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Thiazolidinone as a Core unit Biological evaluation Agent

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A B S T R A C T

The article is aimed to discuss characterize and screening the biological activity of a series of Thiazolidinone-as a Core Biological evaluation Agent Thiazolidinones are of great biological interest, especially as anti-tubercular antibacterial. The important and structural diversity of biologically active antibiotics led to the development of many novel methods for the construction of appropriately substituted Thiazolidinone with attendant control of functional group and stereochemistry. Thiazolidinone derivatives are reported to show a variety of antimicrobial, anticonvulsant, anti-inflammatory and cardiovascular activities, antimycobacterial activity, antibacterial activity , antihypertensive activity.

Keywords: Antibacterial activity, Antifungal activity, Schiff bases

A R T I C L E I N F O

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1. Introduction

4-thiazolidinone is a derivative of thiazolidine with a carbonyl group at 4th position which belongs to an important group of heterocyclic compounds. The methylene carbon atom at fifth position of 4-thiazolidinone possesses nucleophilic activity and attacks an electrophilic center. The reaction product loses water, forming a 5-unsaturated derivative of the 4-thiazolidinone. The reaction occurs in the presence of a base and the anion of the 4-thiazolidinone is the attacking species [1]. The ease of formation of the anion and hence the degree of the nucleophilic activity is dependent not only on the electron-withdrawing effect of the adjacent carbonyl group, but also on the presence of

other electron-withdrawing groups such as those attached to the second carbon atom[2]. The electron attraction of sulfur of 2-thione group is greater than that of the oxygen of a 2-carbonyl group. The nucleophilic activity of 5-methylene carbon atom of 2-aryl-4-thiazolidinone or 2-arylimino-4-thiazolidinone should be influenced by the nature of the substituents attached to the aryl group. The mobility of the hydrogen atoms in the methylene group depends much upon the electro-negativity and co-planarity of substitution on the exocyclic nitrogen. The aldehydes, however, react only on one 4-thiazolidinone moiety to give the corresponding 5-unsaturated products. The condensation of aldehydes with 2-alkylor-aryl-4-thiazolidinones does not occur due to acetic acid and sodium acetate, possibly because of the decreased reactivity of the methylene group. The reactivity is increased due to presence of imino or thioxo groups at second position at 4-thiazolidinone. Three components substituted aromatic amines, substituted aromatic aldehydes and a mercapto acid are used to synthesize 4-thiazolidinone derivatives. These processes can be conducted in two ways, one pot (one step) and two step reactions [3-4].

4-thiazolidinone is a useful moiety for a variety of heterocyclic products including drugs[5-6], dyes and intermediates such as thiazol yellow, thioflavin T., thidiazuron[7], the uses of this class of chemicals (4-thiazolidinone derivatives) are as herbicides [8], insecticides [9-10] etc. The thiazolidinones moiety is also associated with broad spectrum of biological activities including antibacterial [11-12], antifungal, anti-inflammatory, hypnotic, anticonvulsant, antitubercular, antiviral, antihistaminic, anthelmintic, cardiovascular and anticancer. A number of 4-thiazolidinones derivatives were investigated for their inhibitory effects on the oxidation of the substrates of the tricarboxylic cycle and β-hydroxybutyrate by rat brain homogenates for respiratory activity [13]. Several thiazolidinone analogues have been reported to show considerable biological activities as antibacterial, antifungal, anti-inflammatory, anticonvulsant, hypnotic, antitubercular, anthelmintic, cardiovascular, anticancer, antiviral and antihistaminic.

Studies have shown that thiazolidinones were more active than thiazoles against some common bacteria [14]. Kavitha [15] reported more than twenty thiazolidinone derivatives were tested against *Bacillus subtilis* and *Escherichia coli* and compared with reference drugs. He concluded that synthesized compounds exhibited more activity then reference drugs. This significant inhibitory activity can be attributed to fluorine atoms and has been observed in thiazolidinone derivatives with different positions .Several analogues of 4-thiazolidinones were synthesized and employed for their antibacterial studies against different strains like *S. aureus, B. subtilis, S.typhi and E. coli* of bacteria and were found to have significant antibacterial activity. It was seen that the presence of thiazolidinone ring was essential for antibacterial activity [16]. The functional groups of organic molecules relationship with thiazolidinone proved the importance of basic precursor (thiazolidine).This antimicrobial activity attracted the attention of Bondock *et al*.[17] and they synthesized novel 4-thiazolidinone derivatives of 6-chloro-1-oxo-2,3a,8,9-tetrahydro-1*H*-thiazolo[3,2-a]quinoline-7-carboxaldehyde and evaluated biological activity (antibiotic). Several 4-thiazolidinone derivatives were screened *in vitro* against different bacterial strains *E. coli B. subtilis and B. megaterium* by the agar diffusion technique [18]. Some derivatives of 4-thiazolidinone were prepared and reported considerable biological activity by Vicini *et al*.[19].

Compound 8-(2-Amino-3-phenyl-propionyl)-4-dodecyl-1-thia-4-aza-spiro[4,5]decan-3-one and its derivatives were prepared and screened by Katti *et al*.[20] against two strains of *C. albicans* and one strain of *C. neoformans*. They were also evaluated of MIC in 100 mmoles followed double dilution standard method and found that the antifungal activity was of average to higher level against the various fungal strains. Dandia *et al*.[21] prepared various derivatives of thiazolidinone using microwave and screened it for antifungal activity. Three fungal strains, namely *R. solani*, (causing root rot of okra), *C. capsici*, (causing leaf spot) and *F. oxysporum*, (causing wilt of mustard) were used in this screening and it was seen that the prepared derivatives showed significant antifungal activity against different fungal strains under test. The addition of thiazole ring increased the antifungal activity of these synthesized substances.

Anti-inflammatory agents are used to cure chronic and acute inflammation along with many others diseases. Ottana *et al*.[22] synthesized 4-thiazolidinone derivatives and used them as anti-inflammatory agent. They found that 2-(2-(4-oxo-2-pentylthiazolidin-2-yl)ethyl)-2-pentylthiazolidin-4-one and other derivatives were good analgesic and anti-inflammatory agents. Cuzzocrea *et al.*[23] Investigated derivatives of 2-imino-4-thiazolidinones and 5-amino-2-(3-hydroxyphenyl)thiophen-3(2*H*)-one. These were applied in rats and paw edema for anti-inflammatory activity *in vivo* and received very promising results.*Goel et al.*[24] described and evaluated novel substituted thiazolidinones for anti-inflammatory activity. These were employed in albino rats as anti-inflammatory agent and showed very good results. The potency of 5-bromo-2-(2-(2-flourophenyl)-5-methyl-4-oxothiazolidin-3-yl)benzoic acid (49) derivatives were compared with reference drug (phenylbutazone) of known potency applied with four different doses i.e. 25, 50, 75 and 100 mmoles. The results were equal to the reference drug. The anti-inflammatory activity of 2-amino-5-(3-hydroxyphenyl)-1,3-thiazolidin-4-one was shown by Ottana *et al*.[25] Almost all the derivatives showed considerable activity in acute inflammation in rats. (2*Z*,5*Z*)-5-(4-methoxycyclohexa-2,4-dien-1-ylidene)-2-(phenylimino)-3-propyl-1,3-thiazolidin-4-one showed very good paw edema inhibition as compared with indomethacin.

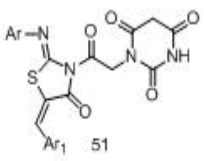
Shiradkar *et al* [26] synthesised a new series of clubbed thiazolidinone–barbituric acid (51) and thiazolidinone - triazole derivatives (52) to study the effect of a hydrophobic

unit, hydrogen bonding domain and electron-donor group on the compounds on its anticonvulsant activity. Their studies proved that the presence of -OH function at the 4th position of the phenyl ring is essential for anticonvulsant activity, the removal or replacement of -OH functional group by a -Cl, CH_3 or -NO_2 moieties responsible for loss of activity. The replacement of the hydroxyl group responsible for hydrogen bonding resulted in lack of a HBD (hydrogen bonding domain) leading to abolishment of the activity. In a series of thiazolidinonyl-2-oxo/thiobarbituric acids derivatives, compound having p-methoxyphenyl (53) substitution at C-2 of thiazolidinone ring was found to be favourable for activity and exhibited more potent anticonvulsant activity as compared to standard drug sodium phenytoin [27].

A number of substituted thiazolidinonyl carbazol derivatives are potent antipsychotic and anticonvulsant agent. Compounds having thiazolidinone ring demonstrated more potent antipsychotic as well as anticonvulsant activities as compared to compounds having azetidinone ring. Among these, compound (54) exhibited very good response against psychotic disorders by recording their responses towards amphetamine induced stereotyped, cataleptic behavior by Rota rod performance and MES test for anticonvulsant activity [28].

Kucukguzel et al. reported antimycobacterial activity of substituted 4-thiazolidinones and found that only compounds **(55)** and **(56)** showed 90 and 98% inhibitions at 6.25 µg mL^{-1}, respectively [29]. Jaju and co-workers had synthesized isonicotinylhydrazide derivatives and screened their in vitro antimycobacterial activity against M. tuberculosis H37Rv using alamar-blue susceptibility test. They found that the antitubercular activity was considerably affected by various substituents on the aromatic ring of 4-thiazolidinone and it was proved by the fact that compounds with no substitution at the aromatic ring did not show any considerable activity. The hydroxyl and methoxyl group on aromatic ring substituted compound **(**57**)** was found to be more active (MIC = 0.31 µg/mL) [30]. Karali et al. tested 4-(3-coumarinyl)-3-cyclohexyl-4-thiazolin-2-one benzylidene hydrazone derivatives for antitubercular activity. Most of the compounds showed less than 90% inhibition and considered to be inactive and compound **(**58**)** showed maximum inhibition of 42% [31].

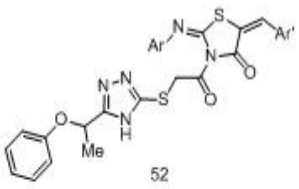
Protein tyrosine phosphatases A (MptpA) and B (MptpB) secreted into the host cell by growing Mycobacterium tuberculosis potently to be active selectively showed a target for the treatment of tuberculosis. Vintonyak et al. designed a novel series of indolin-2-one-3-spirothiazolidinones as a new class of potent and selective inhibitors of MptpB. They studied the modification on phenyl substituent on the thiazolidinone and 2-indolinone positions. The SAR studies suggested that two fluorine atoms or a fluorine and a chlorine atom in meta and para positions of the phenyl ring attached to thiazolidinone were found to be more potent than analogues bearing mono or dialkyl substituents. Introduction of sulfonamide, trifluoromethoxy or methoxy group led to loss of inhibitory activity. Compound (59) was found to be highly active against M. tuberculosis protein tyrosine phosphatise B enzyme (IC_{50} 1.1 µM) [32]. Babaoglu et al. reported the activity of 1,3-thiazolidin-4-ones (60) against M. tuberculosis by inhibition of dTDP-rhamnose synthesis 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. Synthesized compounds were then docked into the active site cavity of 6-hydroxyl; dTDP-6-deoxy-D-xylo-4-hexulose 3,5-epimerase (RmlC) from M. Tuberculosis [33].



51

Ar, Ar′ = 2-OHC_6H_4 , -2-OHC_6H_4

Ar, Ar′ = -2-OHC_6H_4 , -4-$CH_3C_6H_4$



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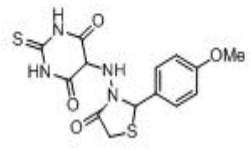
Ar, Ar′ = -2-OHC_6H_4, -2-OHC_6H_4

Ar, Ar′ = -2-OHC_6H_4 , -4-$CH_3C_6H_4$



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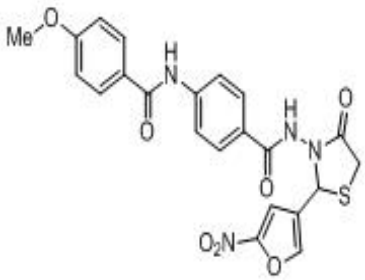

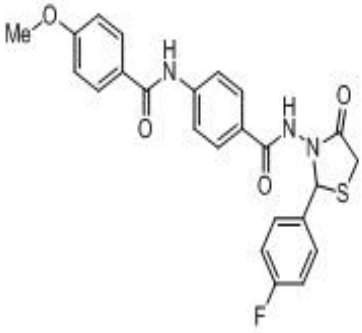

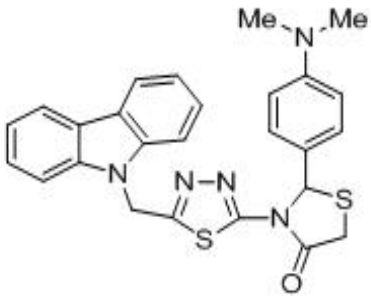

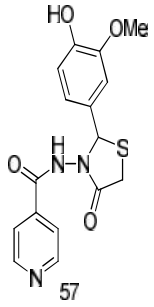

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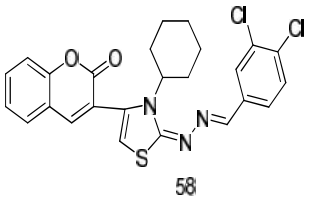

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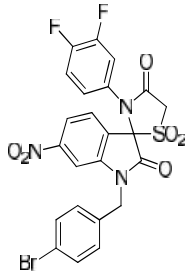

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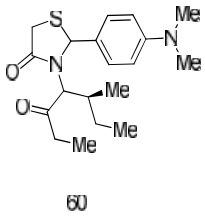

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2. Conclusions

a. Furthermore the substitution with phenyl group having a chloro group at p-position showed better activities.

b. The Thiazolidinones showed better anti-inflammatory and analgesic activities.

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