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Mini-review

4-Thiazolidinone – A biologically active scaffold

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Abstract

The broad and potent activity of 4-thiazolidinones has established it as one of the biologically important scaffolds. This article is an effort to highlight the importance of the 4-thiazolidinones in the present context and promise they hold for the future.

Keywords: 4-Thiazolidinones; Solid-phase synthesis; Spectral studies; Stereochemistry; Biological activity

1. Introduction

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures [1], with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry [2]. There are numerous biologically active molecules with five-membered rings, containing two hetero atoms. Thiazolidine (**A**) is an important scaffold known to be associated with several biological activities (Fig. 1) [3].

2. 4-Thiazolidinones

2.1. Chemistry of 4-thiazolidinones

4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the 4-position (**1**). Substituents in the 2-, 3-, and 5-positions may be varied, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position (R and R′ in **2** or X in **3**). Variations in the substituents attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by **2** and **3** (Fig. 2).

2.2. Syntheses of 4-thiazolidinones

Several protocols for the synthesis of 4-thiazolidinones are available in the literature [4–12]. Essentially they are three-component reactions involving an amine, a carbonyl compound, and a mercapto-acid. The process can be either a one-pot three-component condensation or a two-step process [13–15].

An improved protocol has been reported wherein *N*,*N*-dicyclohexyl carbodiimide (DCC) or 2-(1*H*-benzotriazo-1-yl)-1,1,3,3-tetramethyl uraniumhexafluorophospate (HBTU) (Scheme 1) is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and improved yields [16,17]. The DCC/HBTU-mediated protocol has the advantage of mild reaction conditions, a very short reaction time, and product formation in almost quantitative yields. More importantly, yields of the 4-thiazolidinones are independent of the nature of the reactants. This modification is compatible with a solid-phase combinatorial approach to generate a library of compounds.

Cesur et al. and Vicini et al. have reported another method of synthesis of 4-thiazolidinones by the use of thiocyanate, alkylisothiocynate and ammonium thiocyanate with hydrazide/

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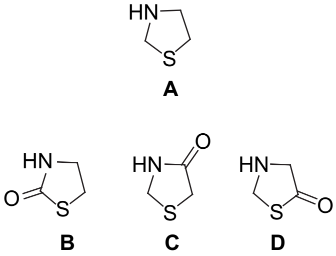


Fig. 1. Substructures based on thiazolidine.

acetamide, followed by the treatment with ethyl bromoacetate and sodium acetate [18,19].

Ottana et al. also reported synthesis of 4-thiazolidinones using the starting material *N*-propyl-*N′*-phenylthiourea, obtained by the reaction of propylamine and phenylisothiocyanate in chloroform at room temperature for 4 h followed by work-up under acidic conditions [20].

Fraga-Dubreuil et al. pioneered the use of task-specific ionic liquid as synthetic equivalent of ionic liquid-phase matrice for the preparation of a small library of 4-thiazolidinones [21]. The starting ionic liquid-phase (ethyleneglycol) is functionalized in good yields with 4-(formylphenoxy)butyric acid by using usual esterification reaction conditions (DCC/DMAP as catalyst). The synthesis of the ionic liquid-phase bound 4-thiazolidinones was performed by a one-pot three-component condensation under microwave dielectric heating.

Recently Dandia et al. have reported a microwave-assisted three-component, regioselective one-pot cyclocondensation method for the synthesis of a series of novel spiro[indole-thiazolidinones] using an environmentally benign procedure at atmospheric pressure in an open vessel. This rapid method produces pure products in high yields within few minutes, in comparison to a conventional two-step procedure [22].

Holmes et al. reported solution and polymer-supported synthesis of 4-thiazolidinones derived from amino acids [23] (Scheme 2). A three-component condensation of an amino ester or resin bound amino acid (glycine, alanine, β-alanine, phenylalanine, and valine), an aldehyde (benzaldehyde, *o*-tolualdehyde, *m*-tolualdehyde, *p*-tolualdehyde, and 3-pyridine carboxaldehyde), and a α-mercapto carboxylic acid, led to the formation of 5-membered heterocycles.

Recently Maclean et al. reported an encoded 4-thiazolidinone library on solid phase [24]. Three sets of 35 building blocks were combined by encoded split-pool synthesis to give a library containing more than 42,000 members. Building block selection was based in part on a novel small molecule follicle stimulating hormone receptor agonist hit and in part for diversity. HPLC/MS techniques were applied at the single-bead level to build confidence in the reliability of library construction.

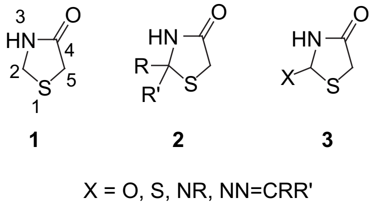
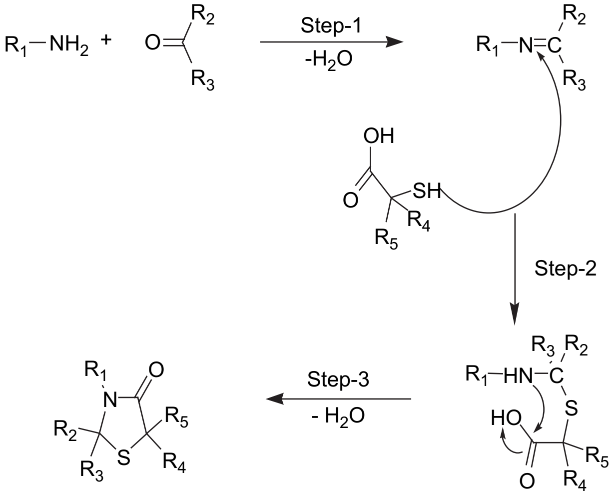


Fig. 2. 4-Thiazolidinone ring and substitutions.



Scheme 1. Syntheses of 4-thiazolidinone derivatives in DCC/HBTU protocol.

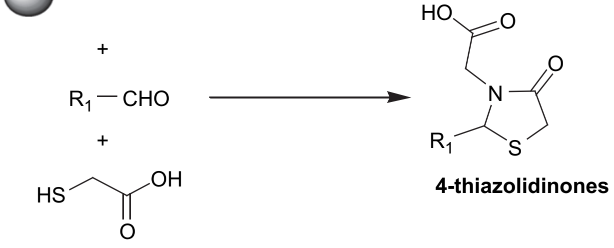
2.3. Spectral studies on 4-thiazolidinones

2.3.1. Infrared

Taylor et al. reported the characteristic bands in the infrared spectra of several 2-substituted 4-thiazolidinones [25,26]. He described the criteria for determining the *cis* and *trans* configurations of these compounds. The *cis* isomer is favored when H-bonding is otherwise impossible. In other circumstances, the *trans* isomer is the stable form. The imino–amino tautomerism of 2-imino-4-thiazolidinones and its derivatives was studied by infrared spectroscopy. The spectral data showed that in crystal state imino isomer is predominant whereas in solution, amino isomer predominates.

2.3.2. ^{1}H NMR

The ^{1}H NMR spectra of the 4-thiazolidinones depend largely on the substituents present at the different positions



Scheme 2. Solid-phase syntheses of 4-thiazolidinones.

of the thiazolidine ring. The 2,3-disubstituted 4-thiazolidinones (Fig. 3) have three characteristic peaks in the NMR spectrum, H(2) appears as a singlet in the range of 5–6 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 3.5–3.9 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 [27].

2.3.3. ^{13}C NMR

Vogeli et al. studied the ^{13}C NMR spectra of a series of substituted 4-thiazolidinones in $CDCl_3$; the chemical shift and C, H spin coupling constants are given. Various constitutional isomers have been differentiated, and the configuration of trisubstituted exocyclic C=C have been established on the basis of C,H spin coupling constants over two and three bonds (Fig. 4) [28].

2.3.4. Mass spectral studies

Mass spectra of different 4-thiazolidinones were studied and reported on the basis of molecular ion peak and fragmentation pattern. The molecular ion peaks in the mass spectra of 2-imino-4-oxothiazolidinyl-5-acetates have been assigned [29]. The principle daughter ion peaks were determined by means of deuterium exchange and high-resolution mass spectroscopy (Fig. 5).

2.3.5. X-ray crystal structure studies

Ottana et al. reported the X-ray diffractometric analysis of a representative compound 5-(4-methoxy-benzylidene)-2-phenylimino-thiazolidin-4-one unambiguously confirmed the *Z* configuration at the chiral axis [20].

Dandia et al. also reported the crystal data and structure refinement parameters of spiro[indole-thiazolidine]-dione (Fig. 6) [22].

2.4. Stereochemistry of 4-thiazolidinones

Theoretically, in the case of 2,3-disubstituted 4-thiazolidinones two diastereoisomers (**I** & **II**, Fig. 7) are possible. However, Vigorita et al. have done the conformational studies on various 2-aryl-3-(2-pyridyl)-4-thiazolidinones and have found that the preferred configuration (**I**, Fig. 7) is that in which the C(2) proton and one of the methylene protons are in *cis* 1,3 diequatorial relationship [30]. It is due to the fact that the phenyl group prefers the axial orientation to avoid the steric crowding with pyridyl group.

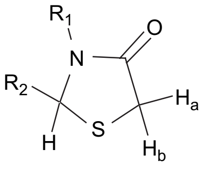


Fig. 3. Substitutions on 4-thiazolidinone ring.

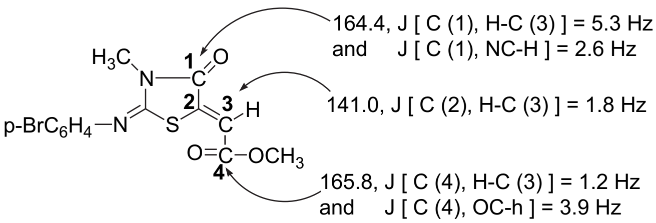


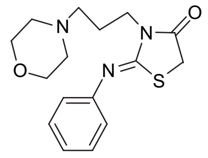
Fig. 4. Representative ^{13}C NMR data of 4-thiazolidinone.

3. Biological activity of 4-thiazolidinones

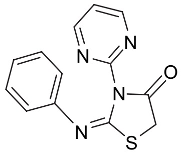
3.1. Anticonvulsant activity

The anticonvulsant activity of several series of 2-(arylimino)/(arylhydrazono)-3-aryl/(alkylaryl)/furfuryl/2-pyrimidyl/cycloalkyl/(substituted amino)/(3-(*N*-morpholin-4-yl-propyl)-4-thiazolidinones has been studied against pentylenetetrazol-induced seizures [31–34] in albino mice of either sex at a dose of 100 mg/kg. Most of the compounds were found to exhibit protection against pentylenetetrazol-induced seizures, and the degree of protection ranged up to 80%. However, no definite structure–activity relationship could be observed regarding the anticonvulsant activity possessed by thiazolidinones.

3.2. Hypnotic activity



3-(3-(N-Morpholin-4-yl)-propyl)-2-phenylimino-4-thiazolidinone



2-Phenylimino-3-(pyrimidin-2-yl)-4-thiazolidinone

Several 3-(3-(*N*-morpholin-4-yl-propyl)-2-(arylimino)-4-thiazolidinones [35] and 2-(arylimino)-3-(pyrimidin-2-yl)-4-thiazolidinones [36] 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. The increase in the duration of sleep ranged from 10 ± 3 min in untreated control to 98.6 ± 10 min in mice pretreated with substituted thiazolidinones.

3.3. Antitubercular activity

The emergence of multi-drug resistant tuberculosis, coupled with the increasing overlap of AIDS and tuberculosis

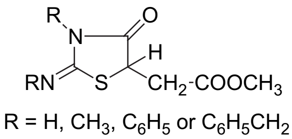


Fig. 5. Representative mass data of 4-thiazolidinone.

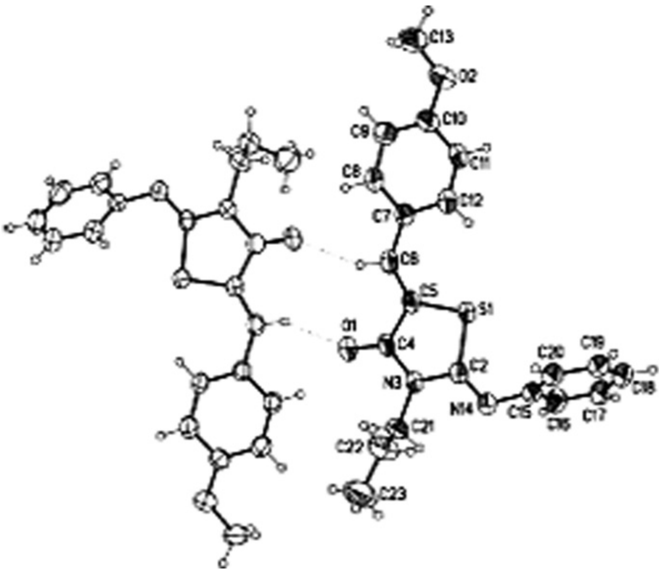
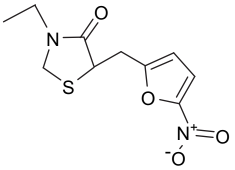
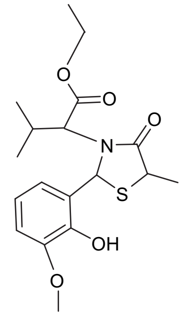


Fig. 6. X-ray structure of 5-(4-methoxy-benzylidene)-2-phenylimino-4-thiazolidinone.

pandemics has brought tuberculosis to the forefront as a major worldwide health concern.



3-Ethyl-5-(5-nitro-furan-
2-ylmethyl)-
4-thiazolidinone



2-[2-(2-Hydroxy-3-methoxy-phenyl)-
5-methyl-4-oxo-thiazolidin-3-yl]-
3-methyl-butyric acid ethyl este

Turkevich et al. reported few 2-imino-4-thiazolidinone derivatives as possible antitubercular compounds [37]. In other study, 5-(5-nitrofurfurylidene)-3-ethylrhodanine has been found to be a promising tuberculostatic compound [38]. Few derivatives of 2-imino-4-thiazolidinones have also been reported as having antitubercular activity with low toxicity. Repeated therapeutic doses were found to possess antitubercular activity comparable to streptomycin or phthivazid [39]. Kapustayak et al. has studied structure–tuberculostatic activity relationship of some 4-thiazolidinones [40]. Another study reported chemotherapeutic effectiveness against *Myobacterium tuberculosis*. A few derivatives were found to inhibit the growth of human tubercle bacilli, *H37Rv* strain, in a concentration of 12.5 μg/mL [41]. Several other derivatives of thiazolidinones have also been found to inhibit the growth of *Myobacterium tuberculosis H37Rv* strain [42,43]. In an attempt to find new inhibitors of the enzymes in the essential rhamnose biosynthetic pathway, a virtual library of 2,3,5 trisubstituted-4-thiazolidinones was created. These compounds were developed as diphosphate surrogates and inhibitors of **MurB** that bind at the nucleotide sugar site. It was found that the 4-thiazolidinone scaffold mimicked the diphosphate and specificity was generated through the different R-groups placed around the ring. These compounds were then docked into the active site cavity of 60 hydroxyl; dTDP-6-deoxy-D-xylo-4-hexulose 3,5-epimerase (**RmlC**) from *Mycobacterium tuberculosis*. The resulting docked conformations were consensus scored and the top 94 compounds were successfully synthesized and initially tested. Of those, 30 (32%) have >50% inhibitory activity (at 20 μM) in the coupled rhamnose synthetic assay. This work proposed a hypothesis that the thiazolidinone scaffold can act as a diphosphate mimetic [44]. The effects of thiazolidinone derivatives on other *Myobacterium* strains had also been found [45–47].

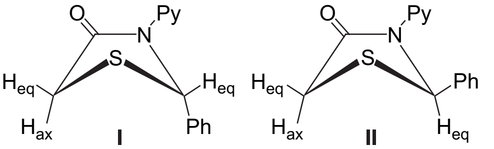
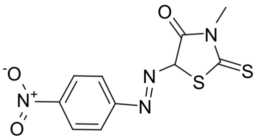
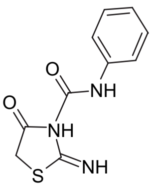


Fig. 7. Stereochemical orientation of 4-thiazolidinone.

3.4. Anthelmintic activity



3-Methyl-5-[(4-nitrophenyl)azo]
rhodanin

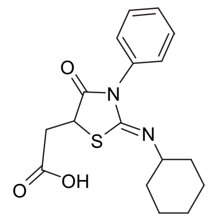


2-Imino-3-(2-acetamidophenyl)-
4-thiazolidinone

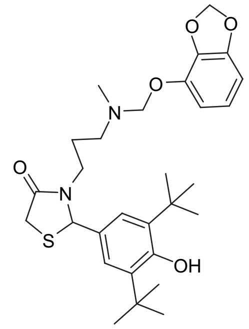
3-Methyl-5-[(4-nitrophenyl)azo]rhodanin, nitrodan, was reported as a potent anthelmintic compound [48–50] which was effective when administered in feed against *Hymenolepsis nana* and *Syphacia obvelata* infections in mice, *Asceridia galli* infections in chickens, and *Toxocera canis*, *Ancylostoma caninum*, and *Uncinaria stenocephala* infections in dogs, pigs and horses. 2-Imino-3-(2-acetamidophenyl)-4-thiazolidinone derivatives have been found to be effective in vitro against horse Strongyloids at concentration of 10^{-3}–10^{-6} M [51]. Various 2-thiono-3-substituted-5-[(2-methyl-4-nitrophenyl) azo]-4-thiazolidinones and 2-thiono-3-methyl-5-[(2,4-dinitrophenyl)azo]-4-thiazolidinone as potent anthelmintic agents, which were not only effective alone but also showed activity with other parasiticides [52,53].

3.5. Cardiovascular effects

Cardiovascular effects of a series of 2-cyclopentyl/(cyclohexylimino)-3-aryl-4-thiazolidinone-5-ylacetic acids on adult cats of either sex were reported [54]. All substituted 4-thiazolidinones induced hypotension of varying degree. The duration of hypotensive activity observed with most of these compounds was less than 15 min.



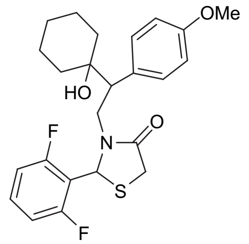
2-(cyclohexylimino)-3-phenyl-4-thiazolidinone-5-ylacetic acid



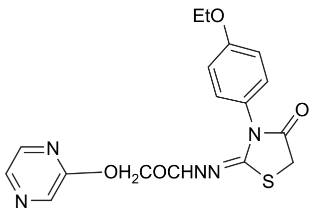
3-{3-[(Benzo[1,3]dioxol-4-yloxymethyl)-methyl-amino]-propyl}-2-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-thiazolidin-4-one

Suzuki et al. examined the effects of CP-060S (3-{3-[(Benzo[1,3]dioxol-4-yloxymethyl)-methyl-amino]-propyl}-2-(3,5-di-*tert*-butyl-4-hydroxy-phenyl)-4-thiazolidinone) on cardiac function and myocardial oxygen consumption (MVO$_2$) in anesthetized dogs [55]. CP-060S (10–300 mg/kg IV) decreased heart rate, increased aortic flow and decreased mean blood pressure in a dose-dependent manner. The PR (pulse rate) interval was significantly prolonged by administration of CP-060S (300 mg/kg IV). It increased coronary blood flow in a dose-dependent manner (10–300 mg/kg IV). Left ventricular end-diastolic pressure and maximal first derivative of left ventricular pressure were not significantly affected. CP-060S (10–300 mg/kg IV) increased coronary sinus blood flow and decreased arteriovenous oxygen difference and MVO$_2$ in a dose-dependent manner. Its effect on cardiac function and MVO$_2$ are qualitatively similar to those of diltiazem, a typical Ca-channel blocker.

3.6. Antibacterial activity



2-(2,6-Difluoro-phenyl)-3-[2-(1-hydroxy-cyclohexyl)-2-(4-methoxy-phenyl)-ethyl]-4-thiazolidinone



(Pyrazin-2-yloxy)-acetic acid [3-(4-ethoxy-phenyl)-4-oxo-thiazolidin-2-ylidene]-hydrazide

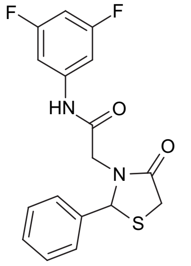
Several 2-[(dichlorophenyl)imino]-4-thiazolidinones and 2-(arylhydrazino)-4-thiazolidinones and their corresponding 5-arylidine derivatives were tested against *Staphylococcus aureus*. The antibacterial activity of 5-arylidine derivatives of both 2-[(dichlorophenyl)imino]/2-(arylhydrazino)-4-thiazolidinones was found greater than that of the parent compound [56]. The screening data of more than 50 thiazole and thiazolidinone derivatives against some common bacteria revealed that the thiazolidinones were more active than the thiazoles [57]. An enhancement in the activity was observed with mercurated thiazolidinone derivatives as compared to nonmercurated derivatives. Novel 2,3-disubstituted-1,3-thiazolidin-4-one derivatives which are venlafaxine analogs were tested against *Bacillus subtilis* and *Escherichia coli*, and found to exhibit potent inhibitory activity compared to that of standard drugs at the tested concentrations. From the results obtained, it was concluded that the presence of two fluorine atoms at 2nd and 6th positions in 2-(2,6-difluoro-phenyl)-3-[2-(1-hydroxy-cyclohexyl)-2-(4-methoxy-phenyl)-ethyl]-4-thiazolidinone might be the reason for the significant inhibitory activity [58]. Different derivatives of *N*-[3,4-disubstituted-1,3-thiazol-2(3*H*)-ylidene]-2-(pyrazin-2-yloxy)acetohydrazide and *N*-[(2)-3-(4-alkyl/aryl substituted)-4-oxo-1,3-thiazolidin-2-ylidene]-2-(pyrazin-2-yloxy)-acetohydrazide compounds when evaluated for antibacterial activity against the Gram-positive (*S. aureus* and *B. subtilis*) and Gram-negative (*E. coli* and *S. typhi*) strains of bacteria, showed good antibacterial activity. The structure–activity relationship revealed that thiazolidine ring is essential for antibacterial activity [59].

Bondock et al. reported some new 4-thiazolidinones synthesized from 1-chloro-3,4-dihydronaphthalene-2-carboxaldehyde for their antimicrobial activity [60]. Thirteen compounds were screened in vitro for their antimicrobial activities against three strains of bacteria *Bacillus subtilis*, *Bacillus megaterium* and *Escherichia coli* by the agar diffusion technique [61]. A 1 mg/mL solution in dimethylformamide was used. The bacteria were maintained on nutrient agar and Czapek's-Dox agar media, respectively.

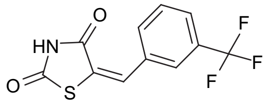
Vicini et al. and other workers also examined some 4-thiazolidinone derivatives for their antimicrobial activity [19].

3.7. Anticancer activity

A new series of 2-aryl-4-oxo-thiazolidin-3-yl amides and derivatives were synthesized and evaluated for their ability to inhibit the growth of prostate cancer cells. The antiproliferative effects of synthesized compounds were examined in five human prostate cancer cell lines (*DU-145*, *PC-3*, *LNCaP*, *PPC-1*, and *TSU*), and in *RH7777* cells (negative controls).



N-(3,5-Difluoro-phenyl)-2-(4-oxo-2-phenyl-thiazolidin-3-yl)-acetamide



5-(3-trifluoromethylbenzylidene)-2,4-thiazolidinedione

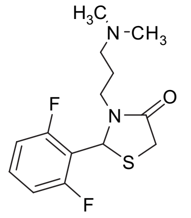
From that study, few potent compounds were detected, which were effective in killing prostate cancer cells with improved selectivity compared to serine amide phosphates (SAPs) [62].

Cyclooxygenase (COX) is a well-known enzyme that catalyzes the conversion of arachidonic acid to prostaglandins (PGs) in the cells. However, PGs are also important in cancer pathogenesis. Study reported COX-2 inhibitors as potential drugs aimed at the prevention and treatment of cancer, especially colorectal cancer. Some representative 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* [63], *HCT-116* [64], *HT-29* [65], *HCT-8* [66], and *H-630* [67], obtained from the American Type Culture Collection (Manassas, VA); among them, *HT-29* cell line expresses high COX-2 levels [68–70]. 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* [71].

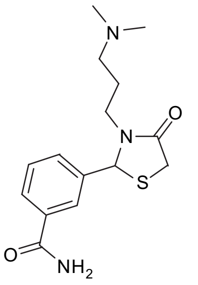
3.8. Antihistaminic activity (H1-antagonist)

Thiazolidinones are known to show their action on histamine receptors. The geometrical similarity between 2-aryl-3-[3-(*N*,*N*-dimethylamino)propyl]-1,3-thiazolidin-4-ones and different histamine (H1) antagonists such as bamipine, clemastine, cyproheptadine, triprolidine, promethazine, chlorpheniramine, and carbinoxamine [72,73] prompted Diurno et al. to evaluate these compounds for antihistaminic activity [74].

Singh et al. have investigated the antihistaminic (H1-antagonist) activity of 2,3-disubstituted thiazolidin-4-ones and concluded that the hydrophobic substitution at the 4-position of the phenyl ring and cumulative negative polar effects of all the substituents in the phenyl group are advantageous for antihistaminic activity [75,76].



2-(2,6-Difluoro-phenyl)-3-(3-dimethylamino-propyl)-4-thiazolidinone



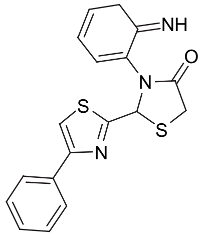
2 -(3 -Carbamoyl-phenyl)-3 -[3 -(N,N-dimethylamino) -propyl] -1,3 -thiazolidin-4 -one

In another study, Diurno et al. synthesized, characterized and evaluated a new series of 2-(substituted-phenyl)-3-[3-(*N*,*N*-dimethylamino)-propyl]-1,3-thiazolidin-4-ones for their capacity to inhibit the contraction induced by histamine on guinea pig ileum [77]. 2-(3-Carbamoyl-phenyl)-3-[3-(*N*,*N*-dimethylamino)-propyl]-1,3-thiazolidin-4-one and derivatives of series as free bases were converted into the corresponding hydrochlorides for the pharmacological assays. The H1-antihistaminic activity of the synthesized compounds was evaluated in vitro by measuring their ability to inhibit the histamine-induced contractions of isolated guinea pig ileum [78]. Results show that whenever the phenyl moiety of the 4-thiazolidinones interacts with a complementary area of the H1-receptor, the **p** interaction was enhanced by hydrophobic substituents increasing the HOMO energy and is affected by the size of the 4-alkyl substituent. These studies have highlighted the importance of overall hydrophobicity of the compounds in deciding the antihistaminic activity [79,80].

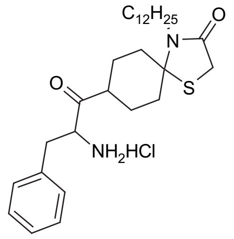
3.9. Antifungal activity

Rao et al. reported high fungal activity of some mercurated derivatives of 4-thiazolidinones against *Aspergillus niger* at a dilution of 1:10,000. Various 2-(4′-arylthiazolyl-2′-imino)-3-aryl-4-thiazolidinones have been found to be sufficiently active against *A. niger* and *Alternaria tenius* at a dilution of 1:10,000 [81].

Matolcsy et al. have found very high antifungal activity associated with the derivatives of 2-thiono-4-thiazolidinones against *A. tenius* and *Botrytis allii*. Several 2-[(*o*-methylphenyl) imino]-3-aryl-4-thiazolidinones and their 5-phenyl azo derivatives have been found to be very good fungicidal agents against *Helminthosporium euphorbiae* [82]. 3-Ethyl-5-methyl-2-[(4-chlorobenzo thiazol-2-yl)imino]-4-thiazolidinone and 3-ethyl-5-methyl-2-[(5-chlorobenzothiazol-2-yl)imino]-4-thiazolidinone were found to exhibit 100% inhibition of spore germination of *A. tenius* at concentration of 1:1000, 1:5000 and 1:10,000 [83].



2-(4'-phenylthiazolyl-2'-imino)-3-phenyl-4-thiazolidinones



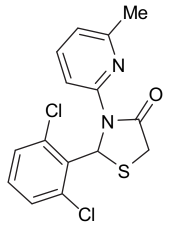
8-(2-Amino-3-phenyl-propionyl)-4-dodecyl-1-thia-4-aza-spiro[4.5]decan-3-one

Katti et al. synthesized 8-(2-amino-3-phenyl-propionyl)-4-dodecyl-1-thia-4-aza-spiro [4.5] decan-3-one and derivatives and evaluated against two strains of *Candida albicans* and one strain of *Cryptococcus neoformans* in terms of (MIC) in 50 μg/mL, following the Serial Double Dilution reference method [84] and found to possess moderate to good activity against the three fungal strains [85].

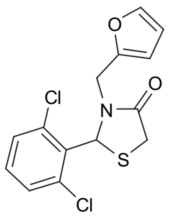
Recently Dandia et al. screened few microwave synthesized spiro[3*H*-indole-3,2′-thiazolidine]-3′(1,2,4-triazol-3-yl)-2,4′(1*H*)-dione for their antifungal activity against three pathogenic fungi, namely *Rhizoctonia solani*, causing root rot of okra, *Fusarium oxysporum*, causing wilt of mustard and *Colletotrichum capsici*, causing leaf spot and it was found that all compounds show good activity against these pathogens, indicating that the incorporation of triazole ring enhances the antifungal activity of compounds [22]. Baynate and Thiram, recommended as standard fungicides as seed dressers to control this disease, also have a –N–C–S linkage, similar to the synthesized compounds, which is responsible for their antifungal activity.

3.10. Antiviral activity

Recently, there are several reports in the literature regarding the anti-HIV activity of 2,3-diaryl-1,3-thiazolidin-4-ones. Some derivatives proved to be highly effective in inhibiting HIV-1 replication at nanomolar concentration with minimal cytotoxicity. They act by inhibiting reverse transcriptase enzyme, which plays an essential and multifunctional role in the replication of the human immunodeficiency virus (HIV). Barreca designed and synthesized 2,3-diaryl-1,3-thiazolidin-4-one derivatives as new NNRTIs [3a].



2-(2,6-Dichloro-phenyl)-3-(6-methyl-pyridin-2-yl)-4-thiazolidinone

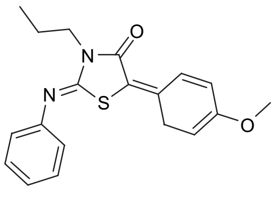


2-(2,6-Dichloro-phenyl)-3-furan-2-ylmethyl-4-thiazolidinone

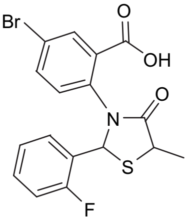
Results show that the compounds were highly potent anti-HIV agents, up to 10-fold more active than the corresponding 1-arylsubstituted 1*H*,3*H*-thiazolo[3,4-a]benzimidazole derivative (TBZs) lead compounds, probably because conformational changes may allow the correct positioning of the new molecules for a facile attack at the active site residues. Mechanism of action of the compounds was attributed to the inhibition of HIV-1 RT. In addition, these compounds were minimally toxic to MT-4 cells and their selectivity indices were remarkably high. In fact, 6-methylpyridin-2-yl derivatives, particularly compound 2-(2,6-dichlorophenyl)-3-(6-methyl-pyridin-2-yl)-4-thiazolidinone, possessed the most promising selectivity index of 6470 and activity with EC50 value of 0.044 μM. In terms of SARs, anti-HIV activity was strongly enhanced by introducing a 2-pyridinyl substituent at the N-3 atom of the thiazolidinone ring and in particular by two chlorine atoms at 20 and 60 positions of the phenyl rings at C-2. In another study, Katti et al. in collaboration with E. De Clercq and his group have reported that some novel 2,3-diaryl substituted 4-thiazolidinone derivatives containing N3-substituted furfuryl amine particularly, 2-(2,6-dichloro-phenyl)-3-furan-2-ylmethyl-4-thiazolidinone, show 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 μM [86].

3.11. Anti-inflammatory activity (COX-inhibitors)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are an inhomogeneous family of pharmacologically active compounds used in the treatment of acute and chronic inflammation, pain, and fever. Although several mediators support the inflammatory processes, the main target of NSAIDs is Cyclooxygenase (COX) [87], the enzyme involved in the first step of the conversion of arachidonic acid to prostaglandins (PGs). The latter regulate important functions in the gastric, renal, and emetic systems and are known to mediate all inflammatory responses [88,89]. The therapeutic effects are mainly due to the decrease of proinflammatory PGs produced by COX-2, whereas their unwanted side effects result from the inhibition of constitutive COX-1 isoform.



5-(4-Methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone

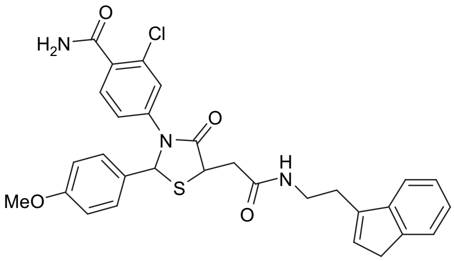


3-(4-bromo-2-carboxyphenyl)-2-(fluorophenyl)-5-methyl-4-thiazolidinone

Ottana et al. investigated 3,3′-(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinone] derivatives, which showed interesting stereoselective anti-inflammatory/analgesic activities together with better gastrointestinal safety profile than known NSAIDs [90], suggesting that they might preferentially interact with inducible COX-2 isoform. Synthesized 2-imino-4-thiazolidinones and 5-arylidene-2-imino-4-thiazolidinones were tested for in vivo anti-inflammatory activity in models of acute inflammation such as carrageenan-induced paw edema and pleurisy assays in rats [91,92]. All derivatives exhibited significant activity levels. In addition, the ability of such a new class of anti-inflammatory agents to inhibit COX isoform was assessed in murine monocyte/macrophage *J774* cell line assay. 5-(4-Methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone, the most interesting compound, showed promising interaction for COX-2 selectivity at concentration of 1 and 10 μM with 35 and 55% inhibition, respectively. In another study, Ashok Kumar et al. synthesized some new anthranilic acid derivatives, 2-substituted-3-(4-bromo-2-carboxyphenyl)-5-methyl-4-thiazolidinones and evaluated them for anti-inflammatory activity against carrageenan-induced edema in albino rats. The most active member of the series, 3-(4-bromo-2-carboxyphenyl)-2-(fluorophenyl)-5-methyl-4-thiazolidinone was compared with phenylbutazone for its relative anti-inflammatory potency at three graded oral doses (25, 50 and 100 mg/kg) and were found nearly equipotent, with ED50 = 100.0 and 94.4 mg/kg, respectively [3c].

Ottana et al. described the anti-inflammatory activity of 5-arylidene-2-imino-4-thiazolidinones [20]. All derivatives exhibited significant activity in models of acute inflammation such as carrageenan-induced paw and pleurisy edema in rats. In particular, 5-(3-methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone displayed high levels of carrageenan-induced paw edema inhibition, comparable to those of indomethacin. In addition, the ability of such a new class of anti-inflammatory agents to inhibit COX isoforms was assessed in murine monocyte/macrophage *J774* cell line assay. 5-(4-Methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone, the most interesting compound in such an experiment, was docked in the known active site of COX-2 protein and showed that its 4-methoxyarylidene moiety can easily occupy the COX-2 secondary pocket considered as the critical interaction for COX-2 selectivity.

3.12. Follicle stimulating hormone (FSH) receptor agonist activity



2-Chloro-4-[5-{[2-(3*H*-inden-1-yl)-ethylcarbamoyl]-methyl}-2-(4-methoxy-phenyl)-4-oxo-thiazolidin-3-yl]-benzamide

Maclean et al. reported the FSH agonist activity of an encoded 4-thiazolidinone library [24]. Among the hits discovered in these studies was compound 2-chloro-4-[5-{[2-(3*H*-inden-1-yl)-ethylcarbamoyl]-methyl}-2-(4-methoxy-phenyl)-4-oxo-thiazolidin-3-yl]-benzamide, which possessed moderate activity as an agonist of FSH, by virtue of its ability to stimulate a reporter cell line expressing the FSH receptor [93]. FSH is a 31-kDa heterodimeric glycoprotein, and the discovery of a small molecule FSH agonist was an unprecedented achievement [94]. An orally active compound of this class could be a useful addition to the portfolio of drugs available for the alleviation of female infertility. The potency of **1** was, however, too weak to be considered as a drug candidate (EC50 of 5−10 μM), and initial analoging studies failed to significantly improve on this activity.

4. Conclusion

The article has outlined the chemistry and biological activities of the 4-thiazolidinone scaffold. The synthetic methodologies indicate the simplicity, maneuverability and versatility, which offer the medicinal chemist a complete range of novel derivatives. The stereochemical orientation provides a further variety of products.

The high degree of protection against seizures can be positive signs for further investigation of 4-thiazolidinone derivatives as anticonvulsants. The activity of 4-thiazolidinones as antitubercular compounds in multi-drug resistant tuberculosis and their potent anthelmintic activity are promising. The broad spectrum antibacterial and antifungal activity of these compounds could lead to a new series of antimicrobials. The 4-thiazolidinone derivatives have demonstrated significant antiviral and anticancer activities. The follicle stimulating hormone receptor agonist action of these derivatives furthers their biological importance.

Thus 4-thiazolidinone scaffold is not only synthetically important but also possesses a wide range of promising biological activities. Future investigations of this scaffold could give some more encouraging results.

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