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A review on anti microbial activity of 4-thiazolidinone derivatives

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ABSTRACT

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. The process of establishing a new drug is exceedingly complex and involves talents of people from variety of disciplines. An important aspect of medicinal chemistry has been to establish a relationship between chemical and biological activity. It has been established that half of the therapeutic agents consist of heterocyclic compound. The heterocyclic ring comprises the core of the active moiety or pharmacophore. An especially big attention is given to sulphur and nitrogen containing heterocyclic compounds, as they possess a broad spectrum of biological activity, and are used in various fields of pharmacy. It is well known that a number of heterocyclic compounds containing nitrogen, oxygen and sulphur exhibit a wide variety of biological activity. Compounds carrying the thiazolidinone ring have reported to demonstrate a wide range of pharmacological activities which include anti microbial antifungal activity, antitubercular antitumor, antidiabetic activity anti inflammatory, anticonvulsant. Until the seventies of the 20th century, fungal infections were rather easily cured and the need for new antifungal drugs was low. Low choice of antifungal preparations, toxicity, and limited spectrum of action as well as risk of resistant strains prove the need of new effective medicines for systemic fungal diseases. Therefore, it is necessary to seek for new and less toxic antifungal compounds. Fungemia is an important cause of morbidity and mortality in hospitalized patients. Moreover, the emergence of resistance to currently available antifungals is of great concern and has led to susceptibility testing of new antifungal agents. To investigate the activity profile of thiazolidinone derivatives bearing different substituent at 2, 3 and 5 position have been prepared.

KEY WORDS: Thiazolidinone, Heterocyclic, Antimicrobial activity, Anti fungal, Antibacterial.

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1. INTRODUCTION:

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. The process of establishing a new drug is exceedingly complex and involves talents of people from variety of disciplines. An important aspect of medicinal chemistry has been to establish a relationship between chemical and biological activity. Although many natural products are used in pharmaceuticals in their original chemical structures, successful efforts have been made to improve their pharmaceutics and therapeutics property by structural modification. Another approach to improve therapeutic property is to identify that portion of a natural molecule responsible for biological activity and to synthesize new molecules, which are based on it. For more than a century heterocyclic compounds rank against the most important organic compounds. They participate in important biochemical processes, and are the constituents of main substances (DNA, RNA) in live cells. It has been established that half of the therapeutic agents consist of heterocyclic compound. The heterocyclic ring comprises the core of the active moiety or pharmacophore. An especially big attention is given to sulphur and nitrogen containing heterocyclic compounds, as they possess a broad spectrum of biological activity, and are used in various fields of pharmacy. Fungemia is an important cause of morbidity and mortality in hospitalized patients. Moreover, the emergence of resistance to currently available antifungals is of great concern and has led to susceptibility testing of new antifungal agents. The incidence of fungal infections have increased over the last two decades and candida species were the predominant mycotic pathogen candida species produce broad range infections, ranging from superficial illness to life threatening disease[1].

1.1 HETEROCYCLIC COMPOUNDS:

Heterocyclic compounds, or heterocycles, are cyclic compounds in which one or more of the atoms of the ring are heteroatoms. A heteroatom is an atom other then carbon. The name comes from the Greek word heteros, which means "different." A variety of atoms, such as N, O, S, Se, P, Si, B, and As, can be incorporated in to ring structures. By far the most numerous and most important heterocyclic systems are those of five and six members.

Heterocyclic make up an exceedingly important class compounds— more than half of all known organic compounds are heterocyclic. Almost all the compounds we know as drugs, vitamins, and many other natural products are heterocyclic.

1.2 4-THIAZOLIDINONE:

The importance of heterocyclic compounds has long been recognized in the field of synthetic organic chemistry. It is well known that a number of heterocyclic compounds containing nitrogen, oxygen and sulphur exhibit a wide variety of biological activity. Compounds carrying the thiazolidinone ring have reported to demonstrate a wide range of pharmacological activities which include anti microbial[2-12] antifungal activity[13], antitubercular14,antitumor15,antidiabeticactivity[16,17] anti inflammatory [18,19], anticonvulsant[20].

2. PREPRATION OF THIAZOLIDINONES

To investigate the activity profile of thiazolidinone derivatives bearing different substituent at 2, 3 and 5 position new thiazolidinone have been prepared employing the following three procedures.

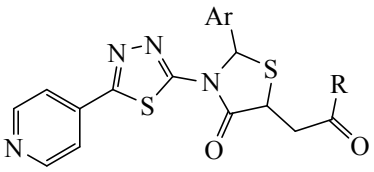
Nucleophilic addition of ethyl bromoacetate to thiosemi carbazides: Acylthiosemicarbazide obtained from the reaction of hydrazide and isothiocynates were reacted with ethyl bromoacetate in absolute C_2H_5OH in the presence of sodium acetate to furnish 2-hydrazono-4-tiazolidinone derivatives.

Nucleophilic addition of thioglycolic/thiolactic acid to C=N double bond: Hydrazide hydrazones obtained from the condensation reaction of hydrazides and aldehydes were treated with thioglycolic and thiolactic acid in anhydrous benzene using a Dean Stark water separator to furnish3-acylamino-2-substituted-4 thiozolidinones and 3-acylamino-2, 5-disubstituted-4-thiazolidinones, respectively.

Reaction of α-halogenated amide with HN_4SCN: Halogenated amide were reacted with NH_4SCN in EtOH in the presence of sodium acetate to furnish-2-imino-4-thiazolidinone via rearrangement reaction.

3. ANTI-MICROBIAL ACTIVITY

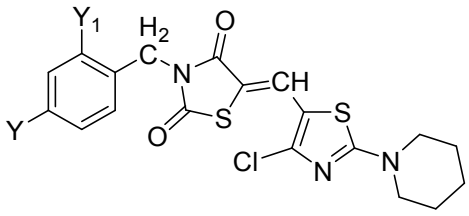
Ranjana Sharma et al synthesized phthalimido [2-aryl-3-(5'-(4''-pyridyl)-1',3',4'-thiadiazol-2'-yl)-4-oxothiazolidin-5-yl] ethanoates and evaluated their anti-microbial activity using *Escherichia coli*, *Proteus vulgaris, Klebsiella pneumoniae, Pseudomonas auregenosa, Salmonella typhi* and *Bacillus subtilis* bacterial strain by cup or well method **.**In their studies they found that all synthesized compounds have shown very little activity against *B.subtilus, P. vulgaris* and *S. typhi*, moderate activity against *E. coli* and very strong activity against *K. pneumoniae* and *P. auregenosa* as compared to standards used i.e. Ciprofloxacin and Gentamicin. In their Comparative study of the substitution pattern of the aryl group towards antibacterial activity they found that electron withdrawing group causes more activity and donating group causes less activity[2].



Ar (a-h) = 4-$OCH_3.C_6H_4$, 4-$Cl.C_6H_4$, 3,4,5-$OCH_3.C_6H_2$, 3-$NO_2.C_6H_4$, 4-$NO_2.C_6H_4$, 4-$(CH_3)_2NH.C_6H_4$, C_6H_5, C_4H_3O (2-furyl) R = phthalimidoxy.

Figure 1: Phthalimido[2-aryl-3-(5'-(4''-pyridyl)-1',3',4'-thiadiazol-2'-yl)-4-oxothiazolidin-5-yl] ethanoates

Meltem Ceylan et al synthesized 3-(substituted-benzyl)-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene)-thiazolidine-2,4-dione derivatives and evaluated their anti -microbial activity against *Staphylococcus aureus* ATCC 250 and *Escherichia coli* RSKK 313 and antifungal activity against *Candida albicans* RSKK 628 by disk difusion method.in the studies they found that compounds having no substitution, fluoro, bromo, nitro substitution at para posision of benzyl and dichloro substitution at ortho and para position of benzyl showed high activity against *Escherichia coli* comparable to ampicillin. All synthesized Compounds were found to be inactive against *Candida albicans*[3].



Y= H, Br, Cl, F, NO_2 Y_1= H,Cl

Figure 2: **3-(substituted-benzyl)-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene)-thiazolidine-2,4- dione derivatives**

Ameya A. Chavan and Nandini R. et al synthesized 2- [5- (arylidene) -2-imino-4-oxo-thiazolidin-3-yl] benzothiazole-6-carboxylic acid and evaluated their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Psuedomonas aeruginosa* and *Escherichia coli* by Cup plate method using Hi-Media agar medium and antifungal activity against four different fungi such as *C. albicans, C. pannical, A. niger* and *R. oryzae* by filter paper disc technique. In their studies they found that All the newly synthesized compounds show antibacterial activity against *S. aureus, B.subtilis, P. aeruginosa* and *E. coli* and show slight to moderate antifungal activity[4].

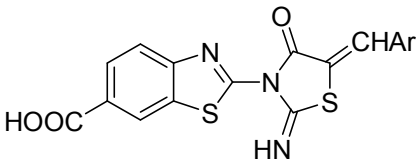


Figure 3: 2-[5-(arylidene)-2-imino-4-oxo-thiazolidin-3-yl]benzo thiazole-6-carboxylic acid

Vagdevi H.M, Vaidya V.P, Latha K.P et al synthesized 2-[2-(2-Aryl-4-thiazolidinono)thiazol-4-yl] naphtha furans and found their antimicrobial activity against *Staphylococcus aureus*, *Klebsiella pneumonia*, *Aspergillus niger* and *Candida albicans* by cup-plate method, antihelmintic activity (on *Pheritima posthuma*, Order-annelida, Class-oligichaeta), anti-inflammatory activity and diuretic activity[5].

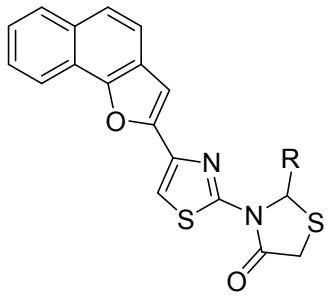


Figure 4: 2-[2-(2-aryl-4-thiazolidinono) thiazol-4-yl] naphtho furans

Patel K.H. and Mehta A.G. synthesized 3-(4-(naphthalen-2-yl)thiazol-2-yl)-2-arylthiazolidin-4-one derivatives and evaluated antibacterial activity against *Bacillus subtillis*, *Staphyloccous aureus*, *E.Coli* ,*Salmonella typhi* found that Compound (where Ar is 4-Methoxy Phenyl, 2-Hydroxy Phenyl and 4-Methyl Phenyl) were more active against the above microbes[6].

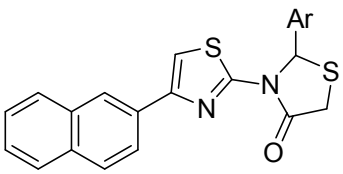


Figure 5: 3-(4-(naphthalen-2-yl)thiazol-2-yl)-2-arylthiazolidin-4-one derivatives

Handan altintas at el synthesized 5-substituted 5-(N,N-disubstituted aminomethyl)-2-[(4-carbethoxymethylthiazol-2-yl)imino]-4-thiazolidinones and evaluated antibacterial activity against *S. aureus, S. epidermidis, E. coli, K. pneumoniae, Ps. aeruginosa, S. typhi, Sh. flexneri* and *Pr. mirabilis* using disk dilusion and the antifungal activity against *M. gypseum, M. canis, T. mentagrophytes, T. rubrum* and *C. albicans* using Microdilution and found that compound (where R=C_2H_5 and R1=piperidine moiety) is more active than compound(where R=C_6H_5 and R1=piperidine moiety) against *M. canis, T. mentagrophytes* and *T. rubrum*. In the same way, compounds (where R=C_2H_5 and R1=morpholine moiety) is more active than compound (where R=C_6H_5 and R1=morpholine moiety) against *M. gypseum, M. canis, T.mentagrophytes* and *T. rubrum*. Both results indicate that the presence of ethyl groups in both compounds caused potential antifungal activity when compared to phenyl groups in same compounds**.** Compound (where R= C6H5 and R1=dimethylamine) was also found to be more active than compounds (where R=C6H5, R1=heterocyclic ring)[7].

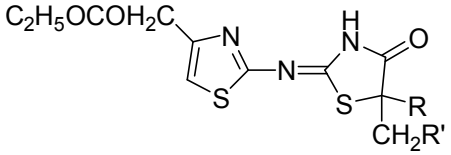
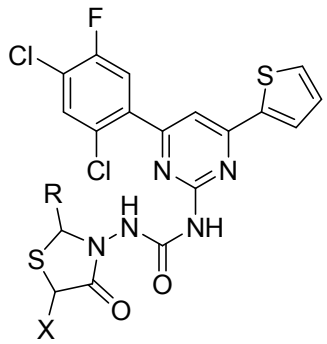


Figure 6: 5-substituted 5-(n,n-disubstituted amino methyl)-2-[(4-carbethoxy methyl thiazol-2-yl) imino]-4 thiazolidinones

Tejaskumar J. Shah and Vikas A. Desai synthesized a series of 2-(substitutedphenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6-(2thienyl)pyrimidine-2ylureido]5H/methyl/carboxymethyl-4-thiazolidinones and evaluated their anti bacterial activity against *Escherichia coli* (ATCC 8739), *Pseudomonas aureginosa* (ATCC 1539) and *Staphylococcus aureus* (ATCC 6538), *Bacillus substilis* (ATCC 6633) bacteria using the cup-plate agar diffusion method and antifungal activity against *Candia crusei* (ATCC 14243) and *Candida albicans* (ATCC 64550). In their study they found that some of the compounds possess considerable antibacterial activity due to the presence of methoxy, fluoro and chloro groups. However the activity of the tested compounds is less than that of streptomycin and that some of the compounds possess good anti fungal activity. However, none of compounds was superior to standard used against any of the fungi[8].



R = aryl; X = H , CH3 , CH2COOH.

Figure 7: 2-(substituted phenyl)-3-[4-(2,4-dichloro-5-fluorophenyl)-6- (2thienyl)pyrimidine-2-ylureido] 5h/methyl/carboxymethyl 4-thiazolidinones

Bhoot D.P. and Khunt R.C. et al synthesized 2-arylimino-3-aryl-5-[5′-(3,4-dichlorophenyl)-2′furylidene]-4-thiazolidinones and evaluated their anti microbial activity against *B. megaterium, S. aureus, E. coli, P. vulgaris, A. niger* and in their study they concluded that remarkable inhibition was observed in compounds bearing R=phenyl, 2-methoxyphenyl, 2-methylphenyl, 3-methylphenyl 4-nitrophenyl substituents[9].

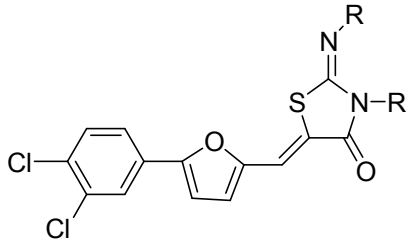


Figure 8: 2-arylimino-3-aryl-5-[5′-(3,4-dichlorophenyl)-2′furylidene]-4-thiazolidinones

Sharma M.C., Sahu K. et al synthesized N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide and investigated anti microbial activity against *B. Subtilis, S. aureus, E. coli., A-niger* and *C.albicans*. In their study they found that the positive coefficient of the log P descriptor, which relates to the hydrophobicity of the molecule, suggested that an increase in the lipophilicity might increase the activity. This corresponds to the presence of hydrophobic binding site in the N-(5-Dimethyl-4-oxo-thiazolidin-3-yl)-nicotinamide[10].

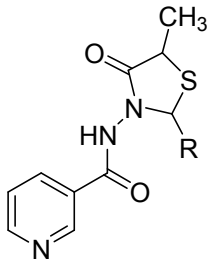


Figure 9: N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide

Ravi Kumar P. and Shanta Yadav et al synthesized 2-(substituted phenyl)-3-substituted phenoxy-acetamido-4-thiazolidinones and investigated anti-bacterial activity of against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* and antifungal activity of against *Candida albicans* and *A. niger*. They used Ampicillin and Griesofulvin (6 g/cup and 25 g/cup respectively) as standard reference drugs. In their study they found that compounds having electron releasing groups like methyl, hydroxy and methoxy may be responsible for antibacterial and antifungal activities[11].

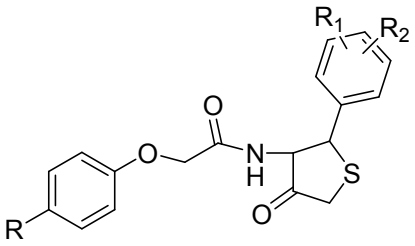


Figure 10: 2-(substituted phenyl)-3-substituted phenoxy-acetamido-4-thiazolidinones

Paola Vicini et al synthesized 2-Heteroarylimino-5-benzylidene-4-thiazolidinones analogues of 2-thiazolylimino-5-benzylidene-4-thiazolidinones and evaluated their anti- microbial activity[12].

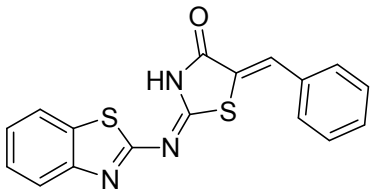


Figure 11: 2-heteroarylimino-5-benzylidene-4-thiazolidinones analogues of 2-thiazolylimino-5-benzylidene-4-thiazolidinones

Hui-Ling Liu et al synthesized 2-Imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and Their 5-Arylidene Derivatives and evaluated their fungicidal activity against 7 agricultural fungi, *Pleurotus ostreatus, Aspergillus niger, Pythium aphanidermatum, Gaeumannomyces graminis, Fusarium graminearium, Pyricularia oryzae* and *Botrytis cinerea*, by the agar growth medium poison technique. In their study they found that compounds (where Ar is 2,4-$(Cl)_2$-5-FC6H2 and 2,4-$(Cl)_2C_6H_3$) have higher fungicidal activity than the others. Compounds (where Ar is C_6H_5, p-ClC_6H_4 , 2,4-(Cl)2-5-FC_6H_2 and 2,4-$(Cl)_2C_6H_3$ were more fungicidal against *Pythium aphanidermatum* than against the other 6 fungi. Introduction of benzylidene group at C-5 decreased the fungicidal activity. The inhibition of all of the 5- arylidene-4-thazolidinones was low[13].

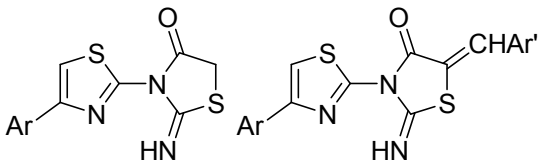
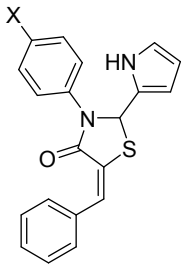


Figure 12: 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and their 5-arylidene derivatives

Feray Aydogan et al synthesized 5-Benzylidene-3-(4-substitutedphenyl)-2-(2-pyrrolyl)-4-thiazolidinone and evaluated their anti tubercular activity against *Mycobacterium tuberculosis*. In their study they found that compounds (where x=-ethoxy and chloro) gave zone diameter of growth inhibition less than 20 mm[14].



(X) a,b,c,d,e=H, metoxy ,ethoxy,phenoxy,chloro.

Figure 13: 5-benzylidene-3-(4-ethoxyphenyl)-2-(2-pyrrolyl)-4-thiazolidinone

4. FUTURE PROSPECTS:

Until the seventies of the 20th century, fungal infections were rather easily cured and the need for new antifungal drugs was low. Low choice of antifungal preparations, toxicity, and limited spectrum of action as well as risk of resistant strains prove the need of new effective medicines for systemic fungal diseases. Therefore, it is necessary to seek for new and less toxic antifungal compounds.

Fungemia is an important cause of morbidity and mortality in hospitalized patients. Moreover, the emergence of resistance to currently available antifungals is of great concern and has led to susceptibility testing of new antifungal agents[1].The incidence of fungal infections have increased over the last two decades and candida species were the predominant mycotic pathogen candida species produce broad range infections, ranging from superficial illness to life threatening disease[2]. Recently, there has been growing concern of rapidly increasing bacteria resistance to the antibacterial preparations in the markets. Although, at present many and various cures are used for the infections, more effective and safe preparations are still missing, and the death-rate from infections takes second place in the world. The search of new high–effective antimicrobial drugs is issue of the day because of the appearance of a large group of antibiotic resistant strains.

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