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Review Article

4-Thiazolidinone- A New Profile of Various Pharmacological Activities

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ABSTRACT

Thiazolidinone, a five-member heterocyclic compound involved in research aimed at evaluating new product that possess interesting biological activities and play vital role owing to its wide range of pharmacological activities like antibacterial, antifungal, antitubercular, anti-inflammatory, analgesic, anti-HIV, antidiabetic, anticancer, anticonvulsant, anthelmintic, insecticidal, hypnotic, amoebicidal, antipsychotic, antiparkinsonian, hypolipidemic and FSH agonist activity. The present review focuses on the development of 4-thiazolidinone with their potential activities.

INTRODUCTION

4-Thiazolidinones are the derivative of thiazole which belongs to five member heterocyclic ring system with multiple applications. The thiazole ring has been extensively studied and it forms a part of vitamin-B, Penicillins and the antibacterial thiazoles. Reduced thiazole serves in the study of polypeptide and proteins and occurs as structural units in compound of biological importance.Tetrahydro derivative of thiazole is known as thiazolidine and the oxo derivative of thiazolidine is known as thiazolidinone. The oxo group is at 4th position i.e. 4-thiazolidinone 1. Substituents in the 2-,3-, and 5- position may be varied, but the greatest difference in the structure and properties is exerted by the group attached to the carbon atom in the 2- position. Variation in the substituent attached to the nitrogen atom and the methylene carbon atom are possible for the structures represented by (2) and (3). 4-thiazolidinones gained attraction by researchers due to their broad spectrum of biological and pharmacological activities[1]. Several substituted thiazolidinone have been found to be possessed antitubercular, anthelmintic, analgesic, anti-inflammatory, anticancer, antidiabetic, hypnotic, hypolipidemic, and anticonvulsant. Cardiovascular activity is also found to be exhibited by some 4-thiazolidinone derivatives. A novel thiazolidinone herbicide is found to be potent inhibitors of glucose incorporation into cell wall material[66]. Present review is a brief account

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of various alteration conducted on 4-thiazolidinone ring and their associated biological and pharmacological activities.

Synthesis of 4-thiazolidinone

There are many protocols for the synthesis of 4-thiazolidinone, but the most common method is simple condensation of schiff's bases with mercapto acid (scheme-1)[2,3], The key functional group required for the reaction is an amine, carbonyl compound, and mercapto acid. By the classical method it required about 12 h, while the same reaction using microwave irradiation[4,5] required only 6-8 minutes.

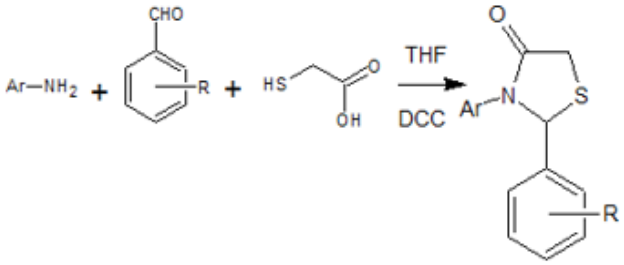
Antimicrobial activity

4-thiazolidinone show a broad spectrum of activity on various pathogens and a considerable research has been done on the synthesis of new potent antibacterial[6-9] and antifungal[10,11] 4-thiazolidinone. Novel 2-thiazolylimino-5-arylidene- 4-thiazolidinones[12], unsubstituted or arrying hydroxy, methoxy, nitro and chloro groups on the benzene ring (4), were synthesized by Paola Vicini, *et al.*, and assayed *In vitro* for their antimicrobial activity against various *Gram positive* and *Gram-negative* bacteria, yeasts and mould. The antimicrobial susceptibility testing was performed in vitro by the twofold broth dilution technique, The *Gram-positive* bacteria utilized in this study consisted of *Bacillus megaterium* BGSC 7A2, *Bacillus subtilis* ATCC 6633, *Bacillus thuringiensisvar*. kurstaki BGSC 4D1, *Sarcina lutea* ATCC 9341, *Staphylococcus aureus* ATCC 25923, *Staphylococcus* epidermidis ATCC 12228 and clinical isolates of methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Streptococcus agalactiae*, *Streptococcus faecalis*, *Streptococcus faecium* and *Streptococcus pyogenes*. The *Gram negative* bacteria included *Escherichia coli* SPA 27 and a clinical isolate of Haemophilus influenzae. The antifungal activity was assayed against yeasts (*Candida tropicalis* ATCC 1369 and *Saccharomyces cerevisiae* ATCC 9763) and moulds (*Aspergillus niger* ATCC 6275). The minimal inhibitory concentrations (MIC, µg/mL) were defined as the lowest concentrations of compound that completely inhibited the growth of each strain. The compounds were very potent towards all tested *Gram positive* microorganisms (MIC ranging from 0.03 to 6 µg/mL in most of the cases) and *Gram negative Haemophilus influenzae* (MIC 0.15–1.5 µg/mL), whereas no effectiveness was exhibited against *Gram negative Escherichia coli* and fungi up to the concentration of 100 µg/mL. The 5-arylidene derivatives showed an antibacterial efficacy considerably greater than that of the parent 2-(thiazol-2-ylimino) thiazolidin-4-one, suggesting that the substituted and unsubstituted 5-arylidene moiety plays an important role in enhancing the antimicrobial properties of this class of compounds. The remarkable inhibition of the growth of penicillin-resistant *staphylococci* makes these substances promising agents also for the treatment of infections caused by microorganisms resistant to currently available drugs. C. V. Kavitha, *et al.*, has carried out the synthesis of some novel bioactive venlafaxine analogs such as 2,3-disubstituted-1,3-thiazolidin- 4-ones[13]. All the synthesized compounds were screened for their efficacy as antimicrobials in vitro by the disk diffusion and microdilution method against pathogenic strains such as *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas fluorescens*, *Xanthomonas campestris* pvs, *Xanthomonas oryzae*, *Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporum*, *Trichoderma species*, and *Fusarium monaliforme* species. From the results obtained, it reveals that the presence of two fluorine atoms at 2nd and 6th positions in 2-(2,6-Difluorophenyl)-3- (2-(1-

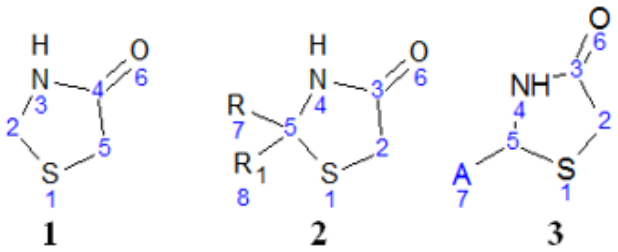
hydroxycyclohexyl)-2-(4-ethoxyphenyl)ethyl) thiazolidin-4-one (5) and the presence of 2-butyl-4- chloro imidazole in 2-(2-Butyl-4-chloro-1H-imidazol- 5-yl)-3-(2-(1-hydroxycyclohexyl)-2-(4-ethoxyphenyl) ethyl) thiazolidin-4-one (5) might be the reason for the significant inhibitory activity. Thiago M. de Aquino, *et al.*, has synthesized a new series of, 2-[(phenylmethylene)hydrazono]-4-oxo-3-phenyl-5-thiazolidineacetic acids[14] (6). All this compounds evaluated for anti-Toxoplasma gondii and antimicrobial activities. For anti-Toxoplasma gondii activity, in general, all compounds promoted decreases in the percentage of infected cells leading to parasite elimination. These effects on intracellular parasites also caused a decrease in the mean number of tachyzoites per cell in 2 mM concentration. In addition, most of the 4-thiazolidinones showed more effective toxicity against intracellular parasites, with IC50 values ranging from 0.05 to 1 mM. According to results of antimicrobial activity, compounds with R = 2-fluoro (MIC = 40 µg/mL; MBC = 30 µg/mL), R = 4-dimethylamino (MIC = 40 µg/mL; MBC = 30 µg/mL), and R = 3,5-di-tert-butyl-4-hydroxy (MIC = 35 µg/mL; MBC = 30 µg/mL) were more active than chloramphenicol against M. luteus, R = 2,4- dichloro, (MIC = 70 µg/mL; MBC = 60 µg/mL) was more active than rifampicin against M. tuberculosis, and the compounds R = 4-fluoro, 4-dimethylamino and R = 2,4-dimethoxy (MIC = 80 µg/mL; MBC = 40 µg/mL) showed same activity as nistatin against *Candida* sp. (IMUR 4249). It can be concluded that and 4-thiazolidinones provide interesting leads for anti-T. gondii drug discovery.

Antitubercular activity

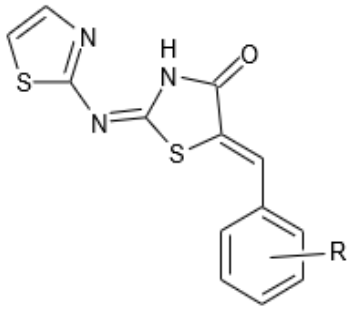
The emergence of multi-drug resistant tuberculosis, coupled with the increasing overlap of the AIDS and tuberculosis pandemics has brought tuberculosis to the forefront as a major worldwide health concern. Kerim Babaoglu et al. in an attempt to find new inhibitors of the enzymes in the essential rhamnose biosynthetic pathway, a virtual library of 2,3,5 trisubstituted-4-thiazolidinones[15] was created. These compounds were then docked into the active site cavity of 60hydroxyl; dTDP-6-deoxy-d-xylo-4- hexulose 3,5-epimerase (RmlC) from Mycobacterium tuberculosis. The resulting docked conformations were consensus scored and the top 5% were slated for synthesis. Thus far, 94 compounds have been successfully synthesized and initially tested of those, 30 (32%) have □50% inhibitory activity (at 20 mM) in the coupledrhamnose synthetic assay with seven of the 30 also having modest activity against whole-cell *M. tuberculosis*.



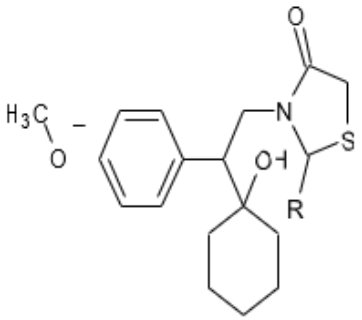
Scheme 1



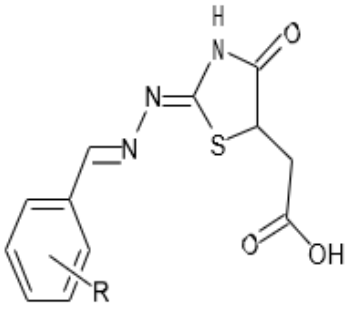
Scheme 2



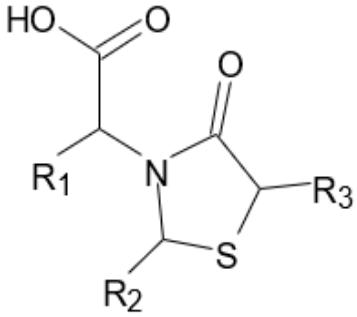
Scheme 2: R=H, 4-OH, OCH_3, 3-OCH_3, 4-OH, 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 3-Cl, 4-Cl



Scheme 3: R = 4-hydroxyphenyl, 4-methylphenyl, 2-nitrophenyl R = 4-methoxyphenyl, 2-butyl-4-chloro-imidazole-5-y



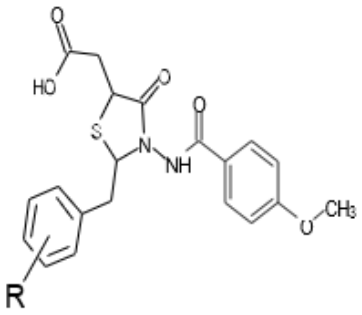
Scheme 4: R = 2-fluoro, 4-fluoro, 4-dimethylamino, 2,4-dimethoxy, 2,4-dichloro, 3,5-di-tert-butyl-4-hydroxy



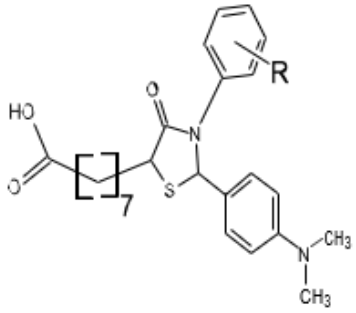
Scheme 5: 2,3,5 Trisubstituted -4-thiazolidinone

J. M. Patel has prepared the various series of 2-aryl-3-(4-methoxy benzamido)-5- carboxymethyl-4-thiazolidinone16 derivatives (8). Antitubercular activity was studied against H37RV strain of Mycobacterium tuberculosis in Lowenstein-Jensen's egg medium (5 ml). The retardation growth rate was studied upto 6 weeks at 37˚. It has been concluded that all compounds possess significant tuberculostatic activity at 30 µg/ml concentration. Anjani solanki and Kishore kapadiya has been synhesised a series of 2,3-disubstituted- 5(□-carboxyheptyl)-4-thiazolidinone17,18 (9)/2- Phenylimino-3-phenyl-5-(□-carboxy propyl)4- thiazolidinone19. Compounds with R=-CH2C6H5, - m - C 6 H 4 C l , - o - C 6 H 4 OCH 3 , - p - C 6 H 4 OCH 3 , - p-C6 H 4OC2 H 5, - 2- C10 H7 were sceened for antitubercular activity against H37RV strain of Mycobacterium tuberculosis in Lowenstein-Jensen egg media at 30 µg/ml concentration. The activity was compared with standard isonicotinic acid hydrazide (INH). Compound with R=-p-C6H4OC2H5 showed activity at 30 µg/ml whereas the other revealed low inhibitory effect. M. P. Dave et al., has performed the work on some 2-aryl-3-[4-chlorobenzamido]-5- substituted-4-thiazolidinones20 (10) and the in vitro antimycobacterial activity of the synthesized

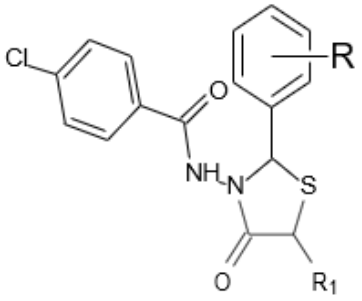
compound have been studied at 0, 5 and 30 µg/ml against H37RV strain of Mycobacterium tuberculosis. The result shows that all compounds are inactive at 0 and 5 µg/ml concentration, but are active at higher concentration at 30 µg/ml. Haresh Oza et al., have reported the series of 2-aryl-3-p-acetamidophenoxy acetamido-5- methyl-4-thiazolidinones21 (11). Primary screening of the compounds for antitubercular activity have been conducted at 12.5 µg/ml against Mycobacterium tuberculosis H37RV in BACTEC 12B medium using BACTEC 460 radiometric system. It can be concluded that compounds exhibited various degree of activity (o to 35%).



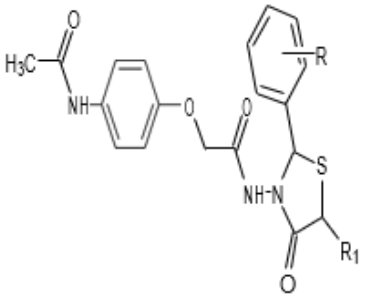
Scheme 6: R=H, 2-OH, 4-OH, 4-OCH_3, 2-Cl, 4-OCH_3, 2-Cl 3-Cl, 4-NO_2, 3-NO_2, 3,4-$(OCH_3)_2$, -CH=CH-,



Scheme 7: R1=H, 2-CH_3, 3-CH_3, 4-CH_3, 4-OCH_3, 2-OCH_3, 3-OCH_3, 2-Cl, 4-Cl, 3-Cl, 4-OC_2H_5



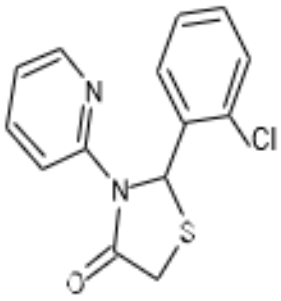
Scheme 8: R1=H, CH_3, CH_2COOH, R=H, 2-NO_2, 4-NO_2, 4-OCH_3, 3, 4-$(OCH_3)_2$



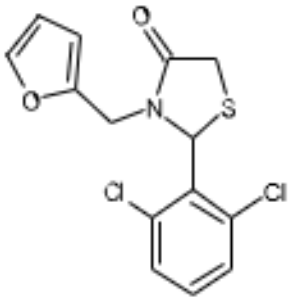
Scheme 9: R1=H,CH_3, R=2-Cl, 4-Cl, 2,4-Cl_2, 3,4-$(OCH_3)_2$, 2-OH,4-OH, 4-OCH_3, 2-NO_2, 3-NO_2, -CH=CH-, 3,4,5 -$(OCH_3)_3$

Anti-HIV activity

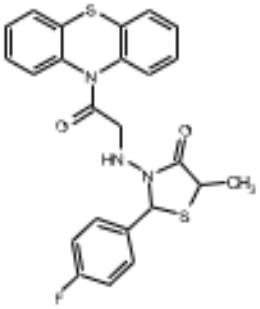
D. sriram et al.,22 has synthesized several 1,3, thiazolidinone-4-one bearing various substituted diaryl ring at C-2 and N-3 position, by utilizing microwave irradiation and evaluated for their anti-HIV and anti YFV activities. The result of the In vitro anti-HIV evaluation showed that 2-(2-chlorophenyl)-3-pyridin-2-yl-1,3-thiazolidin-4-one (12) proved to be-1an effective inhibitors of HIV replication with EC50 of 10 µm, CC50 of 120 µm and percentage protection of 104%. These results indicated that the presence of halogen at C-2 and C-6 position on phenyl ring and the presence of 2-pyridyl substituents at N-3 position of thiazolidinone ring were important requirement for anti-HIV activity. Several 2,3-diaryl-1,3-thiazolidin-4- ones23 bearing a methyl group at C-5 position have been synthesized and tested as anti-HIV agents. The results of the in vitro tests showed that some of them proved to be effective inhibitors of HIV-1 replication.



Scheme 10

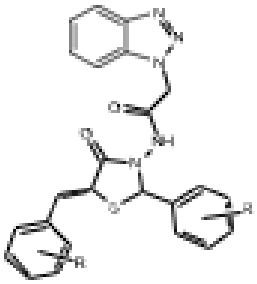


Scheme 11

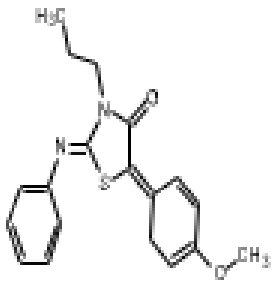


Scheme 12

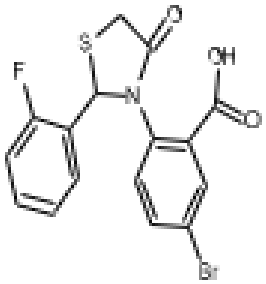
R. K. Rawal et al., has prepared various series of 2-(Aryl)-3-furan-2-ylmethyl-thiazolidin-4-ones24 as selective HIV-RT Inhibitors. All the 15 compounds were evaluated for HIV-RT inhibitory activity by determining their ability to inhibit the replication of HIV-1 (IIIB) in MT-4 cells. From the reported biological activity data, it may be inferred that the anti-HIV activity is strongly dependent on the nature of the substituent at C-2 and N-3 of the thiazolidinone ring. In particular, a high activity level was observed for compounds possessing a 2,6-dihalophenyl group at C-2 and a pyridine- 2- yl or pyrimidine- 2-yl ring at N-3. A series of 4-thiazolidinones were evaluated as selective inhibitors of the HIV-RT enzyme. In an attempt to correlating the derived physicochemical properties with the HIV-RT inhibitory activity resulted in some statistically significant QSAR models with good predictive ability. The QSAR studies indicated the role of lipophilicity, dipole moment and out-of-plane potential energy of the compounds in rationalizing the activity. One of the compounds, 2-(2,6- Dichloro- phenyl)-3-furan-2-ylmethyl-thiazolidin-4-one was found to be the most promising of the series with an EC50 of 0.204 µM and selectivity index of 216. The out-of-plane potential energy term (E_oop), associated with flexibility of the molecule is about six times more for this compound (0.094), as compared to TBZ (0.015) Hence, compound is found to be more active than TBZ. A series of 2-(2,6-dibromophenyl)- 3-heteroaryl-1,3-thiazolidin-4-ones25 were designed, synthesized and evaluated as selective human immunodeficiency virus type-1 reverse transcriptase (HIV-1 RT) enzyme inhibitors. The results of the HIV-1 RT kit and in vitro cell based assay showed that eight compounds effectively inhibited HIV-1 replication at 20-320 nM concentrations with minimal cytotoxicity in MT-4 as well as in CEM cells.



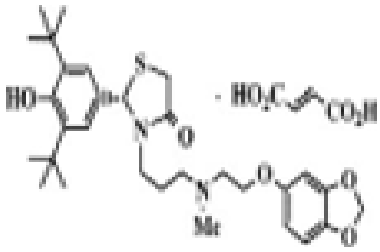
Scheme 13: R=Cl, CH_3, NO_2, Br



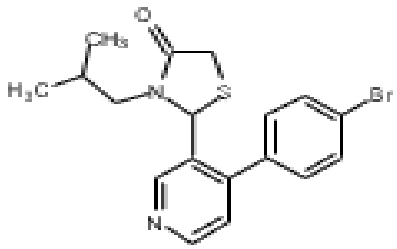
Scheme 14



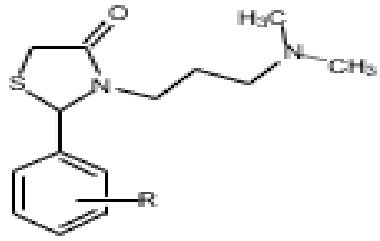
Scheme 15



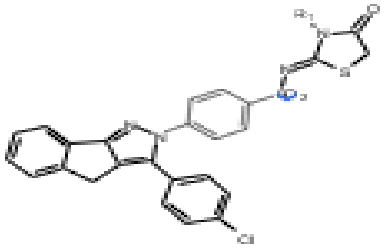
Scheme 16



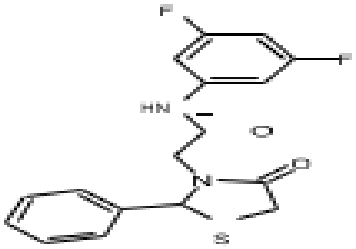
Scheme 17



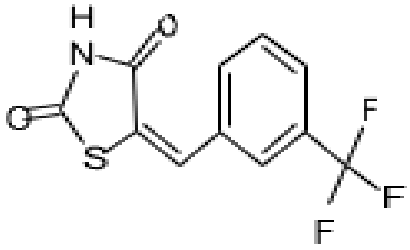
Scheme 18: R=3-CONH$_2$, 3-CHO, 3-CHNOH



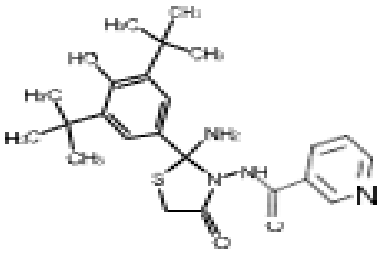
Scheme 19: R=C_6H_5-$CH_2C_6H_5$, -COC_6H_5



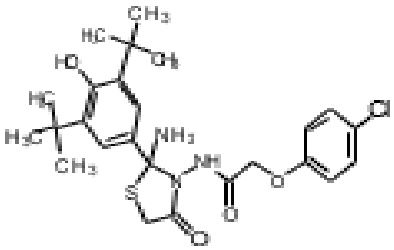
Scheme 20



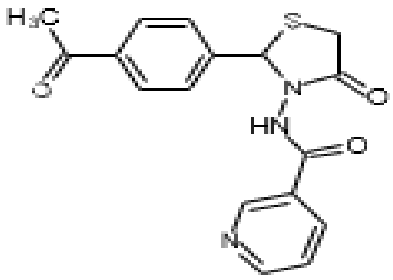
Scheme 21



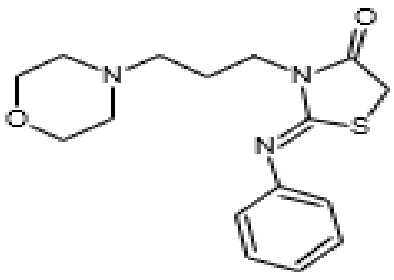
Scheme 22



Scheme 23



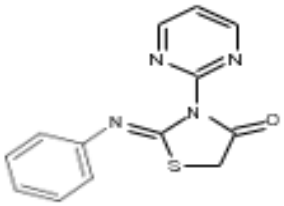
Scheme 24



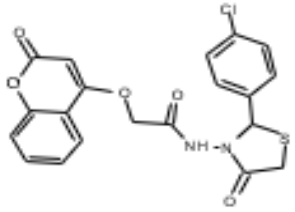
Scheme 24

Analgesic And Anti-Inflammatory Activity

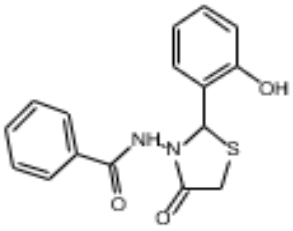
R.Yadav et al.,26 has prepared several series of new 2-[(aryl)-3-(acetylamino)-1,3-thiazolidin-4-one]-2-mercaptobenzothiazol and 2-[5-arylidene-2-phenyl-3-(acetylamino)-1,3-thiazolidine-4-one]-2- mercaptobenzothiazol from 2-mercaptobenzothiazol and tested for their ant inflammatory activity. Carrageenan induced paw oedema method was employed for evaluating anti-inflammatory activity at a dose of 50 mg/kg body weight in albino rats.



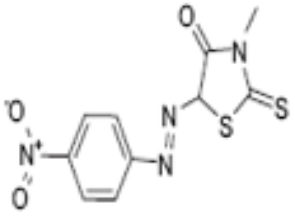
Scheme 25



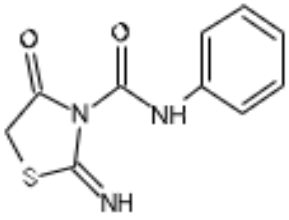
Scheme 26



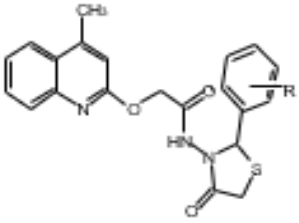
Scheme 27



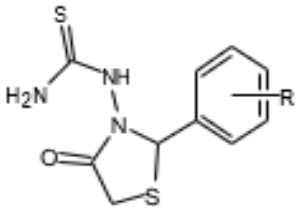
Scheme 28



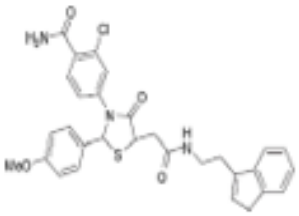
Scheme 29



Scheme 30



Scheme 31: R=4-N(CH$_3$)2, 4-OCH$_3$



Scheme 32

Among these compound with R=2Br-C6H4 showed 44.44% inhibition. Tilak Ram et al.,27 has synthesized various derivatives of thiazolidinones from 2-chloro phenothiazines and screened that compound for anti-inflammatory activity against carageneenan induced oedema in albino rats. All Thiazolidinone derivatives have shown promising antiinflammatoy activity. Out of these compound 2-chloro-10[5-(2- flurophenyl-2-oxo-4-thiazolidin-1-yl)-aminoacetyl] phenothiazine (15) was found to possess the most potent anti-inflammatory activity (38.6%) at the dose of 50 mg/kg which was comparable to standard drug phenylbutazone (38.9%). K. C. Asate et al.,

prepared various series of 5-arylidene-2-aryl-3-(benzotriazoloacetamidyl)- 1,3-thiazolid-4-ones28 (16) and screened that compound for analgesic activity. The activity was performed on albino rats by Eddy and Leimbach method at an oral dose of 25 mg/kg body weight. The compound with R=2-Br, 3-BR, 4-Br, are found to show 141.93, 142.85 and 141.26% analgesic activity respectively. Ottana et al., described the anti-inflammatory activity of 5- arylidene-2-imino-4-thiazolidinones29. All derivatives exhibited significant activity in models of acute inflammation such as carrageenan-induced paw and pleurisy edema in rats. In particular, 5-(4-methoxyphenylidene)-2-phenylimino-3-propyl- 4-thiazolidinone (17) 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 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. Ashok Kumar et al., synthesized some new anthranilic acid derivatives, 2-substituted-3-(4-bromo- 2-carboxyphenyl)-5-methyl-4-thiazolidinones30 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 (18) 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 ¼ 100.0 and 94.4 mg/kg, respectively. Series of 2-(4'- oxo-2'-phenyl-thiazolidin-3'-yl-aminomethyl) - 3-[4''- (p-chlorophenyl)-thiazol-2''-yl]-6-bromoquinazolin-4- ones31 have been synthesized. All the compounds have been screened for their anti-inflammatory and analgesic activities at the dose of 50 mg/kg po. Compound 2-(4'-oxo-2'-(o-chlorophenyl) -thiazolidin- 3'-yl-aminomethyl) - 3-[4''-(p-chlorophenyl)-thiazol-2''-yl]-6-bromoquinazolin-4-ones showed maximum anti-inflammatory (38.35%) and analgesic (37.36%) activities. This Compound was also tested for ulcerogenic activity and the UD50 value was found to be 195.6 mg/kg po.

Cardiovascular effect

Yoshiyuki Suzuki et al., have carry out research on CP-060S 32(19) a Novel 4-thiazolidinone Cardio protective Drug and evaluated for its effect on Cardiac Function and Myocardial Oxygen Consumption (MVO2) in anesthetized dogs. 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 interval was significantly prolonged by administration of CP-060S (300 mg/kg IV).CP-060S (10–300mg/kg IV) increased coronary blood flow in a dose-dependent manner. 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 MVO2 in a dose-dependent manner. The effects of CP-060S on cardiac function and MVO2 are qualitatively similar to those of diltiazem, a typical Ca2+ antagonist. Lars J. S. Knutsen et al.,33 has synthesized a series of new N-type (Cav2.2) calcium channel blockers derived from the 'hit' structures 2-(3-bromo- 4-fluorophenyl)-3- (2-pyridin-2-ylethyl) thiazolidin- 4-one and its 2-[4-(4-bromophenyl)pyridin-3-yl]-3- isobutyl

analogue. Extensive SAR study of these series by using a range of synthetic approaches resulted in novel, patented compounds with IC50 values of up to 0.2 µM in an in vitro IMR32 assay, and selectivities for N/L of up to 30-fold. compound 2-[4- (4-bromophenyl)pyridin-3-yl]-3-isobutyl-thiazolidine- 4-ones (20) found as the most potent, and single enantiomer 2-[4-(4-(tri fluro methyl) phenyl)pyridin- 3-yl]-3-isobutyl-thiazolidine-4-ones found as the most selective compounds in this series. These compounds show promise as lead structures in the quest for clinically effective N-type blockers in the treatment of pain.

Anti-Histaminic Activity

M. Vittoria Diurno et al., has prepared a series of 2-(Substituted-phenyl)-3-[3-(N,N-dimethylamino)propyl]-1,3-thiazolidin-4-ones34 (21). 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 and the activity reported, as pA2 values. The SAR study showed dependence of the potency of the H1-histamine antagonism on the m- and p-substituents suggesting that the aromatic moiety binds the receptor by a strong p-interaction. Electron-withdrawing substituents decrease the potency while the electron-donating alkyl substituents, enhancing the aryl HOMO energy, increase the antihistamine activity. The m-substituents with the capability to form hydrogen bonds, seems to share an extra interaction with hydrogen accepting or donating groups of the histamine receptor and exhibits very high potency. Singh et al., have investigated the antihistaminic (H1- antagonist) activity of 2, 3- disubstituted thiazolidin-4-ones and concluded that thehydrophobic 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 activity35-36.

Antitumor activity

Sherif A. F. Rostom et al., 37 has synthesized 3-Substituted-2-[4-(3-(4-chlorophenyl)- 3a,4-dihydro- 3H-indeno[1,2- c]pyrazol-2- yl)-benzenesulfonylimino]- thiazolidin-4-ones. The synthesized compounds were evaluated for their in vitro antitumor activity. Primary In vitro one dose anticancer assay was performed using the 3-cell line panel consisting of NCI-H460 (lung), MCF7 (breast), and SF-268 (CNS) in accordance with the protocol of the Drug Evaluation Branch, NCI, Bethesda. Compounds passed this primary anticancer assay. For further assay about 60 cell lines of nine tumor subpanels, including leukemia, non small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer cell lines, were incubated with five concentrations (0.01–100 µM) for each compound and were used to create log concentration_% growth inhibition curves. Three response parameters (GI50, TGI, and LC50) were calculated for each cell line. Compound 3-Phenyl-2-[4-(3-(4-chlorophenyl)-3a,4-dihydro-3H- indeno[1,2-c]pyrazol-2-yl)-benzenesulfonylimino]- thiazolidin-4-one (22) exhibited a significant activity against the colon COLO 205 cell line with GI50 value of of 1.73 lM. A new series of 2-aryl-4-oxo-thiazolidin- 3-yl amides (23) 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). 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)38. 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-139 HCT-11640, HT-2941, HCT-842, and H-63043, obtained from the American Type Culture Collection (Manassas, VA); among them, HT-29 cell line expresses high COX-2 levels44-46. Derivative 5-(3-trifluoromethyl benzylidene)-2,4-thiazolidinedione (24) 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-147.

Hypolipidaemic Activity

Gopalan Kutty Nampurath et al., have prepared three 4- thiazolidinones, two with nicotinamide (NAT1 and NAT2) and one with 4-chlorophenoxyacetamide (PAT1)48 (26) side chains. These compounds were evaluated for their hypolipidaemic, hypoglycaemic activity in Swiss albino mice fed a high-fat diet along with fructose administered in drinking water. NAT1 and PAT caused reduction of elevated triglycerides, cholesterol and glucose; NAT2 (25) was effective only against triglycerides and has modest activity. None of them exerted any major adverse effect on the liver. Nicotinamide side chain might have contributed to the lipid lowering effect of both NAT1 and NAT2, but the bulky group of the latter could have affected proper binding to the receptor sites, making it ineffective against elevated cholesterol. On the other hand, the 4-chlorophenoxyacetamide side chain of PAT might have exerted powerful hypolipidaemic activity, despite the bulky substitution at C2. As antioxidants, NAT2 and PAT1 showed superior activity, compared to NAT1. The thiazolidinone ring might be responsible for the lipid lowering effect, which is however, modified by the type of substitutions at C2 and N of the ring. There is a structural resemblance between these molecules (4-thiazolidinones) and the glitazones (thiazolidindiones). The latter drugs act through peroxisome proliferator activated receptor gamma (PPAR□). It is possible that the 4-thiazolidinone derivatives employed in this work may also have exerted some effect through PPAR□ receptors. Therefore it will be worthwhile to make further detailed studies of these molecules with a view to developing a compound, which has multiple beneficial effects on metabolic syndrome and associated debilitating conditions. Work is in progress in this direction. Jacob et al., has prepared a new molecule, incorporating a p-methoxy phenyl ring, a thiazolidinone-4-one and a nicotinyl moiety49, and evaluated for its effect on serum total cholesterol, triglyceride and transaminases in rats. The effects were compared with those of nicotinic acid, a well known hypolipidemic drug. The compound 2-(4-methoxy phenyl)-3-nicotinamidothiazolidin- 4-one (27), exhibited hypolipidemic effect with a significant reduction(19%) in total cholesterol, which was comparable with that of nicotinic acid (23.8%) and a significant reduction of triglycerides level (22.3%) while nicotinic acid caused a 26% reduction. Synthesis of various 2(substitutedphenyl)-3-[{4-(1-naphthyl)-1,3-thiazol-2-yl}amino]-5-methyl-1,3-thiazolidinone-4-one50 evaluated for antihyperglycemic activity by sucrose loaded model (SLM) and alloxan model. All the compound exhibited very good antihyperglyccemic activity.

Anticonvulsant Activity

The anticonvulsant activity of several series of 2-(arylimino)/(arylhydrazono)-3-aryl/ (alkylar yl)/ furfur yl / 2- pyr imidyl/ cycloalkyl/ (substituted amino)/(3-(N-morpholin-4-yl-propyl)- 4-thiazolidinones has been studied against pentylenetetrazolinducedseizures in albino mice of either sex at a dose of 100 mg/kg51-54. 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.

Hypnotoc Activity

Several 3-(3-(N-morpholin-4-yl-propyl)-2-(arylimino)-4-thiazolidinones55 (28) and 2-(arylimino)- 3-(pyrimidin-2-yl)-4-thiazolidinones56 (29) 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.

Antiviral And Cytotoxic Activities

Omaima Mohamed Abd Elhafez, et al., has synthesized a series of 2-Substituted-3-[(coumarin-4- oxy)acetamido]thiazolidin-4-ones57. Antiviral and cytotoxicity assays were carried out essentially according to the reported method. The compounds were tested for antiviral activity against Herpes simplex type 1 (HS-1) grown on Vero African green monkey kidney cells. Each compound exhibited some cytotoxicity. Compound 2-(4-chloro phenyl)- 3-[(coumarin-4-oxy)acetamido]thiazolidin-4-one (30) has the highest activity among all the compounds in this study and was able to reduce the number of plaques by 30% at a concentration of 0.12 mg/mL. CD50 of compounds was in a range of 0.02-0.04 mg/ mL; i.e. good cytotoxic activity. These compounds may be used as potential anticancer agents.

Anthelmintic Activity

Vipin kumar et al. has synthesized a series of 2-aryl-3-substituted benzamido-1,3-thiazolidin- 4-ones58 and all these compounds evaluated for anthelmintic activity against Pheritima posthuma and Eudrilus sp. by Garg's method. Piperazine citrate was used as standard anthelminitic drug to compare the anthelminitic activity of synthesized compounds. The results shows that the compound N-[2-(2-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl] benzamide (31) is a very potent and active against both the sepsis. All other compounds show moderate to good anthelmintic activity.3- Meth yl - 5 - [(4 - nit r o ph en yl) a z o] rhodanin (32), nitrodan, was reported as a potent anthelmintic compound59-61 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(33) have been found to be effective in vitro against horse Strongyloids at concentration of 10-3-10-6 M62. 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 parasiticides63,64.

CNS Activity

M. Kidwai et al., have synthesized various 3-(4-methyl-2'-quinolinyl)oxyacetamido-2-(substituted phenyl)-4-thiazolidinone65 (34) and the compounds were tested for the toxicity and gross central nervous system activity in albino mice. The compounds were found to be moderate toxic and CNS stimulants, they increased the spontaneous motor activity and reactivate to sound and though induced reactivity at all the tested doses.

Antipsychotic Activity

A series of piperazinyl butyl thiazolidinones structurally related to (3-[4-[4-(6-Fluorobenzo[b] thien-3-yl)-1-piperazinyl]butyl]-2,5,5-trimethyl-4- ththiazolidinone maleate67 / 3[4-[1-(6-Fluorobenzo[b] thiophen-3-yl)-4-piperazinyl]butyl]-2,5,5-trimethyl-4 thiazolidinone68 were prepared and evaluated in vitro for dopamine D2 and serotonin 5HT2 and 5HT1A receptor affinity. The compounds were examined in vivo in animal models of potential antipsychotic activity and screened in models predictive of extrapyramidal side effect (EPS) liability.

Antiparkinsonian activity

V. K. Srivastava et al.,69 has synthesized various 2-(substituted phenyl)-4-thiazolidinone-3-yl thioureas (35) and screened for their antiparkinsonian activity by reserpine induced rigidity, hypokinesia, and catonia in rats, the compound having dimethyl amino and 4-methoxy phenyl group at 4th position were found most potent.

Follicle Stimulating Hormone (FSH) receptor agonist activity

Maclean et al., reported the FSH agonist activity of an encoded 4-thiazolidinone library70. Among the hits discovered in these studies was compound 2-chloro-4-[5-{[2-(3H-inden-1- yl)-ethylcarbamoyl]-methyl}-2-(4-methoxy-phenyl)-4-oxothiazolidin-3-yl]-benzamide (36), which possessed moderate activity as an agonist of FSH, by virtue of its ability to stimulate a reporter cell line expressing the FSH receptor.

CONCLUSION

The reviewed new class of various substituted 4-thiazolidinone has shown a wide spectrum of biological activities. The development of new 4-thiazolidinone as an antitubercular agent in multi-drug resistant tuberculosis, broad spectrum of antibacterial activity against variety of gram (+) and gram (-) bacteria and antifungal activity against variety of fungal species of these compound lead a new series of antimicrobials. High degree of potency against HIV viruses can be positive signs for further investigation of this compound as antiaids. The 4-thiazolidinone derivatives have significantly demonstrated the anthelmintic, antiviral, hypnotic, anticonvulsants, antihistaminic, antipsychotic, antiparkinsonian and FSH agonist property. These compounds show promise as lead structures in the quest for clinically effective N-type Ca+2 channel blockers and as acardiovascularagent. Thewiderange of promising biological profile of these new generations represents much progress. Further investigation could give some more encouraging results.

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