



An Insight into 4-Thiazolidinones

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Authors' contributions

This work was carried out in collaboration among all authors. Author SS designed the study, performed the literature searches, wrote the protocol and wrote the first draft of the manuscript. Authors PKU and PM managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This assessment is all about to get imminent into 4-thiazolidinones and comprehensively reviewing this molecule. 4-Thiazolidinones are known for their wide-ranging biological activities. 4-Thiazolidinones contains thiazolidine ring having carbonyl group in the 4-position. The chemistry of thiazolidinones has drawn scientific interest through the years because this particular ring system is the core structure in a variety of synthetic compounds with a broad spectrum of biological activities such as anti-bacterial, anti-fungal, insecticidal, anti-epileptic, anti-mycobacterial, anti-inflammatory, anti-parasitic, hypnotic and anti-cancer. Structural modifications on the 4-thiazolidinone moiety, either by replacing the aryl group with the heteroaryl scaffold or by incorporating different groups and moieties (A&B) on –CH– group of nucleus paving a new pathway for the future research. It necessitates to widely reviewing the structure, chemistry and pharmacological aspects of 4-thiazolidinones.

Keywords: Aldehydes; antibiotic; anti microbial agents; drug resistance; isomerism; Schiff bases; spectroscopy; spectrum analysis; 4- thiazolidinone.

1. INTRODUCTION

There are numerous biologically active heterocyclic molecules with five-member rings, containing two heteroatom. Among these molecules, thiazolidine is a recognized scaffold for potential drugs and drug candidates [1]. Thiazolidine is a heterocyclic organic compound with the formula $(CH_2)_3(NH)S$. It is a five member saturated ring with a thioether group and an amine group in the 1 and 3 positions respectively. In Figs. 1 and 2, it clearly depicts that it is sulfur analog of Oxazolidine.

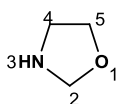


Fig. 1. Structure and numbering of Oxazolidine

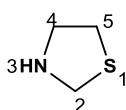


Fig. 2. Structure and numbering of Thiazolidine

Thiazolidine is an important scaffold known to be associated with several biological activities such as Anticonvulsant, sedative, antidepressant, anti-inflammatory, antihypertensive, antihistaminic and antiarthritic [2,3].

4-Thiazolidinones, a fortunate gibbet, have been the focus of medicinal chemistry since 60th. Furthermore, simple chemical transformations in an assorted variety of groups on the thiazolidine scaffold have captivated medicinal chemists and led to the exploration of this biological scaffold into various other heterocycles. Therefore, a conscious effort is made in selective modifications of the thiazolidine skeleton to develop a vast array of a similar yet biologically active scaffold from it, namely 4-thiazolidinones from the thiazolidines. Thus, thiazolidine is acquiescent to selective chemo reactions leading to diverse structural entities.

2. THIAZOLIDINONES

Thiazolidinones, which are derivatives of thiazolidine belong to an important class of heterocyclic compounds. They have molecular formula C_3H_5NOS and a molecular weight 269.40.

Thiazolidinones having a carbonyl group at positions 2, 4 or 5 have been an interest in

extensive study among researchers. A comprehensive review of 4-thiazolidinone came in 1961 [4]. Later on, various researchers published articles on thiazolidinone derivatives as medicinal agents and intermediates in organic syntheses.

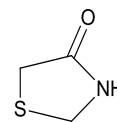


Fig. 3. Structure of Thiazolidinone nucleus

Thiazolidinones are known for their broad spectrum of biological activities such as anti-bacterial, pesticidal, anti-fungal, insecticidal, anti-epileptic, anti-mycobacterial, anti-inflammatory, anti-parasitic, hypnotic and anti-cancer. In recent years, several new methods for the preparation of thiazolidinone derivatives and reactions are reported in the literature. In the presence of various reagents, thiazolidinones, undergo different types of reactions to yield other heterocyclic compound, eg. thiazole, benzimidazole, triazoles, benzothiophenes etc. Thus, structural modifications on the thiazolidinone moiety, either by replacing the aryl group with the heteroaryl scaffold or by incorporating the different groups and moieties may pave the way for the future research [5]. These advances warrant to review the chemistry and biological properties of various 2, 4, 5-thiazolidinones.

3. 4-Thiazolidinones

Thiazolidinones, are derivatives of thiazolidine (a saturated form of thiazole) with a carbonyl group at position 2, 4, or 5 derivatives.) 4-thiazolidinones contains thiazolidine ring having carbonyl group in the 4-position.

Thiazolidine and thiazolidinone templates are considered privileged structural fragments in medicinal chemistry to account for their broad pharmacological activities and affinity for various biological targets [6]. The chemistry of thiazolidinones has drawn scientific interest through the years because this particular ring system is the core structure in a variety of synthetic compounds with a broad spectrum of biological activities [7]. 4-thiazolidinones, which are privileged structures in medicinal chemistry, comprise the well-known class of heterocycles and are a source of new drug-like compounds [8].



Fig. 4. Ring structures of thiazole and its transformed moieties

3.1 Synthetic Routes for Syntheses of 4-Thiazolidinones

A number of protocols for the synthesis of 4-thiazolidinones are reviewed in the literature. Essentially they are three component reactions involving **an amine, a carbonyl compound,** and a **α -mercaptoalkanoic acids**, occurring either in a one-pot three-component condensation or a two-step cyclisation reaction going through imine or Schiff's base formation [9].

The reaction of α -mercaptoalkanoic acids with compounds of the structure $RN=C=X$ basically known as imines, is general method of synthesis of 4-thiazolidinones. The only extensive use of α -mercaptoalkanoic acids in the synthesis of 4-thiazolidinones, has been in the preparation of 2-aryl-4-thiazolidinones. The other component is a Schiff base, typically produced from an aromatic or heterocyclic aldehyde. The reaction takes place in a non-polar solvent such as absolute ethanol, dry ether, ethyl acetate, dry benzene. With the above solvents, yields are of 70-80 per cent. Usage of a water separator preferably, such as DEAN STARK APPARATUS, has been found advantageous, and the course of the reaction can be followed by the volume of water collected in reservoir. With an aromatic or heterocyclic aldehyde or ketone, mercaptoalkanoic acid gives 4-thiazolidinones with a hydrogen attached to nitrogen. The

reaction is believed to take place by the intermediate formation of an aldimine or ketimine (generally known as imines). The reaction proceeds by the attack of the mercaptoacetic acid upon the $>C=N-$ group, with the COOH adding to the carbon atom, followed by the capture of a proton by nitrogen, and subsequent cyclization. The effects of electrophilic and nucleophilic substituents on the positive character of the carbon atom or the negative character of the nitrogen atom of the azomethine linkage can be markedly seen. Therefore, the susceptibility of the carbon towards nucleophilic attack of anion of mercaptoacetic acid is evident in the yields of the 4-thiazolidinones [4].

3.2 Physical Properties of 4-Thiazolidinones

According to literature, substituent at position 2-, 3-, and 5 have a varied impact on pharmacological activity, but the greatest difference in the structure and properties is exerted by the group attached to the carbon atom in the 2-position. 4-thiazolidinone are usually solids, which melts with breakdown frequently, but attachment of alkyl group to the nitrogen, lowers the melting, sometimes enough to make the compounds liquid in nature.

4-thiazolidinone are soluble in water if they do not have aryl or higher alkyl substituents.

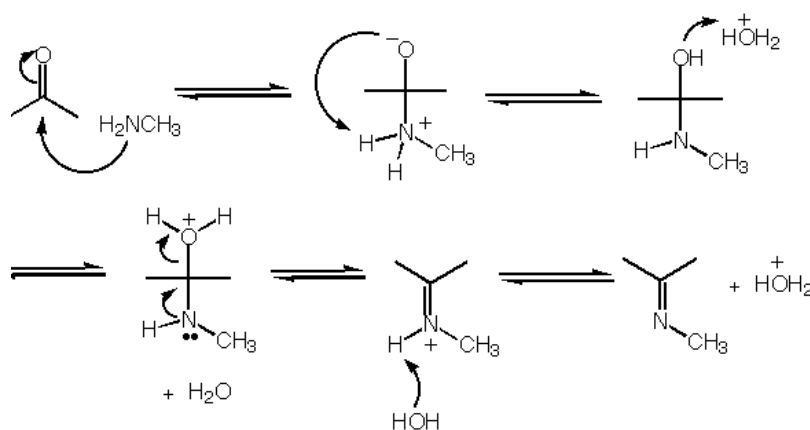


Fig. 5. Mechanism for imine formation

3.3 Chemistry of 4-Thiazolidinones

3.3.1 Synthetic Aspects of 4-thiazolidinones formation

The main synthetic route to 1,3-thiazolidin-4-ones involve three components i.e. an aldehyde, an amine and mercaptoacetic acid [5]. α -mercaptoalkanoic acids have been extensively used for the synthesis of 4-thiazolidinones. The substituted and unsubstituted alpha mercaptoalkanoic acids react conveniently with Schiff's bases of aromatic or heterocyclic aldehydes and aliphatic or aromatic amines in different solvents to give a variety of substituted-4-thiazolidinones. Schiff's bases are obtained by the condensation of ketones and aliphatic or aromatic amines can react with alpha mercaptoalkanoic acids to give 2,2-disubstituted-thiazolidinones [10].

3.3.2 Mechanistic aspects of 4-thiazolidinones formation

The reaction proceeds by an initial formation of an imine (Schiff's base), which undergoes attack by the sulphur nucleophile, followed by intramolecular cyclization on elimination of water.

Initially thioglycolic acid attack upon the $>C=N-$ group, with the SCH_2COOH adding to the carbon atom, followed by the capture of a proton by nitrogen, and subsequent cyclization [5]. The effects of electrophilic and nucleophilic substituents on the electro positivity of carbon atom or the electro negativity of the nitrogen atom of the azomethine linkage are noticeable. Therefore on the susceptibility of the carbon to nucleophilic attack by the anion of the mercaptoacetic acid are important in the yields of the 4-thiazolidinones. While the thiazolidine ring opening and formation are reversible processes, thiazolidinones are formed in an irreversible dehydration step which constitutes the driving force of this reaction eliminating a molecule of water which is removed by water scavenging apparatus. The most common protocol to remove water is by azeotropic distillation, but the use of chemical drying agents (scavengers) such as

DCC and physical scavengers such as molecular sieves has been demonstrated.

The use of a DEAN STARK water separator has been found to be beneficial, and the course of the reaction can be followed by the volume of water collected in reservoir as well [11,12] This reaction which forms five membered heterocyclic thiazolidinone ring is known as 1,3-Dipolar cycloaddition reaction.

3.3.3 Cycloadditions

Cycloadditions are reactions in which two π bonded molecules come together to make a new cyclic molecule with the formation of two new σ bonds. Cycloaddition reactions offer a versatile route for the synthesis of cyclic compounds with a high degree of stereoselectivity under thermal and photochemical conditions [13].

3.3.4 1,3-Dipolar cycloadditions

1,3-Dipolar cycloaddition is a preferable route for synthesis of thiazolidinones, isoxazoles and isoxazolines [9]. 1,3-Dipolar or [3+2] cycloaddition is a reaction between a molecule containing a π bond (an alkene, alkyne, etc) known as 1,3 dipolarophile with a highly polarized ionic compound called a 1,3 dipole. When these two react, a five membered ring is generated. Depending on their nature, carbocyclic or hetrocyclic rings can be formed, and a variety of substituents can be incorporated on the ring.

3.3.5 Dipoles and dipolarophiles

Cycloaddition reactions that involves dipolar species are called as 1,3 dipoles reacting with a π bonds called as dipolarophiles to give a five membered ring are often called as 1,3 dipolar cycloaddition reaction but the formal name is [3+2] cycloaddition reactions. A 1,3 dipole usually contains heteroatoms, having four π electrons distributed over three atoms. The dipolarophile is usually an alkyne or alkene derivative.

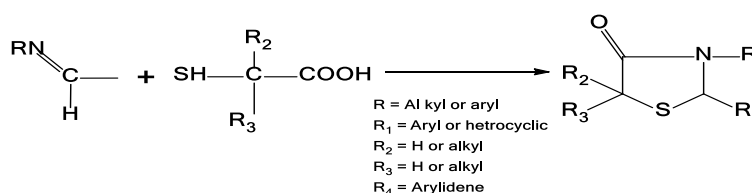


Fig. 6. Reaction for 4-thiazolidinone nucleus formation

The reaction is believed to proceed by a concerted, thermal cyclisation, with a high stereo and regioselectivity. Electrostatic interactions and solvent effects can modify the regiochemical and stereochemical outcome. Both intermolecular and intramolecular cycloaddition reactions are possible.

3.4 Spectral Studies on 4-Thiazolidinones

3.4.1 Infrared spectral studies

It is reported that the characteristic bands in the infrared spectra of several substituted 4-thiazolidinones [14,15]. In the IR spectra an absorption was found in the range of 3407 cm^{-1} [NH str.], 3359 cm^{-1} [C-H str. Ar. H], 1313 cm^{-1} [C-N str.], 1035 cm^{-1} [C-Cl str.], 3002 cm^{-1} [C-C str.], $1550\text{-}1708\text{ cm}^{-1}$ [C=O], 1144 and 690 cm^{-1} (C-S of thiazolidinone ring).

3.4.2 NMR spectral studies

The ^1H NMR spectra of the 4-thiazolidinones depend largely on the substituents present at the different positions of the thiazolidine ring. The 2,3-disubstituted 4-thiazolidinones have three characteristic peaks in the NMR spectrum, H(2) appears as a singlet in the range of $5\text{e}6$ ppm depending upon the nature of the R_2 . In most of the cases H_a and H_b both appears as separate doublets in the range $3.5\text{e}3.9$ ppm. The actual NMR spectra depends upon the nature of the substituents at the C(2) and N(3) positions, i.e., on R_1 and R_2 substitutions.

^{13}C NMR spectra of a series of substituted 4-thiazolidinones, chemical shift and C, H spin coupling constants were exhaustively reviewed by various scientists. Various constitutional isomers have been differentiated, and the configuration of Carbon has been established on the basis of C,H spin coupling constants over two and three bonds [16].

3.4.3 Mass spectral studies

Mass spectra of different 4-thiazolidinones were studied and reported on the basis of molecular ion peak and fragmentation pattern. Actual molecular weight of thiazolidinones depends upon substitutions R on 4-thiazolidinones (where $\text{R} = \text{H}, \text{CH}_3, \text{C}_6\text{H}_5$ or $\text{C}_6\text{H}_5\text{CH}_2$).

The principle daughter ion peaks were determined by means of deuterium exchange and high-resolution mass spectroscopy.

3.5 Stereochemistry of 4-thiazolidinones

Theoretically, in the case of 2,3-disubstituted 4-thiazolidinones two diastereoisomers I & II (Fig. 7) are possible. Moreover, extensive studies have found that the preferred configuration (I) is that in which the C(2) proton and one of the methylene protons are in cis 1,3 diequatorial relationship [17]. It is due to the fact that the phenyl group prefers the axial orientation to avoid the steric hindrance with bulkier pyridyl group.

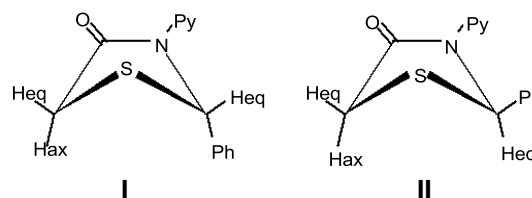


Fig. 7. Stereochemical orientation of 4-thiazolidinone

3.6 Conformational Analysis of 4-thiazolidinones

In addition to this, effects and conformational analysis of some substituted 2,3 - diphenyl -1,3-thiazolidin-4-ones. Substituent's placed on the phenyl rings of 2,3 - diphenyl -1,3 - thiazolidin-4-one affects the electron density surrounding both the methine proton (H_x) and the carbon C(2) because of their location, are possibly sensitive to substituents (X and Y) located at the meta and para position of both the 2 and 3 phenyl rings, respectively. These changes are reflected in the differing chemical shifts for these atoms relative to the parent compound. The other carbons in the heterocyclic ring appear to be similarly affected by substituents on the phenyl rings (Fig 10). Correlations for the effects of various substituents in both the 2- and 3 -phenyl rings with the ^1H and ^{13}C chemical shifts for the aforementioned sites are discussed using both Hammett and Swain -Lupton dual parameter methods. Hammett σ plot using equation (i) where δ_0 is the chemical shift for H_x for unsubstituted thiazolidinones and δ is the chemical shift for the substituted compounds. Whereas equation (ii) is Swain and Lupton equation with (F) and (R) as field and resonance constants of this equation with rest of the symbols being the same [18].

$$\delta - \delta_0 = \rho\sigma \quad \text{eq.(i)}$$

$$\delta - \delta_o = fF + rR$$

eq.(ii)

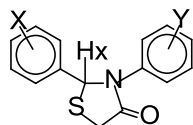


Fig. 8. Effect of substituent X and Y at meta and para position on 2,3 – biphenyl -1,3-thiazolidin-4-ones(where X,Y = H, NO₂, Br, F, Cl, CH₃, OCH₃)

3.7 Photochemistry of 4-thiazolidinones

A new route for synthesis of beta-lactams, by the photolytic ring contraction of mesoionic derivatives of 4-thiazolidinones have been ascertained. Merocyanine, a 4-thiazolidinone derivative, undergoes photo-isomerization, producing two isomers from the excited singlet state during irradiation [19].

4. PHARMACOLOGICAL ACTIVITIES OF 4-THIAZOLIDINONES

Thiazolidinones are the key structures that possess wide array of biological activities. This

ring processes a number of pharmacological activities. The biological investigation of thiazolidinones involves various mechanism like enzymatic action and receptor mediated mechanism. The biological investigation of thiazolidinones has revealed that substitution at 2, 3 and 5 positions imparts different activities. Many of the commercial drugs containing thiazolidinone scaffold show diversity in biological activities such as anti microbial, anti tubercular, anti inflammatory, insecticidal, anti parasitic, anti cancer, anti HIV etc [20].

4.1 Thiazolidinones as Insecticidal and Parasiticidal Agents

Kucuguzel et al prepared and studied novel series of 4-thiazolidinone derivatives as potent antimicrobial, anticancer, antimycobacterial, antitumor and antipyscotic agents. In addition to this, two more novel series of 4-thiazolidinones derivatives i.e. 2-substituted -3-[[4-(4-methoxybenzoylamino) benzoyl] amino]-4-thiazolidinones and 2-[[4-(4-methoxybenzoylamino) benzoyl hydrazono]-3-alkyl-4-thiazolidinones were synthesized [21].

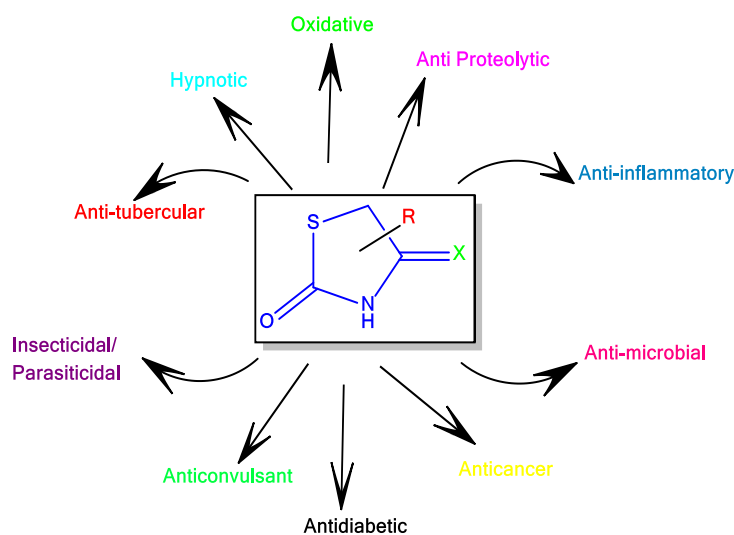
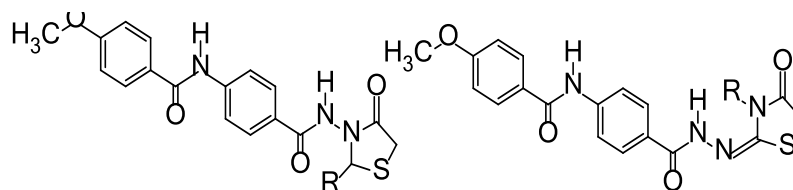


Fig. 9. Biological activity profile of Thiazolidinones



R = CH₃, C₂H₅, C₆H₅, CH₂-CH=CH₂

Fig. 10. Two series of 4-thiazolidinones as insecticidal and parasiticidal agents

4.2 Thiazolidinones as Antibacterial Agents

Several 4-thiazolidinones and their corresponding 5-arylidene derivatives were tested against *Staphylococcus aureus*. The screening data of more than fifty thiazole and thiazolidinone derivatives against some common bacteria revealed that the thiazolidinones were more active than the thiazoles. An enhancement in activity was observed with mercurated thiazolidinone derivatives as compared to nonmercurated derivatives. All of them showed high activity against *S. aureus*. The activity against *E. coli* and *K. aerogenes* was dependent on the size of substituents. 2-Aryl-3-benzothiazolyl-4-thiazolidinones exhibited 35-56% inhibition of Gram positive and Gram-negative bacteria at a final concentration of 10^{-3} M.

4.3 Thiazolidinones as Antifungal Agents

Rao reported high antifungal activity of some mercurated derivatives 4-thiazolidinones against *Aspergillus niger* at a dilution of 1:10000. Matolcsy et al. have found very high antifungal activity associated with the derivatives 2-thiono-4-thiazolidinones against *Alternaria tenuis* and *Botrytis allii*. 3-Ethyl-5-methyl-2-[(4-chlorobenzothiazole-2yl)imino]-4-thiazolidinone and 3-ethyl-5-methyl-2-[(5-chlorobenzothiazole-2yl)imino]-4-thiazolidinone were found to exhibit 100% inhibition of spore germination of *Alternaria tenuis* at concentrations of 1:1000, 1:5000 and 1:10000.

Desai et al reported synthesis and QSAR studies of 4-oxo-thiazolidines and 2-oxo-azetidines as potential antibacteria agents against gram positive and gram negative bacteria. The QSAR studies of these compounds have been carried out in terms of structural and physicochemical parameters where positive contribution of substituents present at various positions with bulkier group indicating increase in hydrophobicity or steric bulk character [22].

Sabin et al reported therapeutic effect of the sulphonamides on injection, by an intra-cellular Protozoon (*Toxoplasma*) [23].

Joshi et al reported a paper describing synthesis, QSAR study and comparative study on antibacterial activities of sulphonamides and Mannich bases derived from them. The

compounds were screened for their antibacterial activity against various gram-positive and gram-negative bacteria and were analysed statistically. The results have shown that the compounds were quite active against pathogens under study & were nontoxic [24].

Mehta et al synthesised and characterised some novel 4-thiazolidinones possessing wide spectrum of biological activity viz. antitubercular, antiinflammatory, anticancer and anthelmintic in addition to their antimicrobial activity [25].

The heterocyclic compounds with both sulphur and nitrogen atoms in the ring system have also been used in the synthesis of biologically active complexes. As it is noteworthy and considerable that the biological activity gets enhanced on undergoing complexation with metal ions.

M. Jain et al. reported the synthesis of organosilicon derivatives of sulphonamides and characterized them on the basis of analytical, conductance and spectroscopic techniques. Biototoxicity studies were conducted to assess the growth-inhibiting potential of synthesized complexes as fungicides, bactericides, nematocides and insecticides against various pathogenic fungal, bacterial strains, root-knot nematode *Meloidogyne incognita*, and insect *Trogoderma granarium* respectively [26].

Mehta et al synthesized a series of 4-thiazolidinones and 2-azetidines by condensation of 4,4'-diaminophenylsulphone with various aromatic and heterocyclic aldehydes to yield the Schiff's bases which upon cyclocondensation with 2-mercaptopropionic acid and chloroacetylchloride in presence of triethylamine (TEA) afforded 4-thiazolidinones and 2-azetidinone derivatives respectively. All the compounds were evaluated for their in-vitro growth inhibitory activity against several microbes with ampicillin as reference standard [27].

Desai et al investigated and reported a novel approach for the rapid and efficient synthesis of heterocyclic Schiff's bases and azetidines under microwave irradiation using N, N-Dimethyl formamide as a reaction mediator, which absorbs microwave energy efficiently through dipole rotation since it can retain water formed in the reaction thus avoiding the need for a water separator. The microwave assisted organic reactions occur more rapidly, safely and with higher chemical yields. These features render

the microwave method superior to the conventional one. The products were screened for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Salmonella typhi* [28].

4.4 Thiazolidinones as Anticonvulsant Agents

Anticonvulsant activity of several series of 4-thiazolidinones has been studied against pentylenetetrazol-induced seizures, in albino mice of either sex at a dose of 100 mg/kg, with the degree of protection ranged upto 80%.

Troutman et al investigated various papers and reported the synthesis of 2,3 disubstituted -4-thiazolidinone and tested as possible anticonvulsants. Exploratory results concluded that derivatives are effective in giving protection against electrically induced convulsions while other members of the series inhibited metrazole induced convulsions [29].

Parmar et al assumed and reported ability of thiazolidinone derivatives to exhibit a wide variety of pharmacological properties including anti convulsant activity. They investigated the ability of such thiazolidinones to inhibit oxidation of the substrates of the tricarboxylic acid cycle like pyruvate, α -ketoglutarate, citrate and β -hydroxy butyrate with a view of studying their chemical mechanism of action. The anticonvulsant activity of these compounds was determined to correlate pharmacological properties with their enzyme inhibitory properties [30].

4.5 Thiazolidinones as Hypnotic Agents

Several derivatives of Thiazolidinones were evaluated for their ability to potentiate pentobarbital-induced hypnosis in mice at a dose of 100mg/kg. All thiazolidinones were found to potentiate pentobarbital sleeping time. The increase in duration of sleep was monitored in mice pretreated with substituted thiazolidinones.

4.6 Thiazolidinones as Oxidative Agents

A number of 4-thiazolidinones were investigated for their inhibitory effects on the oxidation of the substrates the tricarbocyclic cycle and hydroxybutyrate by rat brain homogenates.

All thiazoidinones selectively inhibited NAD-dependent in vitro oxidation of various

substrates, whereas NAD-independent oxidation of succinate remained unaltered. These results have provided evidence for a possible competition between the thiazolidinones and NAD for the active site(s) on the enzyme molecules.

4.7 Thiazolidinones as Antinflammatory Antiproteolytic, and Antihemolytic Agents

The anti-inflammatory activity of 2-[(butoxycarbonyl)methylene]-4-thiazolidinone. A group of 2,3,5-trisubstituted-4-thiazolidinones were studied by patel et al. where 2-(4-methoxyphenyl)-3-(3-methylphenyl)-5-methyl-4-thiazolidinone was found to exhibit inhibition of edema by 13.5% after 24 h. Various -4-thiazolidinones were also studied for their antiinflammatory activity against carrageenin induced edema. The anti-inflammatory activity of these thiazolidinones was correlated with their antiproteolytic activity and their ability to inhibit trypsin induced hydrolysis of bovine serum albumin. Antiproteolytic and antihemolytic properties of several 4-thiazolidinones were investigated by Srinivasa et al. [31].

Mishra et al reported the synthesis of phenothiazine and benzotriazole derivatives of 1,3- thiazolidin-4-ones. All the compounds were screened for their anti-inflammatory activity against the carrageenan induced rat paw oedema in albino rats, anticonvulsant activity against pentylene tetrazole induced convulsions in mice, analgesic activity by the eddy and leimbach method using Technoheated plate analgesic apparatus [32].

Vazzana et al reported the synthesis of two small sets of aromatic Schiff bases and 2, 3-disubstituted -1, 3-thiazolidin-4-one derivatives as antiinflammatory agents and antinonociceptive activities. The thiazolidinone derivatives have been obtained from the aromethines through the addition of α -mercaptoacetic acid. 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 [33].

Murthy et al reported screening of new synthetic thiazolidine-4-ones for anti-inflammatory activity in albino rats and were statistically compared to controls. Results were determined by one-way

ANOVA followed by least significance difference test using SPSS software [34].

Goel et al synthesized and evaluated new anthranillic acid derivatives 2-substituted-3-(4-bromo-2-carboxyphenyl)-5-methyl-4-thiazolidinone, for their anti-inflammatory activity against carrageenan-induced oedema in albino rats. The most active member of the series, 3-(4-bromo-2-carboxyphenyl)-2-(2-fluorophenyl)-5-methyl-4-thiazolidinone was compared with phenylbutazone for its relative anti-inflammatory potency and ulcerogenic liability. ED₅₀, Cardiovascular and Central nervous system effects were also studied [35].

Srivastava et al, as a part of systematic investigation of synthesis of biologically active compounds of 2-mercaptobenzothiazole, reported synthesis of 4-oxothiazolidines and their 5-arylidenes. Compounds were screened and tested for their antimicrobial and anti-inflammatory activities against *E.coli*, *S.dysenteriae* and *S.aures*, *C.albicans*, *R.oryzae* by disc diffusion technique and carrageenan induced rat paw oedema method respectively. Structures of synthesized compounds were determined by spectral and chemical methods [36].

4.8 Thiazolidinones as Antioxidant Agents

Kato et al, reported, design, synthesis and pharmacological activity of thiazolidinone derivatives as a novel type of Ca²⁺ antagonist possessing both Ca²⁺ overload inhibition and antioxidant activity. They also studied the structure – activity relationships for this series of compounds by evaluating three kinds of activity. Ca²⁺ antagonistic was largely determined by the lipophilicity of the phenyl group at the 2-position and the length and the length of the alkyl chains. For the antioxidant activity, it was demonstrated that the phenolic hydroxyl group is an essential structural element compound with a potent activity were evaluated for their effect on the coronary blood flow *in vivo* [19].

4.9 Thiazolidinones as Antitubercular Agents

Litvinchuk reported antitubercular activity with low toxicity associated with a few derivatives of 2-imino-4-thiazolidinones, comparable to streptomycin or phthivazid. Chemotherapeutic effectiveness of various thiazolidinone derivatives against various strains of

Mycobacterium tuberculosis were reported to inhibit the growth of human tubercle bacilli in a concentration of 12.5 µg/mL.

Postel et al reported synthesis of pyrimidine based thiazolidinones and azetidiones and evaluated them for their antitubercular activity against different microorganism. The structures of novel synthesized compounds have been established on the basis of elemental analysis, ¹H NMR and IR spectral data [37,38].

Babaglu et al reported and investigated the substituted thiazolidinones as inhibitor of dTDP-rhamnose synthesis via its essential enzyme inhibition. They created virtual library of 2,3,5 tri substituted-4-thiazolidinones. These compounds were then docked into active site cavity of 6'hydroxyl; dTDP-6-deoxy-Dxylo-4-hexulose-3, 5-epimerase from *Mycobacterium tuberculosis*, as thiazolidinone scaffold functions as a diphosphate mimetic and generate specificity through the different R- group placed around the ring. The resulting docked conformations were consensus scored and top 5% were stated for synthesis and having ≥50% Antitubercular activity in the coupled rhamnose synthetic assay [39].

5. Conclusion

The ongoing prevalence of various diseases and pathogens requires the development of new effective pharmacological agents. This thought suggested us to get insight into thiazolidinones and comprehensively review this molecule. Thiazolidinone is a biologically important five-membered heterocyclic ring having different types of biological activities [40,41]. In search of new potentially active agents, lots of thiazolidinones derivatives have been synthesised and evaluated for their antibacterial, particularly antitubercular activity. These have been conveniently synthesized by performing one-pot cyclocondensation of substituted benzaldehyde, anilines and mercaptoacetic acid and excellent yields of resulting compounds were obtained. 4-Thiazolidinones were thoroughly characterized by their spectral analyses. Molecular docking study has also been performed to know the binding mode of these analogs in to their active sites of enzymes responsible for their corresponding diseases. Thus we can conclude that thiazolidinone is a novel potentially active nucleus and also a promising scaffold for synthesis of other compounds [42].

Synthesis of a novel series of thiazolidin-4-one and thiazinan-4-one using amine precursor were also reported as precursors for the development of new AChE inhibitory agents also. New molecules were tested as enzyme inhibitory factors. The inhibition of the AChE enzyme results in the blockage of ACh hydrolysis. All compounds were again synthesised by one-pot three component cyclocondensation reaction from the amine, a substituted benzaldehyde and a mercaptocarboxylic acid [42-45].

In process of exploration of our study QSAR models could be useful for the design and development of novel potent novel thiazolidin-4-one derivatives, that were optimized as potential drug candidates, designed and created as significant agents. To exhibit this molecular modeling studies, including CoMFA, CoMFA-RF, CoMSIA, and HQSAR could be performed, considering these QSAR models as excellent and robust with better predictive capability about novel thiazolidin-4-one analogs [46].

4-Thiazolidinones, as examples of privileged scaffolds, have been the focus of medicinal chemistry since 60th [47]. Over recent decades, much effort was dedicated to the development of new thiazolidinones. Specifically, there is a significant amount of publications concerning the synthesis, QSAR and pharmacological evaluation of 4-thiazolidinones with potential activities. This review covers various 4-thiazolidinones literature related to the physical properties, chemical reactions, and synthesis for these derivatives has been included. Also biological activities reported for 4-thiazolidinone derivatives have been covered exhaustively in this review. However, from the present study, it is clear that 4-thiazolidinones derivatives can be promising targets for future research in order to discover new, more effective and safer. In lieu of this framework, we can develop and explore new methodologies for thiazolidin-4-ones and their novel analogues avoiding the draw backs encountered previously [48,49,50]. Lastly we can conclude that findings of this study may help in further optimizing and exploring different derivatives of the 4-thiazolidinones as more effective drug agents and considering them as interesting candidates for future research [51,52,53].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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