues, 2-(4'-phenylthiazolyl-2'-imino)-3-phenyl-4-thiazolidinones (5) were evaluated for antifungal activity against different fungal strains. Maximum inhibition of spore germination of *A. tenius* was found by (Z)-2-(4-chlorobenzo[*d*]thiazo-2-ylimino)-3-ethyl-5-methylthiazolidin-4-one and (Z)-2-(5-chlorobenzo[*d*]thiazol-2-ylimino)-3-ethyl-5-methyl-thiazolidin-4-one [29].



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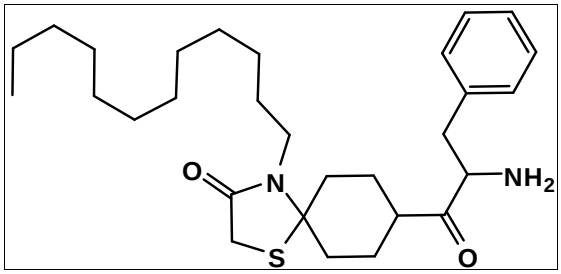

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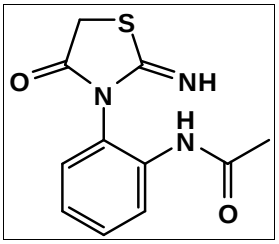
Compound 8-(2-Amino-3-phenyl-propionyl)-4-dodecyl-1-thia-4-aza-spiro [4.5] decan-3-one (06) and its derivatives were prepared and screened [30] against two strains of *C. albicans* and one strain of *C. neoformans* and found that the antifungal activity was of average to a higher level against the various fungal strains. Various derivatives of thiazolidinone using microwave and screened it for antifungal activity. Three fungal strains, namely *R. solani*, (causing root rot of okra), *C. capsici*, (causing leaf spot), and *F. oxysporum*, (causing wilt of mustard) were used in this screening and it was seen that the prepared derivatives showed significant antifungal activity against different fungal strains under test. The addition of thiazole ring increased the antifungal activity of these synthesized substances [31].

Antitubercular activity

Several 4-thiazolidinone derivatives are possible antitubercular substances [32]. Some derivatives of rhodanine have proven to exhibit antitubercular activity with minimum toxic effects [33, 34] and few 4-thiazolidinone analogs regarding tuberculostatic effects [35]. Some derivatives inhibited the growth of *H37Rv* strain, in a particular dilution *i.e* 12.5 µg/mL [36]. Similarly, various thiazolidinone derivatives have been reported to be the cause of inhibition in the growth of *the H37Rv* strain [37]. The activities of some thiazolidin-4-one containing compounds on other Mycobacterium strains havewere found very good activities [38].

Anthelmintic activity

Several derivatives of rhodanine studied were found to be important anthelmintic activities against *Hymenolepsis nana* and *Syphacia obvelata* infections in mice, *Asceridia galli* infections of chickens, *Uncinaria stenocephala* infection in horses, *Toxocera canis* in dogs and *Ancylostoma caninum* infection in pigs [39]. The derivatives of 4-thizolidinone, 2-imino-3-(2-acetamidophenyl)-4-thiazolidinone (7) were very effective anthelmintic agents particularly against horse strongyloids [40]. Some derivatives of 4-thiazolidinone, rhodanine, and psedothiohydentine showed very good anathematic activity [41]. They showed not only anthelmintic activity alone but were also effective as an anti-inflammatory and antibacterial agents. The compound 3-methyl-5-[(4- nitophenyl)azo] rhodanine (8) acts as potent anthelmentic activity [42] and 2-thiono-3-(4-chlorophnyl)-5-[(4-(4-methylpiperazino)phenyl] azo-4-thiazolidinone possessing anthelmentic activity against *N. dubius* in mice [43].



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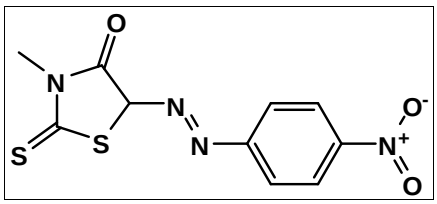
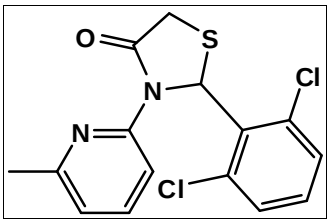


(**8**)

Antiviral activity

Some thiazolidinones like 2, 5-diphenyl-1, 3-thiazolidin-4-one was showed to have high efficacy in inhibition of various viruses (HIV-1) with minimum cytotoxicity. Theyact by inhibiting reverse transcriptase enzymes. The multifunctional ability of enzymes plays an important role in the human immunodeficiency virus (HIV). Some 4-thiazolidinones, 2-(2, 6-dichloro-phenyl)-3-(6-methyl-pyridin-2-yl)-4-thiazolidinone (9) were found good anti-viral effects [44].Few thiazolidinones with furfuryl amine and used as antiviral agents. These derivatives 2,3-diaryl substituted 4-thiazolidinone, 3-substituted 2-(2,6-dichlorophenyl)-3-(6-methylpyridin-2-yl)-1,3-thiazolidin-4-one and 2-(2,6-dichloro-phenyl)-3-furan-2-ylmethyl-4-thiazolidinone (10) showed promising HIV-RT inhibitory activity by determining their ability to inhibit the replication of HIV-1 (IIIB) in MT-4 cells with EC50 value of 0.204 mM [45].



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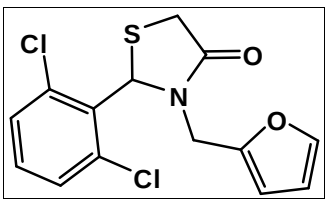
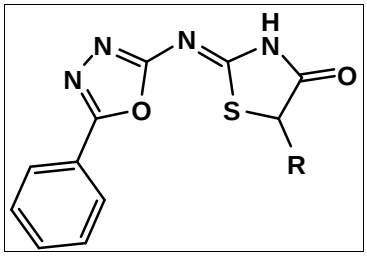


(**10**)

A series of 4-thiazolidinone analogs were screened for various biological activities like antibacterial activity (11), antimycobacterial activity (12), (13), and antiviral activity (14). These derivatives were also employed against various bacteria, fungi and virus strain to determine the efficacy or ability to inhibit their growth and found very promising [46].



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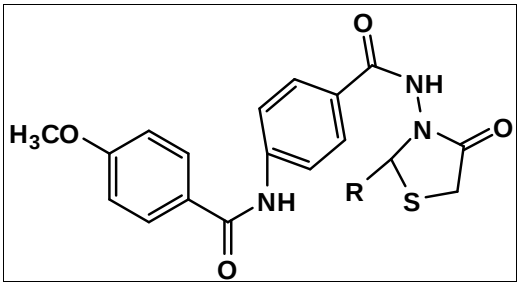

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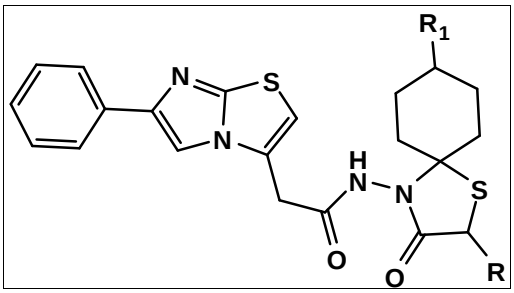

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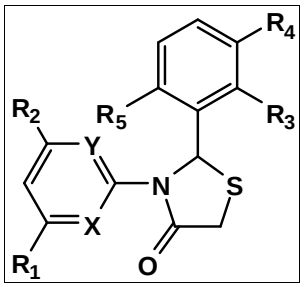
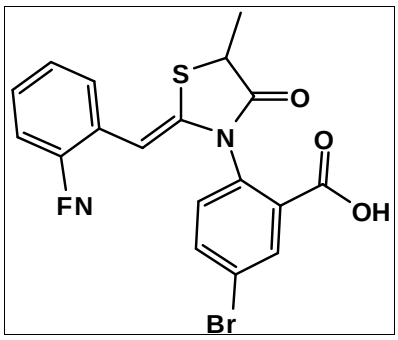


(14)

Anti-inflammatory activity

The 4-thiazolidinone derivatives were used as anti-inflammatory agent. The 2-(2-(4-oxo-2-pentylthiazolidin-2-yl) ethyl)-2-pentylthiazolidin-4-one and other derivatives were good analgesic and anti-inflammatory agents [47]. The 2-imino-4-thiazoli-dinones and 5-amino-2-(3-hydroxyphenyl) thiophen-3(2*H*)-ones were showed promising anti-inflammatory activity [48, 49]. The potency of 5-bromo-2-(2-(2-flourophenyl)-5-methyl-4-oxothiazolidin-3-yl) benzoic acid (15) derivatives were showed good anti-inflammatory activity equal with reference drug, phenylbutazone [50]. Theanti-inflammatory activity of 2-amino-5-(3-hydroxyphenyl)-1, 3-thiazolidin-4-one was shown [51] and most derivatives showed considerable anti-inflammatory activity in rats. The (2*Z*, 5*Z*)-5-(4-methoxycyclohexa-2, 4-dien-1-ylidene)-2-(phenylimino)-3-propyl-1, 3-thiazolidin-4-one (16) was showed very good paw edema inhibition as compared with indomethacin. Thus, the compounds of 4-thiazolidinone and thiazole were found to show a high level of anti-inflammatory activity [52].



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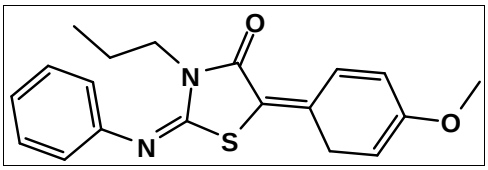

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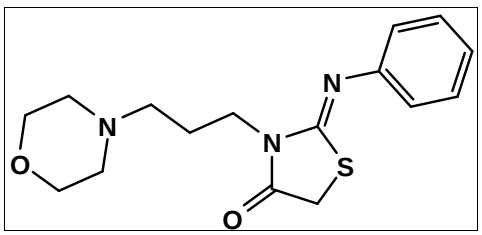
Anticonvulsant activity

Anticonvulsant studies of various thiazolidinone derivatives of 2-(arylhydrazono) / (arylimino)-3-aryl/furfuryl/2-pyrimidyl/(alkylaryl)/(substitutedamino)/cyclo-alkyl/(3-(N-morpholin-4-yl-propyl)-1,3-thiazolidin-4-oneswere evaluated against pentylene-tetrazol (PTZ) induced seizures at dose of 100 mg/kg in albino mice. Most of the compounds were found to exhibited protection against PTZ-induced seizures and the degree of protection ranged up to 80% [53-56].

Hypnotic activity

Some 3-(3-(N-morpholin-4-yl-propyl)-2-(arylimino)-4-thiazolidinones (17) and 2-(arylimino)-3-(pyrimidin-2-yl)-4-thiazolidinones (18) were evaluated for their ability to potentiate pentobarbital-induced hypnosis in mice at a dose of 100 mg/kg. All thiazolidinones were found to potentiate pentobarbital sleeping time [57, 58].



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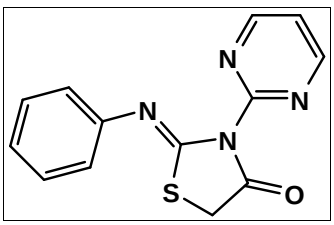
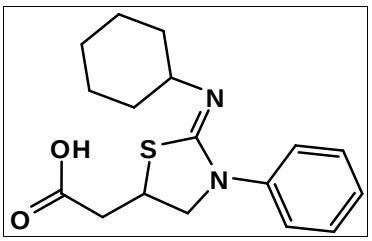


(**18**)

Cardiovascular effects

The cardiovascular effects of different thiazolidinone analogs like [(2*Z*)-2-(cyclohexylimino)-3-phenyl-1, 3-

thiazolidin-5-yl] acetic acid (19) analogs induced hypotension of different levels [59] and the time of this hypotensive activity was less than 15 minutes. The analogs of 4-thiazolidinone induced different cardiovascular effects that depended on the substituents attached with the basic skeleton of thiazolidinone. The analogue, 3-(3-(((benzo[*d*] [1, 3] dioxol-4-yloxy) methyl) (methyl) amino) propyl)-2-(3, 5-di-*tert*-butyl-4-hydroxyphenyl) thiazolidin-4-one (20) was showed positive effects on the myocardial oxygen consumption and the cardiac function in dogs [60].



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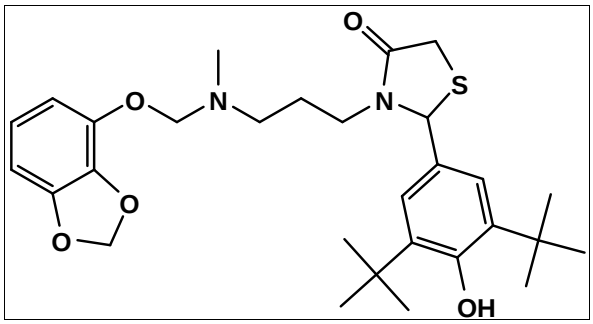

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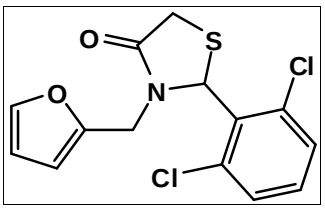
Anticancer activity

A series of 2-aryl-4-oxo-thiazolidin-3-yl amides and derivatives were evaluated for their ability to inhibit the growth of prostate cancer cells [61]. The COX-2 inhibitors as potential drugs for the prevention and treatment of cancer, especially colorectal cancer. Some 2-phenylimino-4-thiazolidinones have been investigated as potent inhibitors of the growth of human colon carcinoma cell lines with a different COX-2 expression. The antiproliferative *in vitro* screening was performed on five cell lines of human colon cancers, such as *DLD-1* [62], HCT-116 [63], *HT-29*[64], *HCT-8* [65], and *H-630* [66], obtained from the American Type Culture Collection (Manassas, VA); among them, *HT-29* cell line expresses high COX-2 levels [67]. Derivative 5-(3-trifluoromethyl benzylidene)-2, 4-thiazolidinedione which does not interact with COX enzymes, inhibited the growth of HT-29 cells. This compound displayed activity on all cell lines, mainly on the DLD-1 [68].

Antihistaminic activity

The antihistaminic activity of substituted 4-thiazolidinones. The substitution of hydrophobic molecules at the benzene ring and the combined effect of negative polar on overall compound increased the efficiency of antihistaminic activity [69, 70]. A series of 4-thiazolidinone derivatives, 2-(2, 6-difluoro-phenyl)-3-(3-dimethylamino-propyl)-4-thiazolidinone (17) and their inhibition ability to the specific quantity applied on pig antihistamine because the compounds were showed excellent results [71]. Some thiazolidinones, 3-{3-[3-(dimethylamino) propyl]-4-oxo-1, 3-thiazolidin-2-yl} benzamide (18) as free bases. These derivatives were used on guinea pig ileum and evaluated for their capability to inhibit the contractions by induced histamine [72]. The thiazolidinone is an essential moiety for antihistaminic drugs. The thiazolidinone analogs were found the application of cumulative hydrophobic effect in addition to antihistaminic activity [73].



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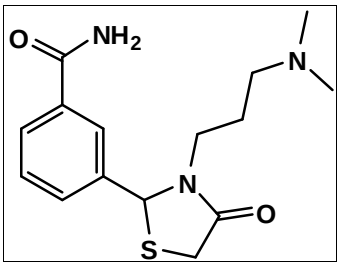

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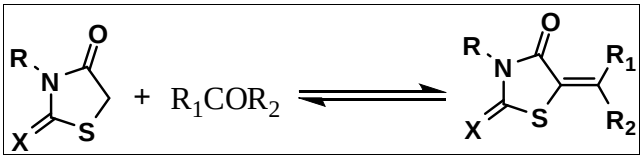
Synthesis of thiazolidinone

The thiazolidinone nuclei have diverse biological activities are found to be associated with thiazolidinone derivatives. The emphasis is being placed on synthesizing new derivatives with therapeutic properties in the quest for compounds that will show significant pharmacological efficiency. Synthesis of known thiazolidinone derivatives along with their various conventional methods is briefly reviewed below:

Aldol condensation

Aldol condensation reaction was the first reaction to be investigated. In this condensation, methylene group was treated with an aldehyde or ketone by loss of water. The product of the reaction was α, β-unsaturated carbonyl group, using sulfuric acid as condensing agent.

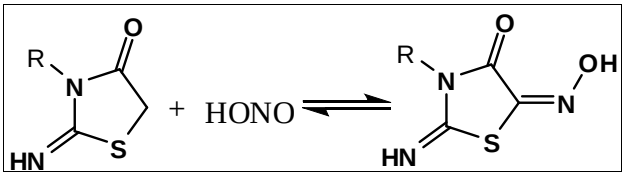


Acetaldehyde was one of the first aldehydes to be condensed with rhodanine and aliphatic aldehydes had been reported to be unsuccessful to condense with rhodanine in presence of sulfuric acid. Aliphatic aldehydes condense with rhodanine on refluxing for several hours in acetic acid solution [74, 75].

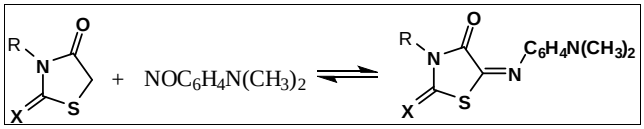
Reaction with nitrous acid and nitroso compounds

Pseudothiohydantoin on treatment with nitric acid gave a low yield of 5-oximino-pseudothiohydantoin. The same product was obtained by the action of nitrous acid, which was prepared by the reduction of nitric acid or by the addition of sodium nitrite to a hydrochloric acid solution of

the pseudothiohydantoin. 3-substituted derivatives of rhodanine were obtained with amyl nitrite135 or isopropyl nitrite and hydrochloric acid [76].

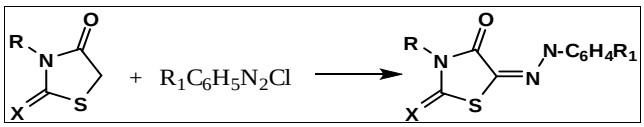


Aromatic nitroso compounds reacted with 3-substituted rhodanines and with 2-substituted-imino-4-thiazolidinones forming 5-arylimino derivatives [77].



Reaction with diazonium salts

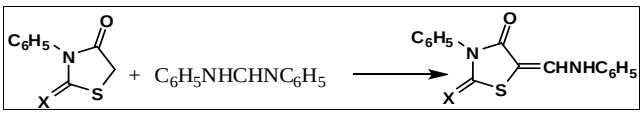
Coupled diazonium salts with 5-methylene group of rhodanine, 2, 4-thiazolidinediones, and 2-substitutedimino-3-substituted (or hydrogen)-4-thiazolidinones [78, 79].



Reduction of the phenyl-azo group of 2-arylimino-5-phenylazo-4-thiazolidinones with sodium hydrosulfite to yield the corresponding 5-amino-2-arylimino-4-thiazolidinones [80].

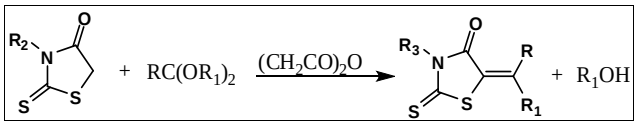
Reaction with diphenylfomnamidine

The electrophilic carbon atom of diphenylformamidine was attacked by the nucleophilic methylene carbon atom of rhodanines, 2, 4-thiazolidinediones and 2-substituted-imino-4-thiazolidinones [81]. The product was 5-anilinomethylene derivative was formed, if the same reaction ran in acetic anhydride then 5-Nacetanilinomethylene derivative formed. The ease of formation of the 5-anilinomethylene derivative depended on the nature of X**.** If X = S, the reactants heated in kerosene at 120°C for 1 hour, if X = O, heated for 3 hrs at 140-150°C, while if X = NC_6H_5, heated for 5 hrs at the same temperature.



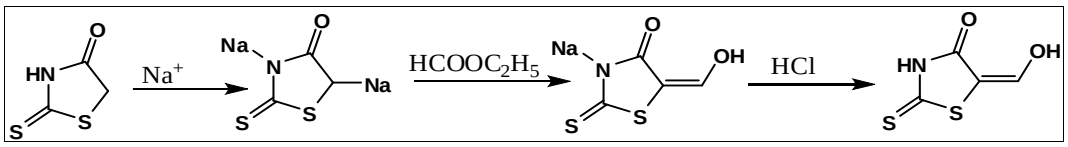
Reaction with orthoesters

Compounds containing an active methylene group reacted with orthoesters, with acetic anhydride being used frequently as a condensing agent. In acetic anhydride solution, rhodanine and 3-substituted derivatives are condensed with methyl or ethyl orthoformate, methyl or ethyl orthoacetate, and ethyl orthopropionate and form the *5-(*alkoxyalkylidene) derivatives [82].

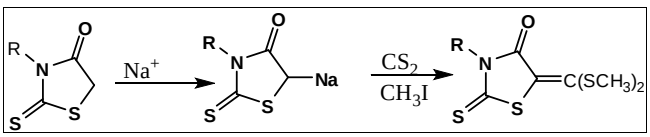


Reaction with sodium

The anhydrous ether solution rhodanine reacted with two moles of sodium. The product which would be a dianion, on condensation with ethyl formate and subsequent acidification forms 5-hydroxymethylene rhodanine. The reaction failed with 3-substituted rhodanine derivatives [83].



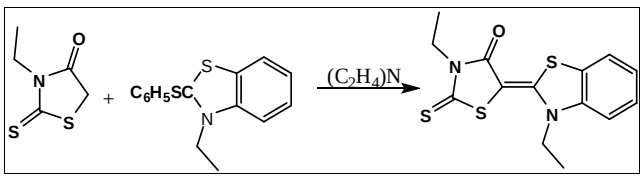
The sodium derivative prepared from 3-substituted rhodanine (35) was treated with carbon disulfide, followed by methyl iodide, to form a 5-di (methylthio) methylene-3-substituted rhodanine [84].



Reaction with electrophilic carbon atoms

Heterocyclic compounds with carbon atoms of electrophilic activity were condensed with the nucleophilic carbon atom of the 4-thiazolidinone nucleus in the presence of a base. The carbonyl and nitrogen portions of an amide group were in different heterocyclic nuclei and separated by one or more vinyl groups.

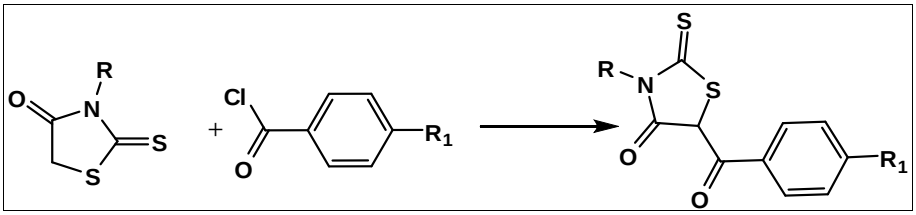
The heterocyclic quaternary ammonium salt with an active alkylthio or arylthio group attached to an electrophilic carbon atom reacted with the nucleophilic methylene groups of substituted rhodanines [85], 2, 4-thiazolidinediones, and 2-imino-4-thiazolidinones (or the isomeric 2-amino-4(5H)-thiazolons). Pyridine [86], triethylamine [87], and acetic anhydride with sodium acetate [88] were used as condensing agents.



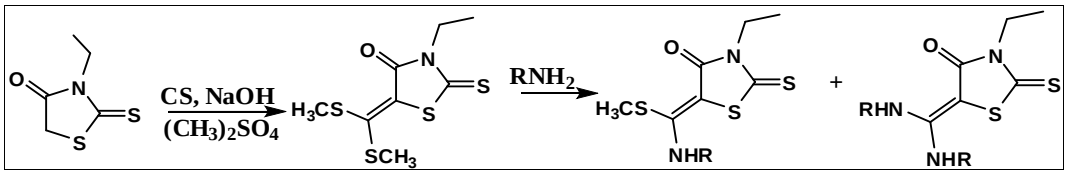
4-thiazolidinone derivatives prepared by other conventional methods

The2-thiazolylimino-5-arylidene-4-thiazolidinones and assayed *in vitro* for their antimicrobial activity against gram-positive and gram-negative bacteria, yeasts, and molds [89]. The studies with poly functionally substituted thiazolines and 1, 2, 4-triazolines: synthesis and chemical reactivity of 4-arylazo-2-isopropyloxy-2-thiazolin-5-ones and 4-arylidene-2-isopropyloxy-2-thiazolin-5-ones. Another method for the preparation of thiazolidinones was reported

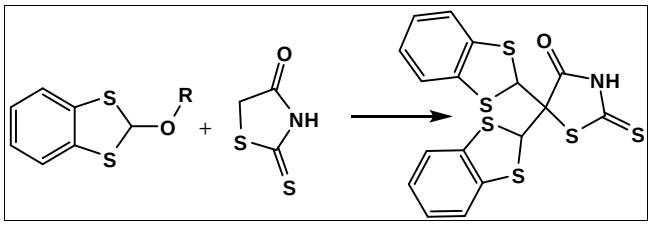
[90, 91]. The alkyl isothiocynate, ammonium thiocyanate, and thiocyanate with acetamide/hydrazide were used and finally, the mixture was treated with sodium acetate and ethyl bromoacetate. The synthesis of 4-thiazolidinones using starting material N-propyl-N-phenylthiourea, obtained by the reaction of propylamine and phenylisothiocyanate in chloroform at room temperature for 4 hrs followed by workup under acidic conditions. The reaction of substituted benzoyl chlorides with various 2-thiono-4-thizolidinones, giving 5-aroyl-4-thiazolidinones [92, 93].



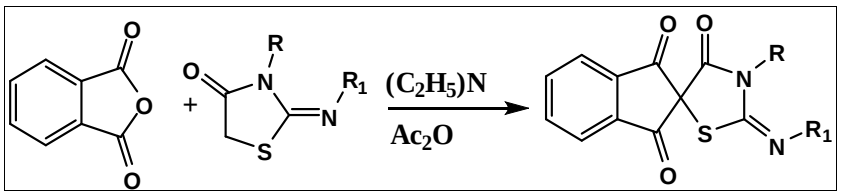
A reaction of 3-ethyl-2-thioxothiazolidin-4-one with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide, giving 3-ethyl-5-bis(methylthio)methylene]-2-thioxo-4-thiazolidinone.This treatment with nucleophilic reagents such as amines or active methylenes yields the corresponding replacement products of one or two methylthio group in good yields, respectively. The active ketone thioacetal group was reacted with active methylene compounds in the presence of K_2CO_3 in dimethyl sulfoxide [94].



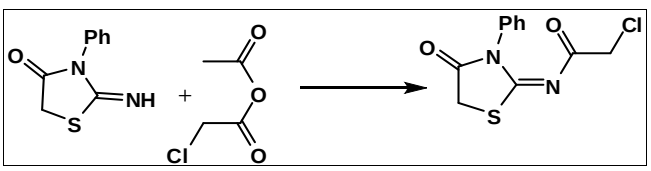
The introduction of cyclic dithioacetal functions into activated methylene compounds by treatment with 2-alkoxy-1, 3-benzodithioles. 5–bis(1, 3-benzodithiol-2-yl)rhodanine produced in high yields by the treatment of 2-(3-methylbutoxy)-1,3-benzodithiole with rhodanine in anhydrous acetic acid [95].



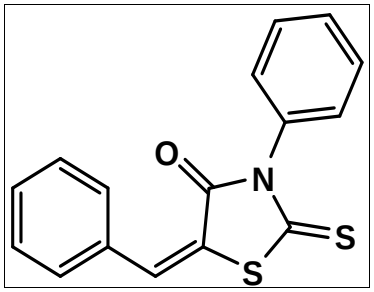
Phthalic anhydride undergoes condensation at 5-position of various 2-substituted imino-4-thiazolidinones in acetic anhydride and triethylamine to give 2-subtituted imino-5-phthalyl-4-thiazolidinones (52) [96].



The anhydride was treated spontaneously with 2-imino-3-aryl-4-thiazolidinones at room temperature to give N-chloroacetyl derivatives [97].



Different 2-thiono-4-thiazolidinones undergo aldol condensation reactions with a variety of aliphatic, aromatic, and heterocyclic aldehydes to give good yields of 5-unsaturated derivatives (23). The reactions were mostly carried out in the presence of anhydrous sodium acetate in benzene or acetic acid with reflux for 6-18 hrs [98]. Substituted 2-imino-4-thiazolidinones (24) was used to carry aldol condensation with ease in the presence of anhydrous sodium acetate in acetic acid refluxed for 8-10 hrs. A wide variety of aliphatic, aromatic and hetrocyclic aldehydes were reported to react with the 4-thiazolidinones [99-102]. The condensation where only one carbonyl group of acenaphthene quinone or its halogen derivatives at the 5-position of 2-imino-4-thiazolidinone (25) occur in hot acetic acid and similarly, isatin also condense only with one of its carbonyl groups at the position of various 2-imino-4-thiazolidinones and refluxed for 12 hrs [103]. Friedel-Craft reactions with 5-arylidene-4-thiazolidinones using benzene and anhydrous aluminum chloride. Amino methylation reactions of 2-aryl-4-thiazolidinones (26) and 4-thiazolidinediones with formaldehyde and amines by heating in alcohol [104].



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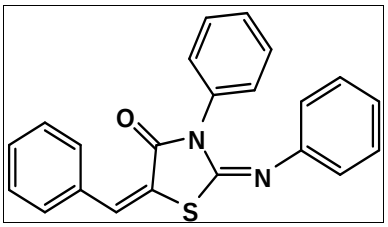

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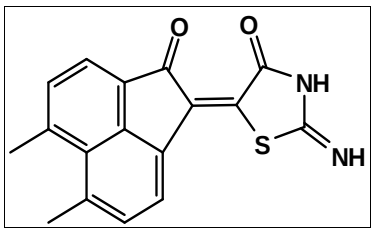

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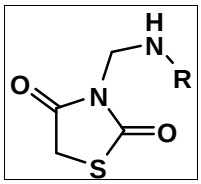
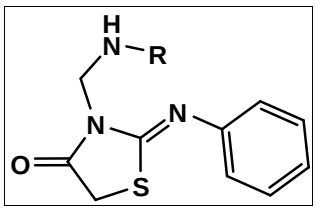


(26)

The 2-(Arylimino)-4-thiazolidinone 1, l-dioxides were treated with aromatic amines in the presence of paraformaldehyde and amine hydrochloride to give 2-(arylimino)-3-(substituted-aminomethyl)-4-thiazolidinonle 1, l–dioxides (27) [105]. Oxidized 2-(Arylimino)-3-substituted-4-thiazolidinones and 2, 3-disubstituted-4-thiazolidinoneasre (28**)** with KMnO4 in glacial acetic acid [106]. Seven thiazolidine and oxazolidinethiones in 35-80% yields by condensing thiones II with CIP (X1) R (OPh). Other reactions phosphorylation and thiophosphorylation of thiazolidine and oxazolidinethiones were also studied [107]. Thebis (aminothiazolyl) methanes (29) from dichloro diketones and RR_1NCSNH_2 and inhibitory activity of their hydrochlorides against acetyl cholinesterase was shown to be higher than that of the corresponding free bases [108].



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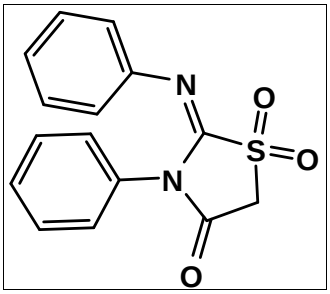

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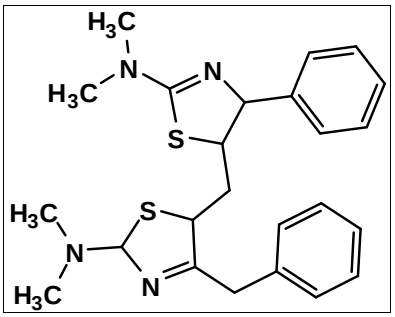
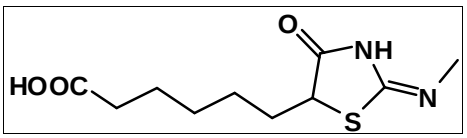


(29)

Thiazolidinone derivatives **(30)** by cyclo condensation of R_1NHC (NH_2) S with HO_2C $(CH_2)_5CHBrCO_2H$ and tested them for antitubercular activity. The activity of the compounds was enhanced with lengthening of the side chain in position 5 and in some cases the activity was doubled [109]. The synthesis of 2-Imino-3-(4-arylthiazol-2-yl)-thiiazolidin-4-ones and their fungicidal activity [110]. The synthesis (31) of 6-substituted imidazo [2, 1-b] thiazoles with a lactam ring connected, by means of a methane group, to the 5-position. The pharmacological results show that interesting cardiotonic activity is obtained when the lactam ring is pseudothiohydantoin or barbituric acid. Even the substituent at position 6 plays an important role in the pharmacological behavior of these compounds. The activity rank order was observed Ph > Me > Chlorine [111]. Some reactions involving thiazolidinone with phenyl isothiocyanate to give 2-imino-5-phenylcarboxamido-4-thiazolidone (32) that was converted to a thiazolodihydropyrazoles, thiazolopyrazole and thiazolopyridine. Thiazolodihydro pyrazoles then reacted with urea in ethanol in the presence of sodium ethoxide generated from sodium and ethanol to give tetrahydro pyrimidothiazole in 90% yield (33) [112].



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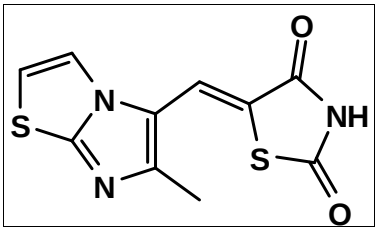

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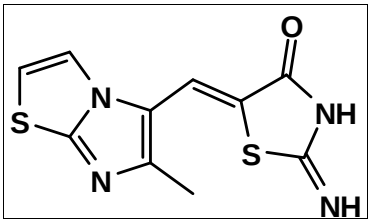

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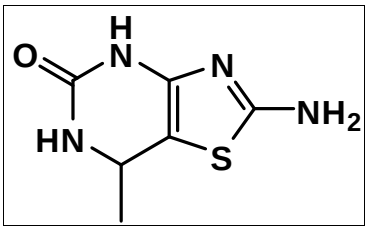
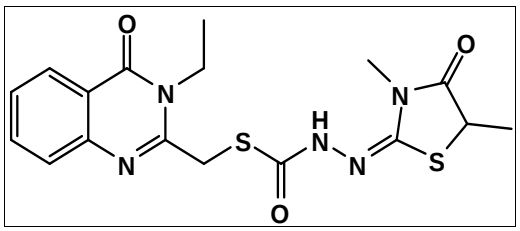


(33)

The synthesis and physico-chemical properties of new 3-benzyl-4-thioxo-5-arylidone-imidazolidine-2-ones and 3-benzyl-5-arylideneimidazolidine-2, 4-dione. These compounds were synthesized by condensation reaction from aromatic aldehydes and 3-substituted imidazolidine-2, 4-diones or 4-thioxoimidazolidine-2-ones and also studied antimicrobial *in vitro* activity on ten compounds [113]. The synthetic studies using 2-imino-4-thiazolidinones and related structures with active Nitriles [114]. Two series of 2-(3-ethyl-4(3H)-quinazolinone-2ylmercaptoacetyl-hydrazono)-3-alkyl/aryl-5methyl-4-thazolidinones (a) and 2-arylimino-3-(3-ethyl-4(3H)-quinazolinone-2ylmercaptoacetylamino)-5-methyl-4-thazolidinones (b) by cyclization of 1-(3-ethyl-4(3H)-quinazolinone-2-ylmercaptoacetyl)-4-alkyl/aryl thiosemi-carbazides (c) with ethyl 2-bromopropionate in the presence of anhydrous sodium acetate in anhydrous ethanolic medium. Synthesized and evaluated antioxidant activity of 4-methyl-2-[(3-arylsydnone 4-yl-methylene) hydrazono]-2, 3-dihydro-thiazole-5-carboxylic acid ethyl ester and 4-phenyl-2-[(3-arylsydnone 4-yl-methylene) hydrazono]-2, 3-dihydrothiazoles [115, 116].



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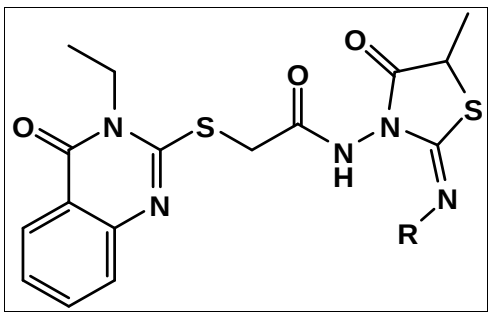

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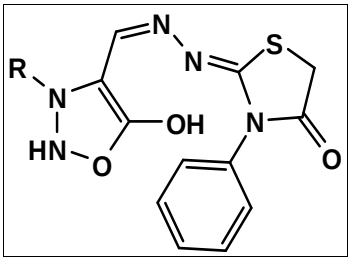

(36)

An efficient and extremely fast procedure for the synthesis of 7, 11-Diphenyl 5, 6a, 7, 11, 11a, 13a-hexahydro-6H-benzo[h] isoxazolo [3', 4', 4, 5] [1, 3] thiazolo[2,3-b]quinazolines through four-step procedure starting from 2-arylidenetetralin-1-one under microwave irradiation. The reaction rate increased considerably with better yield [117]. A rapid and easy solvent-free one-pot synthesis of 5-arylidene-2-imino-4-thiazolidinones by condensation of the thioureas with chloroacetic acid and an aldehyde under microwave irradiation [118]. A series of benzylidene rhodanine derivatives by the crossed aldol condensation of aromatic aldehydes with rhodanine using tetrabutylammonium bromide (TBAB) as phase transfer catalyst in water under microwave irradiation. The reactions were completed in 8~10 min, short reaction times, environmentally benign conditions, and easy workup [119].

Discussion

Thiazolidinone derivatives are a class of important five-member heterocyclic organic compounds which possess diversified biological and pharmacological activities [120-129]. The applications of non-conventional and economic procedures in the preparation of compounds are possessing 4-thiazolidinone ring as an essential moiety. The 4-thiazolidinone derivatives are known to possess diversified pharmacological properties. A variety of 4-thiazolidinone based compounds and intermediates have been prepared [130-135].

Conclusion

Several compounds were prepared and were tested for diverse biological activities. Various compounds were tested and showed a significant difference in the potentials of different compounds. The 4-thiazolidinone analogs exhibited various biological activities and are widely used in medicine, especially as antimicrobial agents.

Acknowledgment

We are very thankful to the Glocal School of Pharmacy, Glocal University, Mirzapur Pole, Saharanpur, Uttar Pradesh, India, for providing necessary facilities.

Compliance with ethical standards

This article does not contain any studies involving human participants performed by any of the authors and does not contain any studies involving animals performed by any of the authors.

Conflict of interest

The authors declare that they have no conflicts of interest.

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