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A Review on Synthesis and Pharmacological Action of Thiazolidinone Derivatives

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ABSTRACT

Numerous pharmaceuticals and physiologically significant compounds comprise heterocyclic systems. One unique class of heterocyclic compounds with a wide range of biological activity is thiazolidinone. Nearly every kind of biological activity is present in thiazolidinone, which is regarded as an active scaffold with biological significance. Numerous researchers are interested in investigating the skeleton's capabilities against various activities due to its diverse biological response profile. In order to determine the potential applications of thiazolidinone derivatives in medicine in the future, this review examines the synthesis and diverse biological activities of thiazolidinone derivatives from past research and review works.

INTRODUCTION

Since heterocyclic compounds exhibit a wide range of biological properties, they have been thoroughly investigated as pharmacological agents. [l] Heteroatoms can interact with various biological targets and act as linkers to generate advantageous conformations when they fuse together in chemical frameworks. Furthermore, the availability of oxygen and nitrogen atoms has been used to enhance the physical characteristics of substances that are biologically active. [2] A class of five-membered rings with a sulphur atom at position 1, a nitrogen atom at position 3, and a carbonyl group at positions 2, 4, or 5 [3] (Figure 1) are known to be advantageous pharmacophores with a variety of biological activities, such as antibacterial, sedative, antioxidant, anticancer, antiviral, antituberculosis, anticonvulsant, antidiabetic, antifungal, anti-inflammatory, and more. In In the current review, various pharmacological characteristics linked to structurally related thiazolidines and substituted thiazolidinones are highlighted.

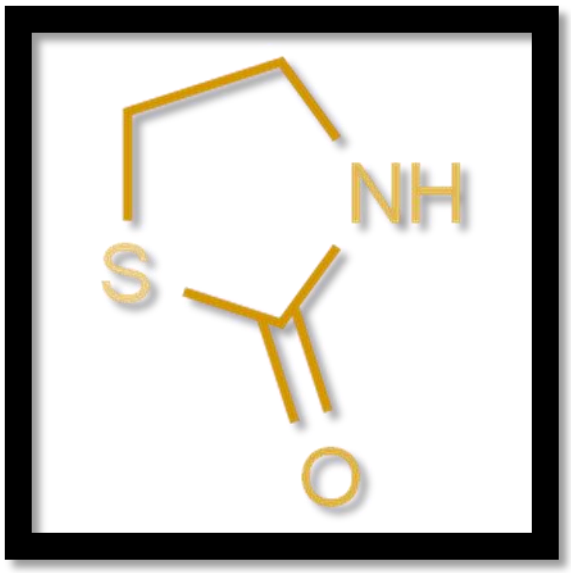


Figure 1: Thiazolidinone

2. MECHANISM OF ACTION OF THIAZOLIDINONE COMPOUNDS

Because of their diverse spectrum of actions, thiazolidinone derivatives have multiple modes of action. It can function as an antifungal agent by preventing the growth of fungal mycelia. Thiazolidinone's anti-inflammatory effect is brought about by its suppression of COX-2. Certain thiazolidinone derivatives have the ability to prevent cancer cells from synthesising

DNA. Some thiazolidinone derivatives have anti-HIV properties and function as non-nucleoside inhibitors of HIV type 1 reverse transcriptase. [14]

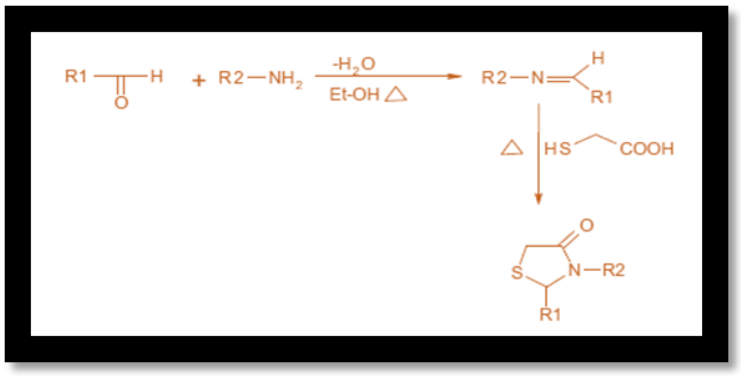
3. PREPARATION

Numerous synthesis techniques for 4-thiazolidinones have been extensively documented in scholarly works. Three ingredients are needed for the main synthesis pathways leading to 1,3-thiazolidin-4-ones: an amine, a carbonyl molecule, and a mercapto-acid. The reported classical synthesis can be either a two-step procedure or a one-pot, three-component condensation (Scheme 1). The reactions start with the creation of an imine (the amine's nitrogen attacking the carbonyl of an aldehyde or ketone), which is then attacked by a sulphur nucleophile produced. Once the water is removed, intramolecular cyclization takes place.

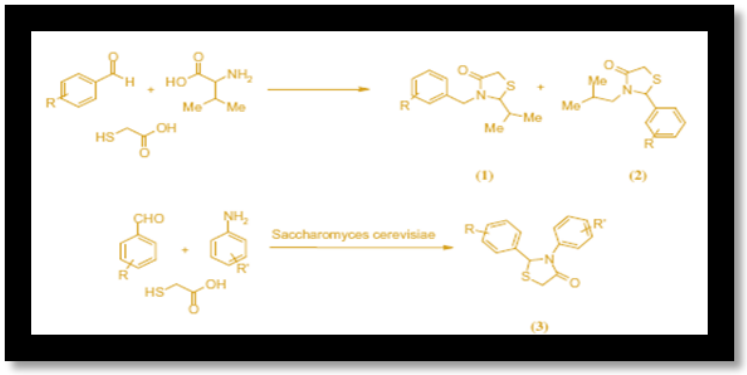
[15-17]

Eltsov et al. proposed a practical one-step cyclization reaction methodology (Scheme 2) in which (imidazolylimino)thiazolidinones are obtained by reacting ethyl 5-phenylthioureido-3H-imidazole-4-carboxylate with bromoacetic acid. In derivatives of 5-thioureido-3H-imidazole-4-carboxylic acid, the cyclization reaction proceeds by one of the nitrogen atoms of the nucleophilic centres, yielding the desired thiazolidinone. [18]

Additionally, Cunico et al. [19] reported a novel method for producing 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones using a 1:1:3 mole ratio of valine, arenealdehyde, and mercaptoacetic acid. This method suggested that the insertion of a strong withdrawing group, NO2, present on benzaldehydes favoured the synthesis of hetero-cycle 1 in good yields, while the type 2 thiazolidinones are produced by the methoxy and fluoro groups. Using phenylhydrazine and 2,4-dinitrophenylhydrazine as the amino cores, the authors reported synthesising five-membered heterocyclic thiazolidinones without the use of solvents. [20] Another method of synthesising 2,3-diaryl-4-thiazolidinones (3) was reported by Pratap et al. [21]. This method involved using Saccharomyces cerevisiae (baker's yeast) with the enzyme lipase as a catalyst to speed up the formation of imines and the cyclo-condensation of amines, aryl aldehydes, and thioglycolic acid.

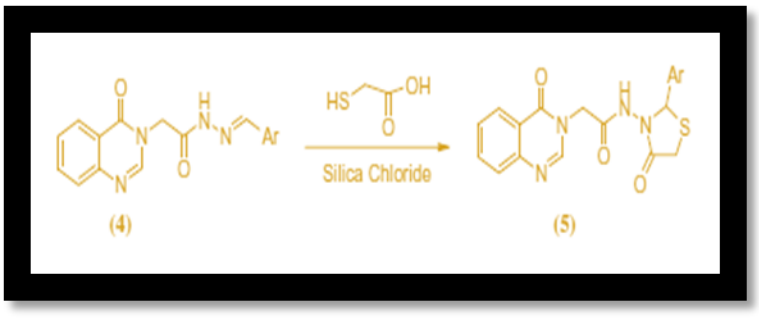


Scheme 1:



Scheme 2:

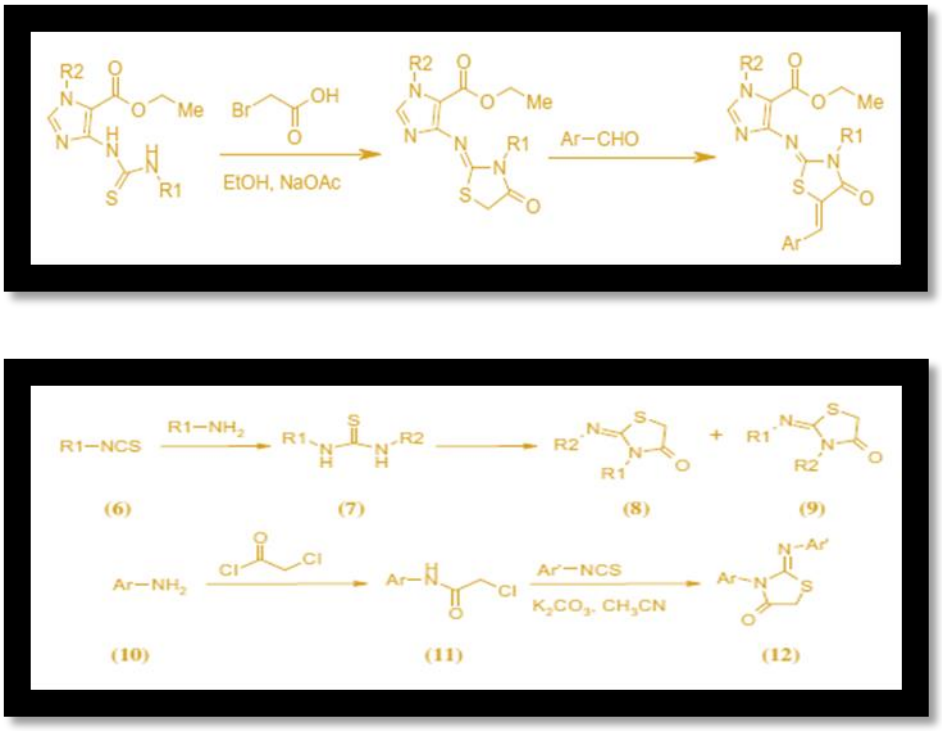
After being treated with mercaptoacetic acid and silica chloride, which was utilised as a heterogeneous catalyst to speed up intramolecular cyclocondensation in a solvent-free environment, a variety of quinazolinyl azomethines (4) give 4-thiazolidinones (5). (**Scheme 3**) [22]



Scheme 3:

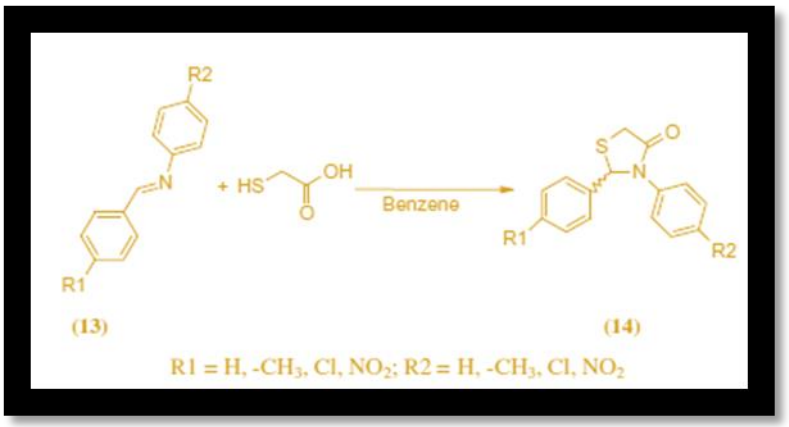
Additionally, the aryl or alkyl isothiocyanate (6) and primary amine reaction produced the corresponding thiourea derivative (7), which was then directly cyclized to yield the corresponding two isomeric 2-imino-thiazolidin-4-ones of the general structures (8) and (9).

This was achieved by treating with halo acetic acid. 23] Moreover, the a-chloro amide derivatives(11) and isothiocyanate coupling process in the presence of a moderate base produced the iminothiazolidinone derivatives (12). [24]



Scheme 4:

A variety of 1,3-thiazolidin-4-one derivatives (14) were produced by Bolognese et al. [25] using a microwave-assisted reaction between mercaptoacetic acid in benzene at 30 °C for 10 minutes and benzylidene-anilines (13) in benzene. Following chromatographic purification, 1,3-thiazolidin-4-ones are obtained with 65–90% yield. (**Scheme 5**)



Scheme 5:

4. PHARMACOLOGICAL ACTIVITY

4.1 Antitubercular Activity: Additionally, the compounds of thiazolidine-4-one exhibit antitubercular action. As a result, a group of derivatives of sulfamethao xazole-thiazolidin-4-one (la-le) (Figure 2) demonstrated potent antitubercular activities against Mycobacterium tuberculosis and Mycobacterium bovis BCG [26]. Ekinci et al. synthesised a series of 2-aryl-5-meth ylthiazolidin-4-ones. Using the microplate alamar blue assay (MABA), all of the compounds in this series were assessed for their antimycobacterial activity against the M. tuberculosis H37Rv strain in vitro [27]. The 2-(4-ethylphenyl) substituent in Compound (2) was the only one to have modest antimycobacterial activity.

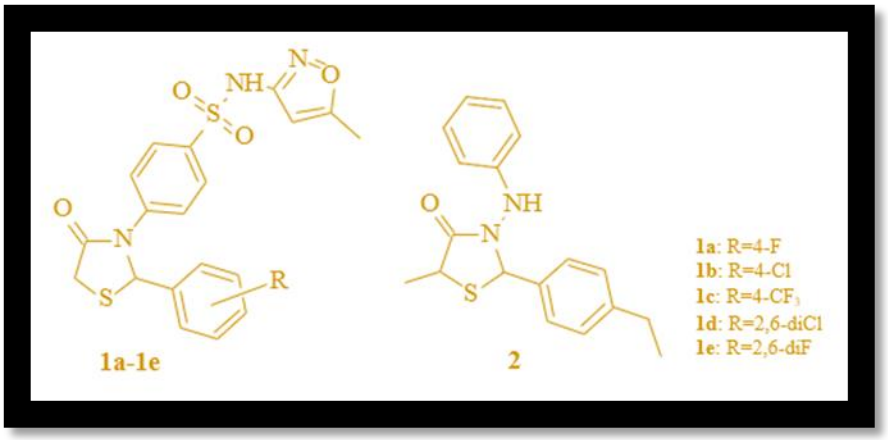


Figure 2: Antitubercular activity of the compounds 2-Arylthiazolidin-4-ones with derivatives

4.2 Analgesic and Anti-Inflammatory Potential: Ibuprofen compounds using the thiazolidine-4-one scaffold (3a-3n) were evaluated by Vasincu et al. for their analgesic and anti-inflammatory properties (Figure 3) [28]. Analysing the data collected 24 hours after treatment revealed that the discovered compounds had long-lasting anti-inflammatory effects, some of which were even greater than those of the reference medication ibuprofen. With an edoema inhibition value of 53.04 ± 13.17%, 3d, which has a 4-fluorophenyl substituent, was the most active of them all.

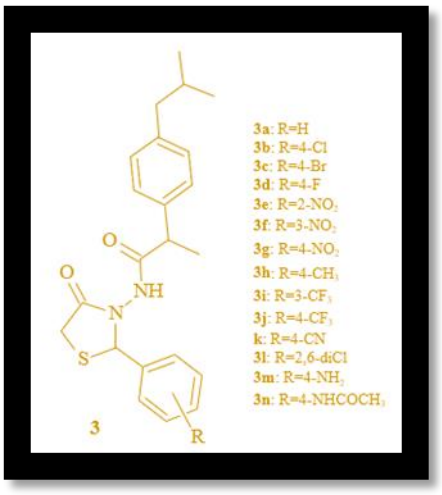


Figure 3: Thiazolidin-4-one hybrids with anti-inflammatory and analgesic activities

The compounds (4a-4c) with chloro, fluoro, and nitro substituents, respectively, demonstrated the most significant anti-inflammatory activity in the carrageenan-induced paw edoema test in rats, out of all the 2-aryl-3-(naphtha-2-yl)thiazolidin-4-one derivatives reported by Agrawal et al. (Figure 4). Furthermore, these compounds were discovered to be the most effective analgesic drugs in mouse experiments involving tail immersion and writhing. [29]

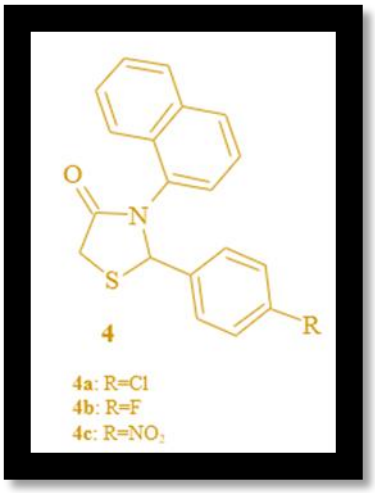


Figure 4: The structure of various 2-aryl/alkylthiazolidin-4-ones

4.3 Anticancer Activity: The HepG2, HCT116, and MCF-7 cell lines were used as test subjects for the 5-(4-Methoxybenzylidene)thiazolidin-2,4-dione derivatives (5a-5f) [30, 31]. The in vitro experiments conducted against HepG2, HCT116, and MCF-7 cell lines revealed that Compounds 5f, 5e, 5d, and 5c exhibited the best antiproliferative activity among all tested derivatives (Model 5). The synthesis of a series of TZD compounds containing a 5-

(3,4,5-trimethoxy benzylidene) moiety by El-Kashef et al. 2020 (Figure 6). In addition to normal, non-cancerous breast cells that were taken from the same patients, the synthesised TZDs were evaluated for their anti-breast cancer action against human breast cancer cells (MCF-7 and MDA-MB-231) [32]. Compounds 6, 7, and 8 had the strongest anticancer activity, according to preliminary screening investigations. These substances (6, 7, and 8) significantly reduced the phosphorylation of AKT and mTOR as well as the production of VEGF and HIF-lα, which in turn prevented the growth of MCF-7 breast cancer cells.

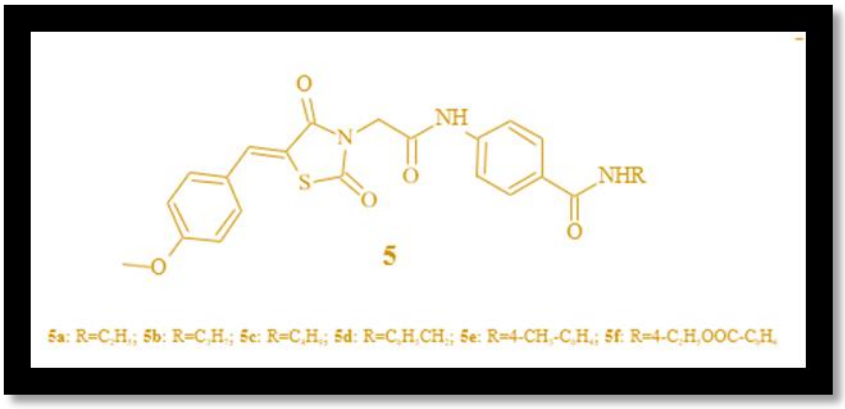


Figure 5. The 5-(4-Methoxybenzylidene)thiazolidin-2,4-dione Derivatives

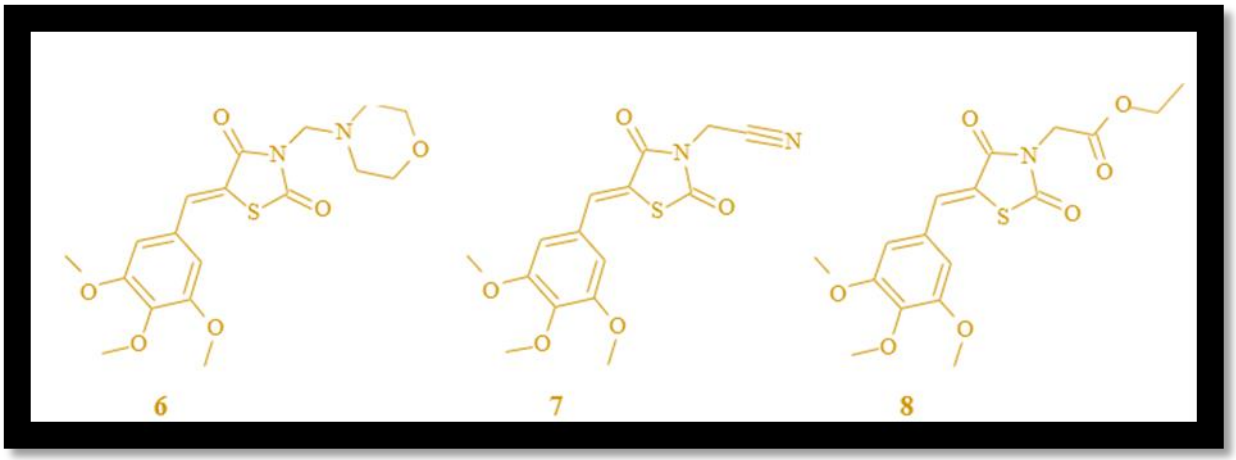


Figure 6: The 5-(3,4,5-trimethoxybenzylidene)thiazolidine-2,4-dione derivatives

4.4 Anti-parasitic Activity: Quinoline-thiazolidin-4-one hybrids (9a-9f, 10, 11 and 12) were synthesised by Bhat et al. (Figure 7) and their inhibitory action against LdMetAPl and HsMetAPl was evaluated in vitro [33]. Compound 12 (IC50 = 3 µM) demonstrated a 20-fold reduction in efficacy for HsMetAPl (IC50 = 58 µM) and a good selectivity towards LdMetAPl.

Figure 7. The quinoline-thiazolidin-4-one Derivatives

Neri et al. synthesised a series of thiazolidine-2,4-dione derivatives (13a–13g) with antileishmanial act1v1ty (Figure 8) [34]. The antileishmanial activity of Compounds 13a–13g was observed in an EC50 concentration range of 44.16–70.98 µM for Leishmania braziliensis and 23.45–68.77 µM for Leishmania infantum. Halogen substituents were present in Positions 3, 4, or 5 of the phenyl group of the most potent compounds against L. infantum (13b, 13d, and 13f, EC50 = 23.45, 35.90, and 30.36 µM, respectively).

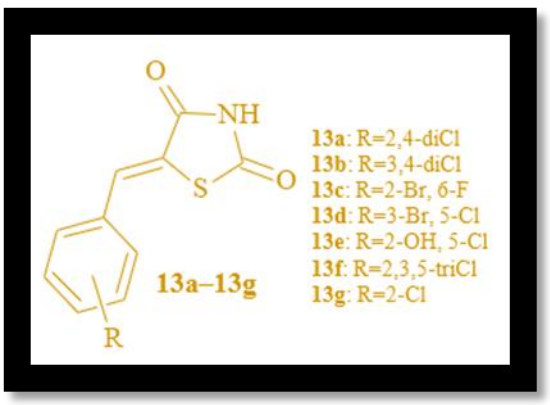


Figure 8. The 5-(Halogenbenzylidene)thiazolidine-2,4-dione derivatives

4.5 Neurological effect: The purpose of the study conducted by Lu et al. was to assess the potential neuroprotective properties of thiazolidin-4-one-1,3,5-triazine derivatives. In vitro, the derivatives significantly reduced NF-kB activity in RAW264.7 cells. In the in vivo trial, Compound 14, with an IC50 of 0.90 ± 0.12 µM, proved to be the most potent NF-kB inhibitor (Figure 9). [35]. In vivo tests, compound 15, a new benzodiazepine agonist, demonstrated suitable sedative-hypnotic activity, strong anticonvulsant activity, decreased memory impairment, and no influence on muscle relaxants. The maximal electroshock seizure threshold was 12.97 mg/kg, the pentabarbital-induced sleeping test had a threshold of 15.94 mg/kg, and the open-field test had a threshold of 21.07 kg/mg. [36]

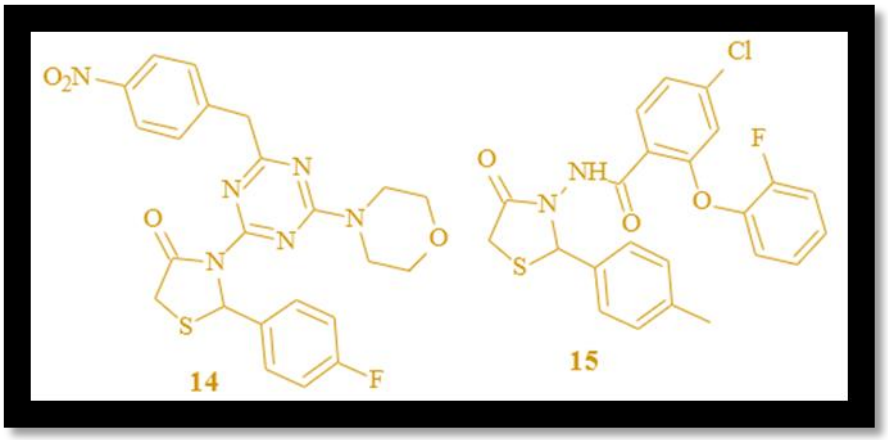


Figure 9. The 2-aryl thiazolidin-4-ones derivatives

4.6 Antimicrobial Activity: The synthesis and antibacterial screening of 4-oxothiazolidin-2-ylidene derivatives were carried out by Chaban et al. [37]. The growth inhibition (%) of tested compounds against four Gram-negative strains (Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, and Acinetobacter baumannii) and two fungal strains (Crypococcus neoformans var. Grubii and Candida albicans) was assessed in the first stage of antimicrobial screening. The compounds (16a–16d, 17a–17b, 18 and 19) (Figure 10) shown considerable microbial growth inhibition and were chosen for the next round of antimicrobial screening. Comparable to ceftriaxone in terms of antibacterial activity, Compounds 16b and 16c demonstrated MIC values between 4 and 32 µg/mL against every tested strain of bacteria. With MIC values of 4 and 8 µg/mL, respectively, Compounds 17a and 17b had the strongest antifungal activity, preventing the growth of C. neoforrnans. With growth inhibition ranging from 85.3 to 97.9%, Compounds 20a–20d and 21 containing unsubstituted amido group demonstrated strong antibacterial action against S. aureus. [38]

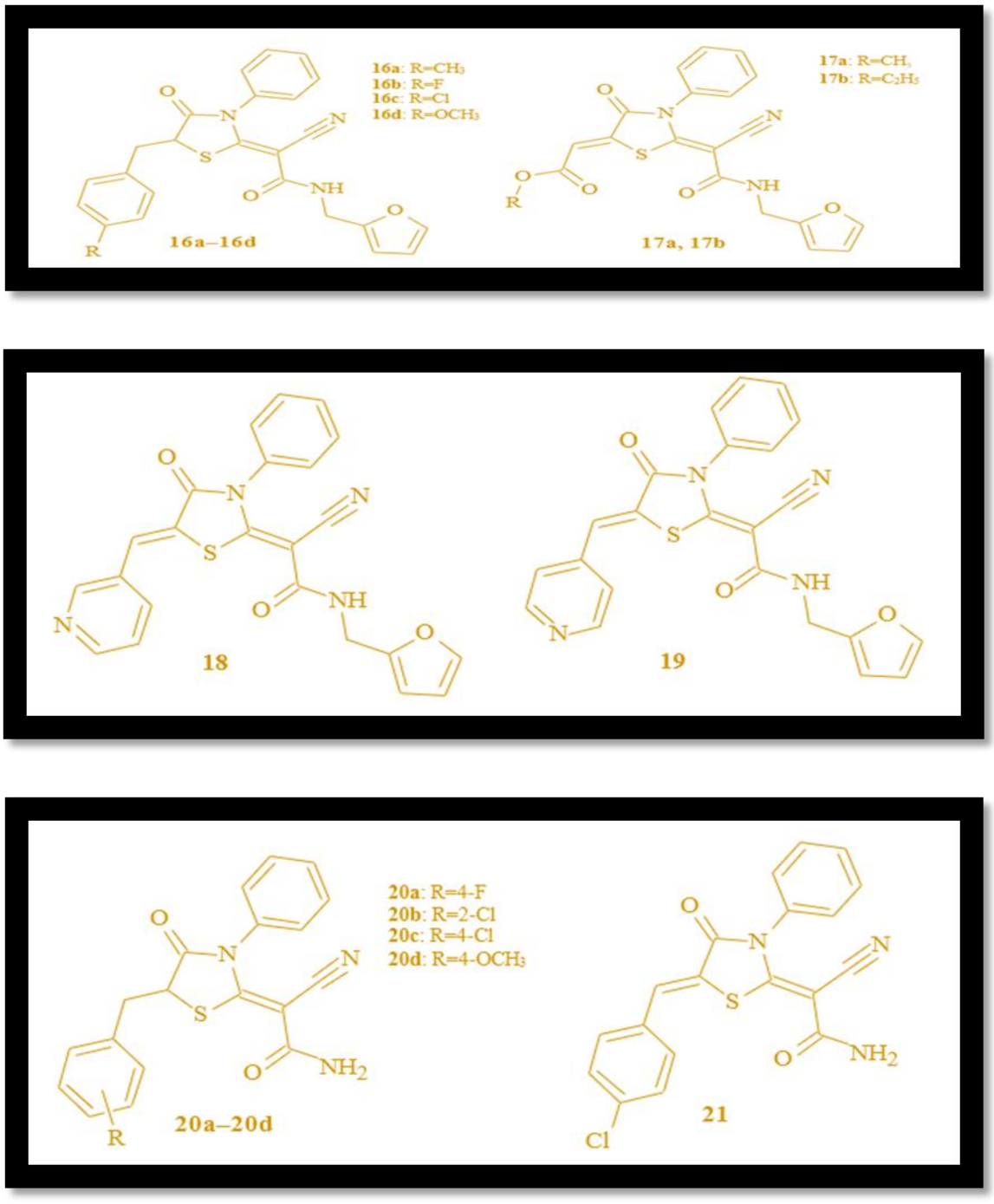
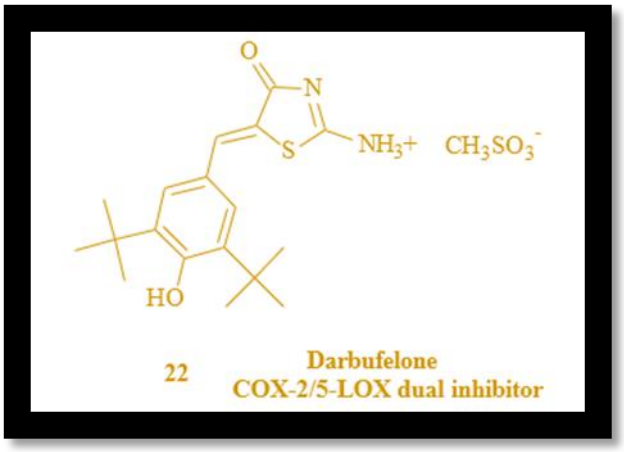


Figure 10. The structures of 4-oxothiazolidin-2-ylidene derivatives

4.7 Anticonvulsant Activity: Darbufelone analogues (23, 24, and 25) were synthesised by Mishchenko et al., who then assessed the anticonvulsant properties of the compounds using the scPTZ test (Figure 11) [39]. In these investigations, sodium valproate, celecoxib, darbufelone methansulfonate, and phenytoin were utilised as reference medications. Rheumatoid arthritis is treated with darbufelone methanosulfonate, a COX-2/5-LOX (22) dual inhibitor with anti-inflammatory properties [40, 41]. Regarding their anticonvulsant

effectiveness, each of the derived compounds exhibited good pharmacological action. In order to ensure the complete life of the studied animals, the action included a reduction in the frequency of seizures, a drop in clonic and tonic seizures, and a protective effect against mortality. When compared to darbufelone, the usage of the compound 25 derivative resulted in a significant reduction in the number of clonic seizures by 16.67% and a reduction in tonic seizures by 50%. Compared to the control group, there was a statistically significant drop in the severity of seizures by 1.52 times, and a decrease in the mortality rate to 69.04%.



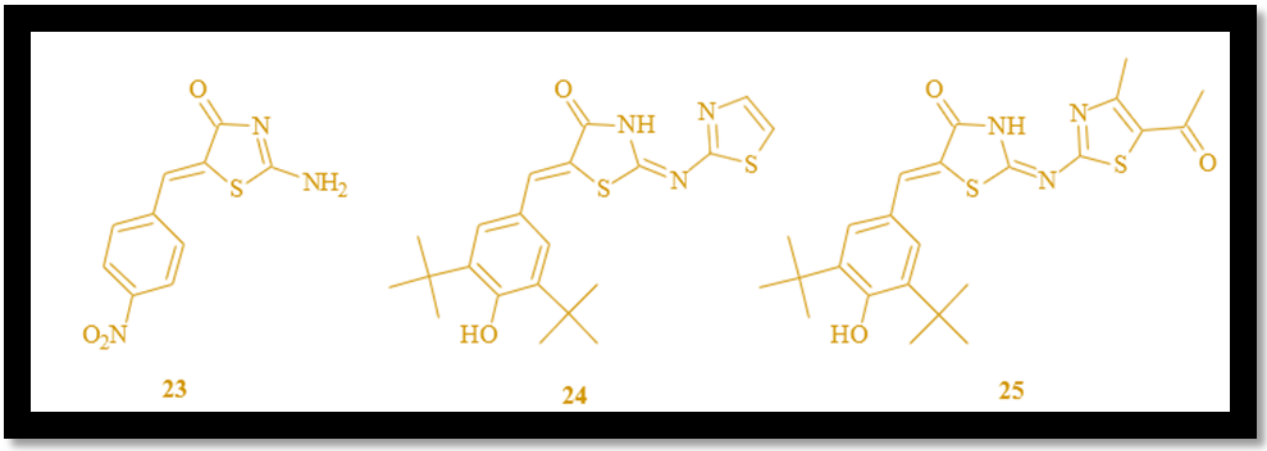


Figure 11. Darbufelone and its analogues

4.8 Antidiabetic Activity: Several compounds (26a-26e, 27a-27e, and 28a-28e) with possible antidiabetic action were synthesised in the 2020 study that was reported (Figure 12) [42]. The Calbiochem PTPI B colorimetric kit was used to assess these compounds for their inhibitory activity against PTPIB in vitro. Standard practice was to utilise suramin. The effect of each chemical on the generation of phosphate was measured in order to determine its inhibitory potency; the findings of the inhibition assay are given as IC50. The resultant compounds

generally shown fair to moderate PTPIB inhibition. The range of their IC50 values was 5.88 µM (27e) to 29.78 µM (28a). In contrast, the reference drug, suramin, had a result of 10.98 µM. [43]

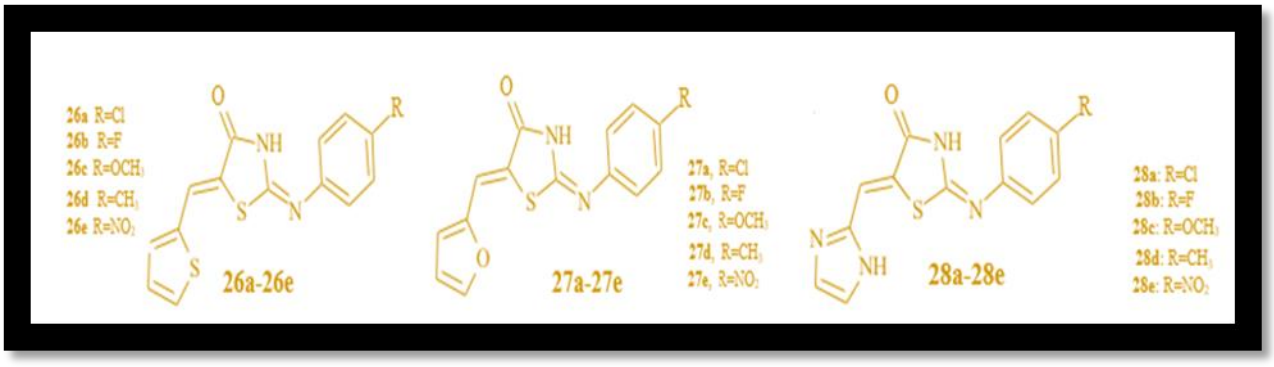


Figure 12: The 5-Heterylmethylidenethiazolidin-4-ones

4.9 Antioxidant Activity: A group of researchers demonstrated in a publication published in 2020 that the thiazolidine heterocyclic ring's adaption to the human peroxiredoxin 5 enzymes may be caused by specific substituents to the ring [44]. This enzyme is crucial in the defence against oxidative stress and the battle against free radicals. The TBARS assay was used to assess the antioxidant activity of compounds 30a–30i, 31, 32a–32r, 33a, and 33b on lipid peroxidation (Figure 13). According to the investigations, the 4-hydroxyphenyl substituent (Compounds 32i and 32r) at Position 4 replaced the cyclohexyl moiety, greatly increasing the structures' antioxidant activity. Compounds 32i and 32r exhibited the highest lipid peroxidation inhibitory action, with respective EC50 values of 0.565 ± 0.051 and 0.708 ± 0.074 mM. It has been demonstrated that the activity reaches a maximum when there is no substitution at the Rl location (Compound 3i). The forerunner of derivatives of thiazolidine-4-one (32a-32r) The EC50 range for compounds 30a–30i's antioxidant activity was 1.128–2.489 mM. [45]

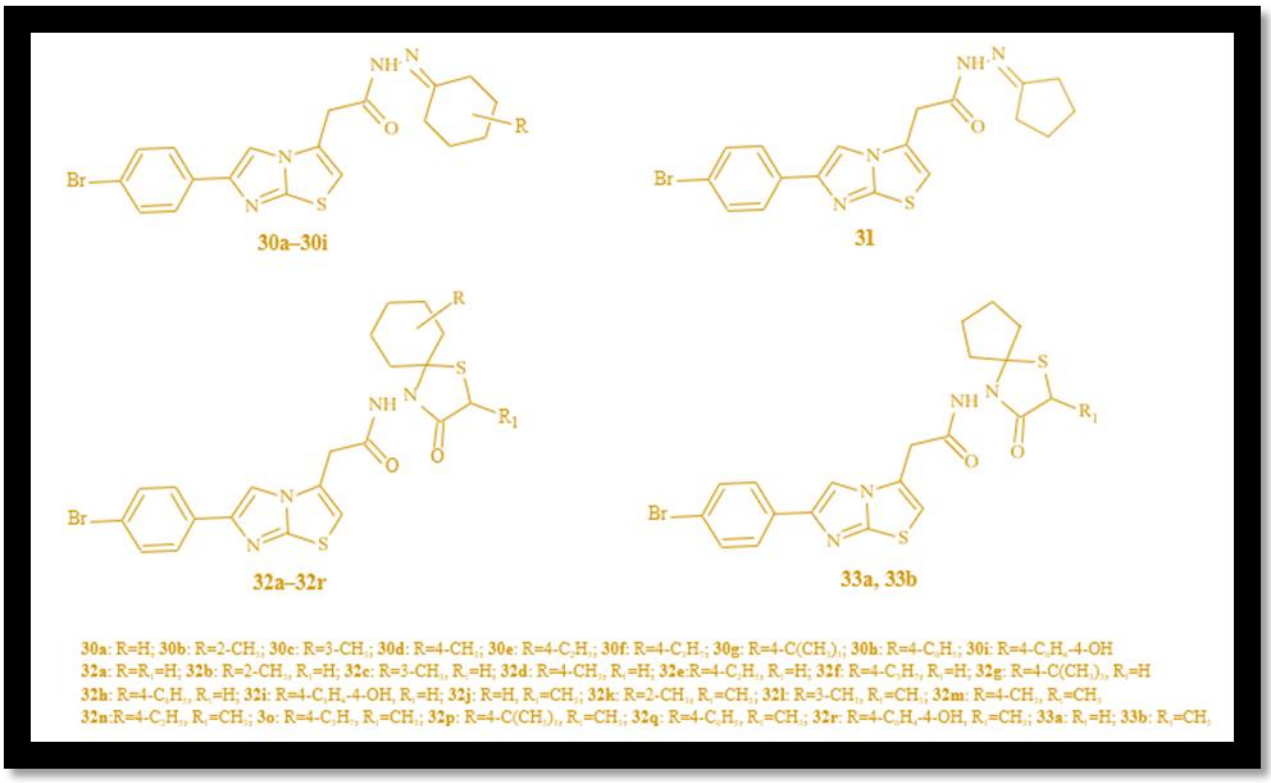


Figure 13. Imidazo[2,1-b]thiazole-thiazolidin-4-one hybrids (32a–32r, 33a and 33b) and their precursors (30a–30i and 31)

4.10 Antiviral Activity: A variety of thiazolidin-4-one-1,3,4-thiadiazole hybrids were evaluated by Al-Behery et al. [46] against the genotype of the hepatitis C virus. The findings verify that the presence of 2-chloro-6-fluorophenyl and 2-chlorophenyl substituents in the benzene ring of the 1,3,4-thiadiazole heterocycle has a greater inhibitory effect on HCV NS5B GT4a than the presence of 3-fluoro, 4-fluoro, and 4-chloro substituents. As opposed to ortho substitution, meta and para substitution in the 5-benzylidene moiety of the thiazolidin-4-one ring was more advantageous for antiviral activity. Compounds 34 and 35 showed the most powerful activity among the series of thiazolidin-4-one-1, 3, 4-thiadiazole hybrids, with IC50 values of 0.338 ± 0.01 and 0.342 ± 0.01 µM, respectively. [47]

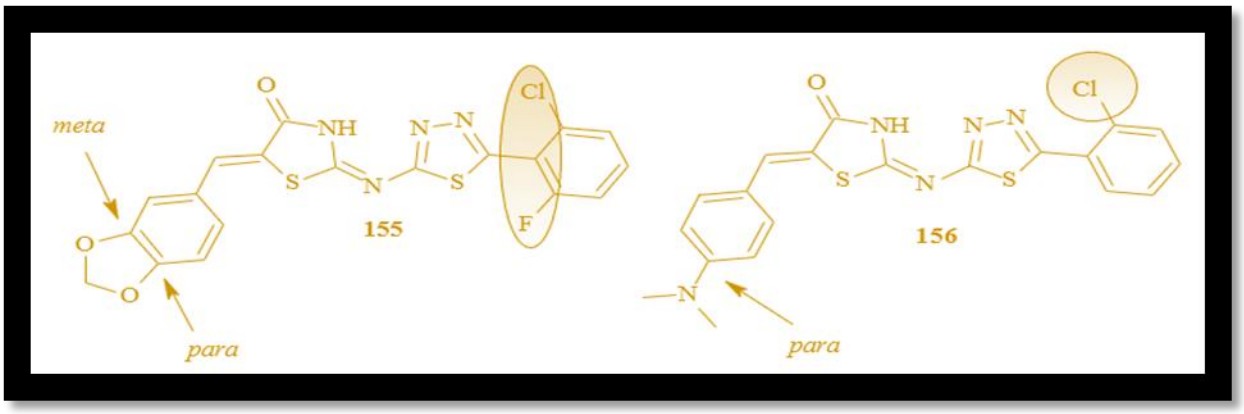


Figure 14. The structures of thiazolidin-4-one-1,3,4-thiadiazoles

5. CONCLUSION

An overview of the most recent research on antiviral, antitubercular, analgesic, analgesic, anticonvulsant, antioxidant, and antitubercular properties is given in this article. In the biological activity types listed above, the thiazolidin-4-one system is quite successful. Moreover, some of them displayed multitarget or dual-target behaviour. When treating complex illnesses like diabetes, cardiovascular disease, neurodegenerative disorders, or cancer, these qualities are advantageous. Consequently, the thiazolidin-4-one derivatives group may benefit from this review's continued development as possible bioactive agents.

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