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Pharmacological Evualation of Thiazolidinone Derivatives: A Prespective Review

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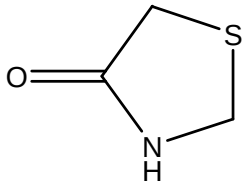
ABSTRACT

Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a magic moiety which posses almost all types of biological activities. It belongs to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. There are a large number of heterocyclic five membered rings are available but thiazolidinone posses a large number of biological activity. It has been found that moiety exhibits remarkable activity against human immunodeficiency viruses type 1 reverse transcriptase inhibitors. In literature survey it has been found that in combination with many group of heterocyclic ring the spectrum of pharmacological activity associated with thiazolidinone and its derivatives can be broden. Present review deals with all the pharmacological activities related with thiazolidinone along with future aspects.

Keywords: Thiazolidinone, Heterocyclic, Biological Activity.

INTRODUCTION

Thiazolidinone derivatives are the subject of renowned interest because they have been found to be useful intermediates for the synthesis of various heterocyclic compounds [1] .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 development in the field of combinatorial chemistry has provided access to chemical libraries based on privileged structures [2]. Substitution can be done at 2, 3 and 5 positions in the moiety, but the greatest difference in structure and properties is exerted by the group attached to the carbon atom in the 2-position. The carbonyl group present in moiety is highly unreactive. Tetrahydro derivative of thaiazole is known as thiazolidine and the oxo derivative of thiazolidine is known as thizolidinone.



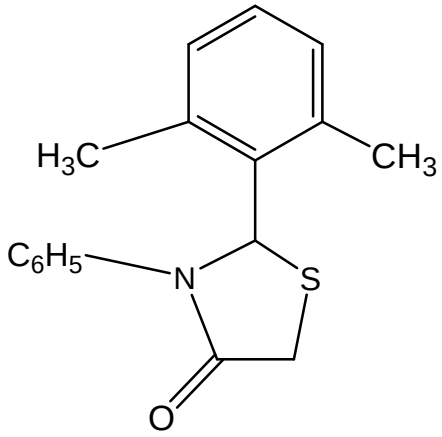
4-Thiazolidinone

The 3-unsubstituted thiazolidinone are usually solids and frequently meltdown with decomposition, but the attachment of an alkyl group to the nitrogen lowers the melting point. The thiazolidinone that do not contain aryl or higher alkyl substituents are somewhat soluble in water [3].4-Thiazolidinone derivatives shows anti-bacterial [4] anti-convulsant [5], anti-fungal [6], anti-thyroid [7], antitubercular and antidiabetic activity [8].

Pharmacological activity of Thiazolidinone

Cytotoxic activity

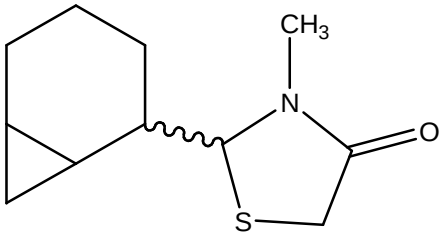
Monforte *et al*. [9] has synthesized several series of 2, 3-diaryl-1, 3-thiazolidin-4-one derivatives. Among them the compound **(I)** was found to be most potent and reported as a new family of anti-viral agents acting as NNRTIs with minimal cytotoxicity. It was found that substitution by aryl group at nitrogen atom increases the cytotoxic activity of compound.



2-(2,6-dimethylphenyl)-3-phenylthiazolidin-4-one

(I)

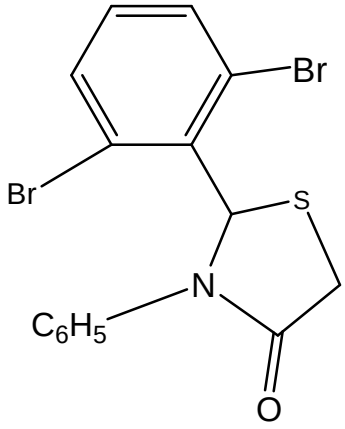
2-adamantyl-substituted thiazolidin-4- one derivatives has synthesized and evaluated its activity against HIV-1 (IIIB) and HIV-2(ROD) in CEM cell cultures, by taking Nevirapine as reference compound by Balzarini et al. [10]. Among them compound **(II)** was found to be more potent**.** Substitution by admantyl at second position was found to shown increased in cytotoxic activity.



2-(bicyclo[4.1.0]heptan-2-yl)-3-methylthiazolidin-4-one

(II)

Rawal *et al*. [11] has synthesized 2-(2,6-dibromophenyl)-3-heteroaryl-1,3-thiazolidin-4-one derivatives.Among the various derivatives compound **(III)** shows the potent activity. Due to substitution of aryl group at nitro atom shows increased in cytotoxic activity.

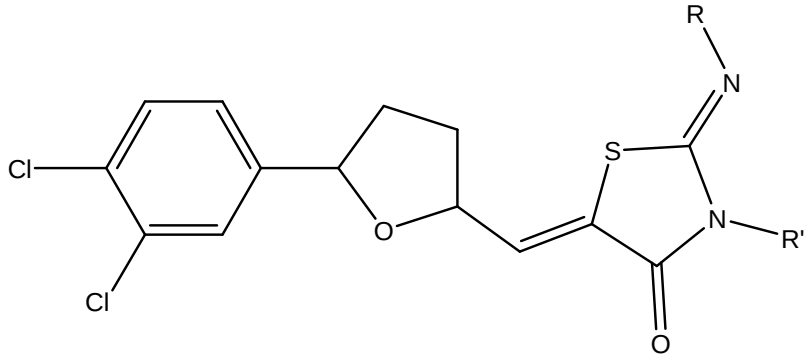


2-(2,6-dibromophenyl)-3-phenylthiazolidin-4-one

(III)

Antimicrobial activity

2-(ptolylimino)-3-(4-tolyl)-5-[5-(3,4-dichlorophenyl)-2 furylidene]-4-thiazolidinone derivatives **(IV)** was synthesized as an anti-microbial agents by Bhoot *et al*. [12] then Compounds were screened *in-vitro* for their anti-microbial activity towards variety of bacterial strains such as *B. mega, S. aureus, E. coli, P. vulgaris* and fungi such as *A. niger* at a concentration of 40µg. Remarkable inhibition was observed in compounds bearing phenyl and 2-methoxyphenyl, 2-dimethylphenyl, 3-methylphenyl, 4-nitrophenyl substituents and from among these derivatives IVa, IVb, IVc, IVd showed the potent activity against the bacterial strains.

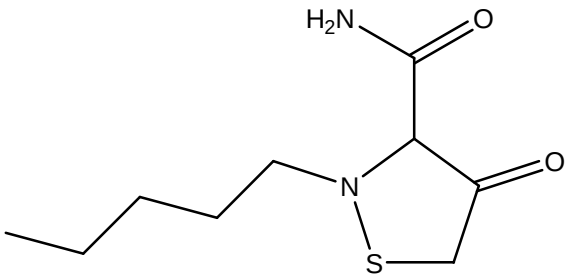


(IV)

Compound	R	R'
Iva	C_6H_5	$C_6H_5OCH_3$
IVb	C_6H_5	$C_6H_5CH(CH_3)_2$
IVc	C_6H_5	$C_6H_5CH_3$
IVd	C_6H_5	$C_6H_5NO_2$

Anti-Cancer Activity

Gududuru et al. [13] has synthesized a series of 2-amyl-4-oxothiazolidin-3-yl amides and these were evaluated for their ability to inhibit prostate cancer cell. Few potent compounds were detected, which were effective in killing prostate cancer cells with improved selectivity compared to serine amide phosphates. The Compound **(V)** was found to be most potent. It was found that substitution at nitrogen atom by long alkyl chain causes increase in anticancer activity.

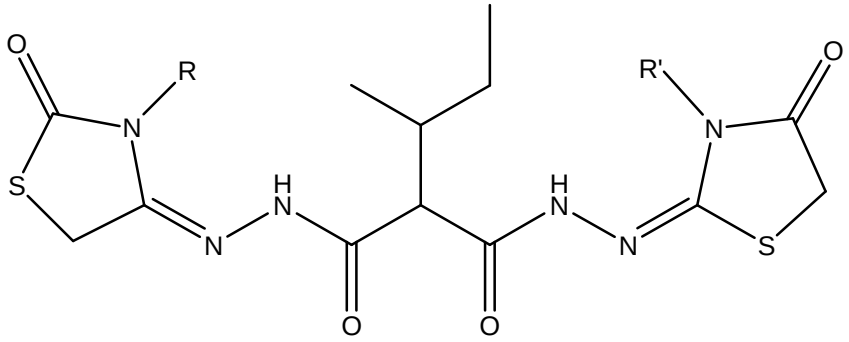


4-oxo-2-pentylisothiazolidine-3-carboxamide

(V)

Anticonvulsant activity

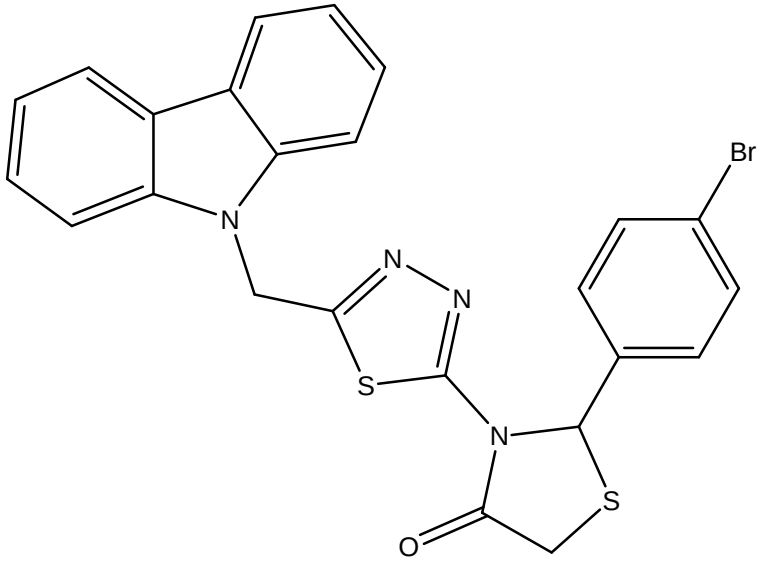
Bis*(4*-thiazolidinone) **(VI)** derivatives were synthesized, characterized and evaluated for their anticonvulsant activity by Ulusoy *et al.* [14]. Compound VIa, VIb derivatives show 90% protection in pentylenetetrazole induced seizure.Substitution by phenyl group and alkyl group is found to shown potent activity.



(VI)

Compound	**R**	**R'**
Via	$C_6H_5CH_3$	CH_3
VIb	C_2H_5	OCH_3

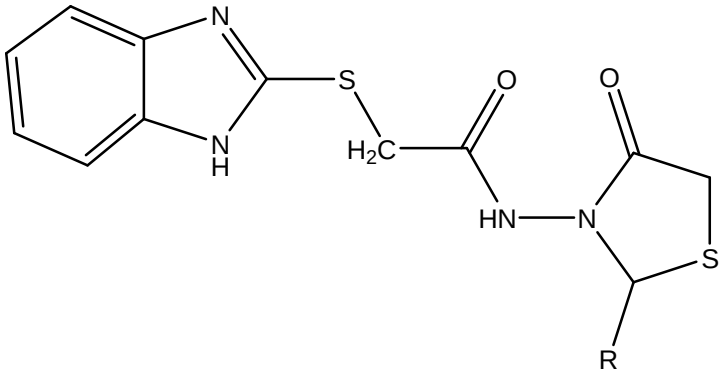
Kaur *et al.* [15] has synthesized novel substituted thiadiazolylazetidinonyl and screened for their anticonvulsant activities. It is concluded that among the various derivatives **(VII)** showed promising anti-convulsant activity.



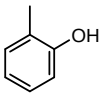
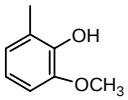
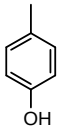
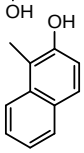
3-(5-((9*H*-carbazol-9-yl)methyl)-1,3,4-thiadiazol-2-yl)-2-(4-bromophenyl)thiazolidin-4-one

(VII)

Shingalapur *et al.* [16] has synthesized a group of 4-thiazolidinones containing 2-mercapto benzimidazole moiety **(VIII)** and screened them for *in-vivo* anticonvulsant activity by Maximal Electroshock (MES) model. The compounds VIIIa, VIIIb, VIIIc and VIIId exhibited potent anticonvulsant results.

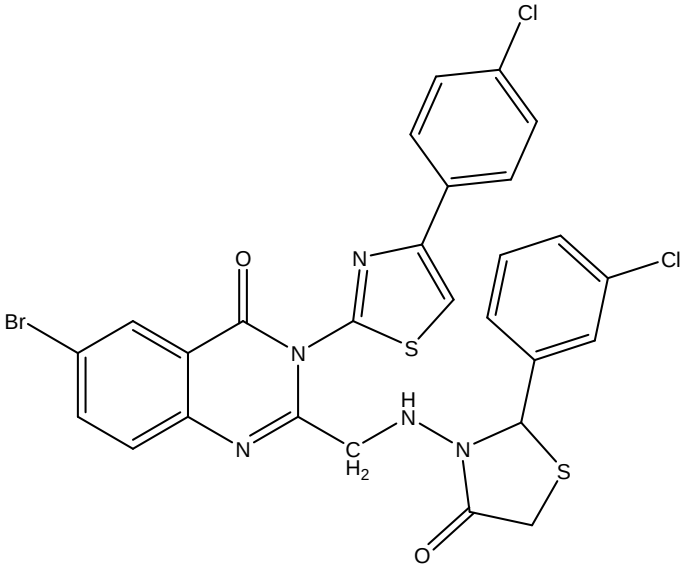


(VIII)

Compounds	R
VIIIa	
VIIIb	
VIIIc	
VIIId	

Anti-Inflammatory Activity

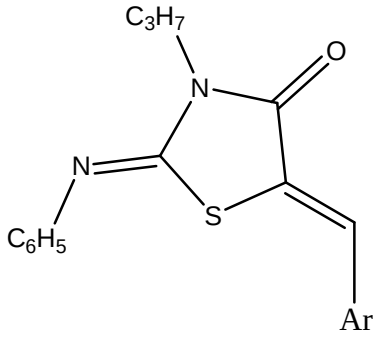
Kumar et al. [17] has synthesized N-Chloroacetyl-5-bromoanthranilic acid, 3-[4'-(p-chlorophenyl) thiazol-2'-yl] -2-chloro methyl-6-bromo quinazolin-4-one,3-[4'-(p-chloro phenyl) -thiazol-2'-yl]-2-hydrazino methyl-6-bromo quinazolin-4-one,3-[4'-(p-chloro phenyl) -thiazol-2'-yl]-2 substituted benzylidene amino methyl-6-bromo quinazolin-4-ones,2-[(4'-oxo-3’-chloro-2’-phenyl azetidin-1'-yl) amino methyl]-3-[4'-(p-chloro phenyl) thiazol-2"-yl]-6-bromo quinazolin-4-ones (12–19) and 2-(4'-oxo-2'-phenyl-thiazolidin-3"-yl-amino methyl)-3-[4"-(p-chloro phenyl) -thiazol-2"-yl] -6-bromo quinazolin-4-ones.Among them **(IX)** showed maximum anti-inflammatory activity.



2-(4'-oxo-2'-(o-chlorophenyl)-thiazolidin-3'-ylaminomethyl)-3'-[4"-(p-chlorophenly)-thiazol-2"-yl]-6-bromoquinazolin-4-one

(IX)

Ottana *et al*. [18] has synthesized 5-arylidene-2-imino-4-thiazolidinone derivatives, anti-inflammatory activity was evaluated by using carrageenan-induced paw and pleurisy edema in rats, by taking indomethacin as standared drug.

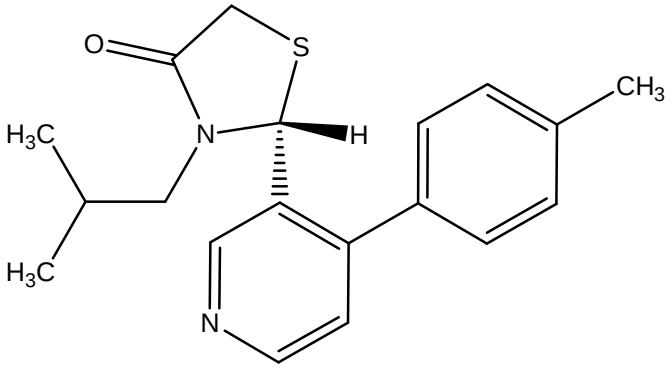


(X)

Compound	**Ar**
Xa	3-CH_3OPh
Xb	4-CH_3SPh
Xc	4-CH_3SO_2Ph
Xd	4-CH_3OPh
Xe	4-ClPh
Xf	3,4 –$(CH_3O)_2Ph$

Analgesic activity

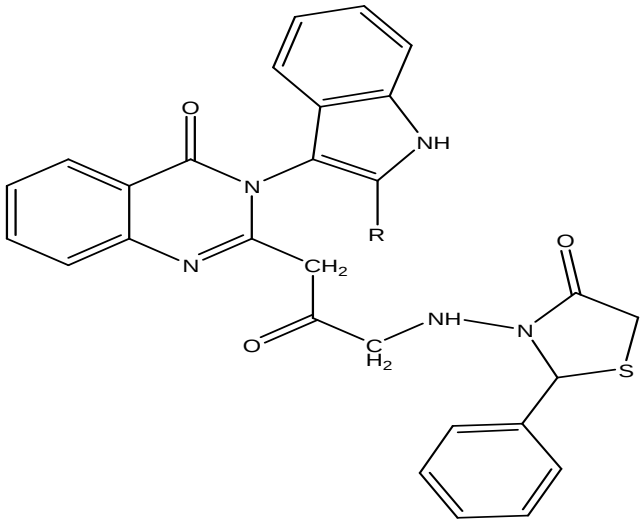
Burley *et al*. [19] has synthesized a series of new N-type (Cav2.2) calcium channel blockers derived from the 'hit' structures 2-(3-bromo-4-fluorophenyl)-3- (2-pyridin-2-ylethyl) thiazolidin-4-one 9 and its 2-[4-(4-bromophenyl)pyridin-3-yl]-3-isobutyl analogue. By SAR (Structure Activity Relationship) compound **(XI)** have been identified as the most potent 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.



(*R*)-3-isobutyl-2-(4-*p*-tolylpyridin-3-yl)thiazolidin-4-one

(XI)

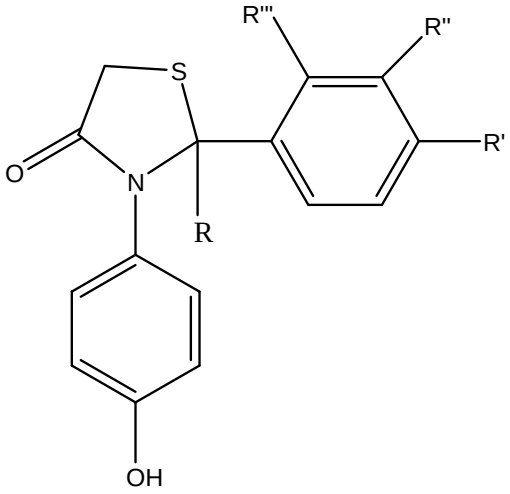
Kumar *et al.* [20] has synthesized 2-(substituted phenyl methylene imino) amino acetyl methylene-3-(2'-substitutedindol-3'-yl)-halosubstituted-4(3H) quinazolinones and 2-(substituted phenyl amino methylene acetyl-4'-oxo-1'-thiazolidinyl-3-(2''-substituted indol-3''-yl) 4(3H) quinazolinone. Compound **(XII)** was found to be most potent.



(XII)

Compound	X	R	R'
XIIa	H	CH_3	2-OCH_3
XIIb	H	CH_3	2-Cl
XIIc	6-I	H	2-OCH_3
XIId	6-I	H	4-Cl
XIIe	6-Br	CH_3	2-OCH3
XIIf	6-Br	CH_3	$N(CH3)_2$
XIIg	6-Br	CH_3	2-Cl

Taranalli *et al.* [21] has synthesized thiazolidine-4-one derivatives and evaluated for anti-inflammatory, analgesic and anti-ulcer activity by carrageenan-induced paw edema test, acetic acid induced writhing method and pylorus ligation ulcer model respectively. All the compounds showed significant anti-inflammatory, analgesic and anti-ulcer activity at 100 mg/kg b.w.

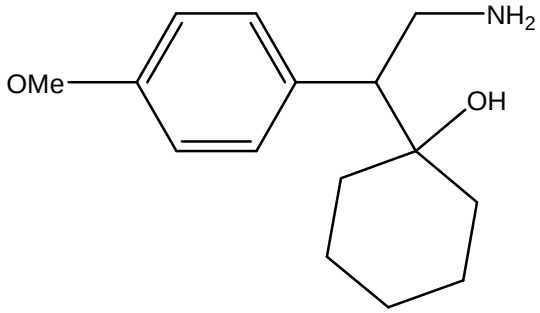


(XIII)

Compound	R	R'	R''	R'''
XIIIa	H	H	H	H
XIIIb	H	OCH_3	H	H
XIIIc	H	CH_3	H	H
XIIId	H	CH_3	CH_3	NH_2

Future aspect of thiazolidinone

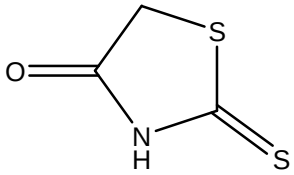
Some of the different derivatives of thaizolidinone with biologically active scaffold have introduced a broad spectrum of the pharmacological activity associated with moiety. Different rings are combined with thiazolidinone to achieve the desirable property. One of them is Venlafaxine **(XIV)** which belongs to class of antidepressants(SNRIs), is quite different from other antidepressants because of its unique structure and morphologicl features. By Using the venlafaxine as a key intermediate 1-[2-amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol we can synthesized 2,3-disubstituted-1,3-thiazolidin-4-ones by using different substituted aromatic and heterocyclic aldehydes [22].



1-[2-amino-1-(4-methoxy-phenyl)-ethyl]-cyclohexanol

XIV

2-thioxo-4-thiazolidinone (rhodanine) derivatives **(XV)** are potential inhibitors of HIV integrase. These structures have been found to impart antitumor properties such as seen in rhodacyanine dyes. Moiety is an important structural scaffold for Integrase inhibitory activity. Such derivatives are suitable leads for antiviral and anticancer drug development [23].



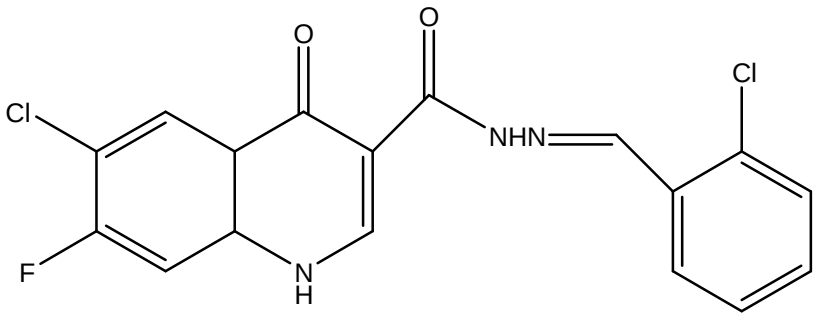
2-thioxo-4-thiazolidinone

XV

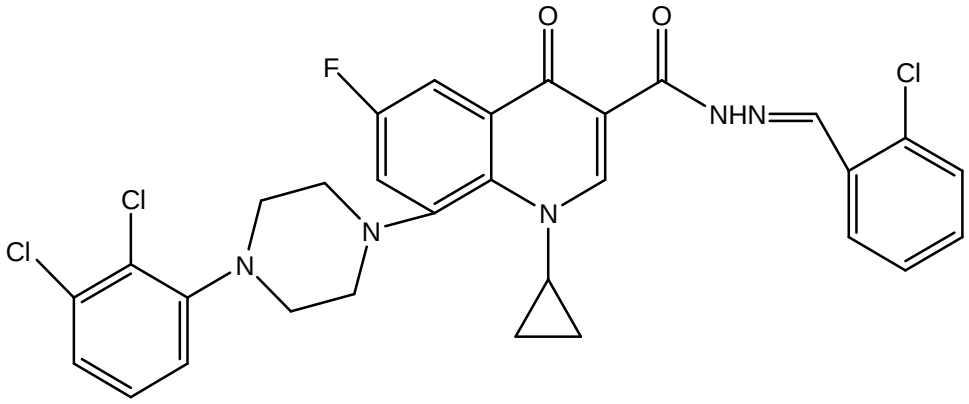
Pyridine Based 4-Thiazolidinones

In recent years a trend has been observed to couple different heterocyclic nucleus to achieve desired therapeutic activity. 4-thiazolidinone derivatives incorporated with 2-amino-6-nitro benzothiazole and pyridine moieties are a great utility to shows properties like antibacterial and antifungal properties [24]**.**

A series of 2-substituted phenyl-3-{1-cyclopropyl-6-fluoro-7-[4-(2,3-dichlorophenylpiperazin-1-yl]-4-oxo-1,4-dihydroquinoline}carboxamido-1,3-thiazolidin-4-ones derivatives **(XVI)** were synthesized by Patel and Patel and screen for its antimicrobial properties. Among them compound **XVI (a)**, **XVI (b)**, **XVI (c)** shows potent activity with (2-Cl, 2-Cl and 4-Cl) substitution respectively [25].

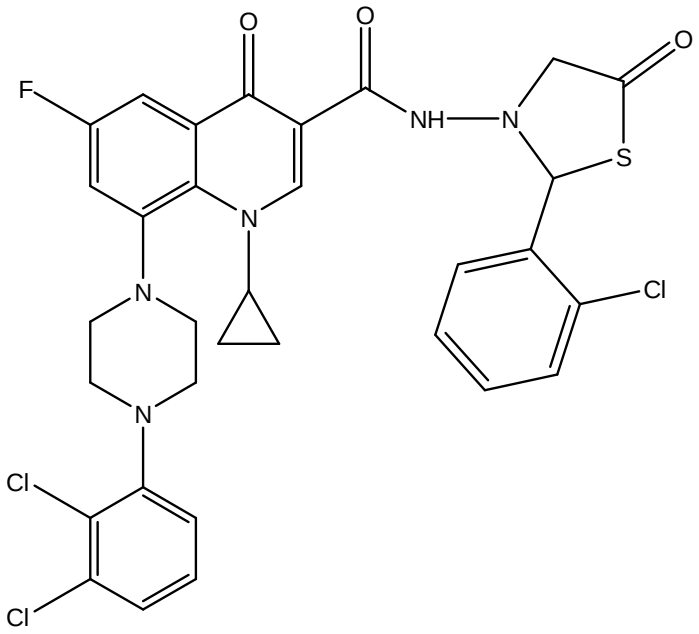


XVI (a)

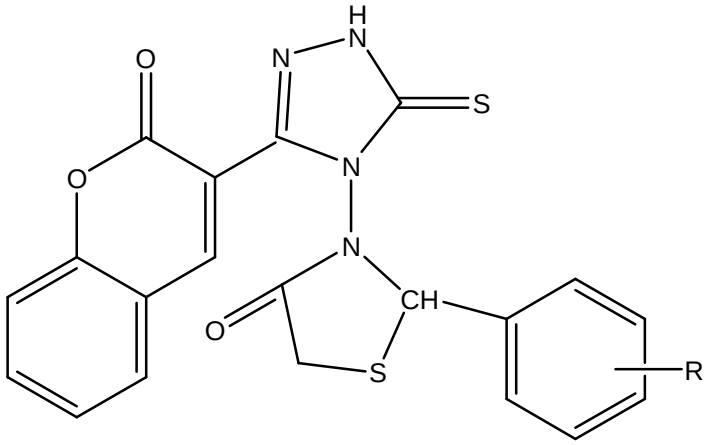


XVI (b)

A series of 2-(substituted phenyl)-3-[3-(2-oxo-2H-chromen-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-ones **(XVII)** were synthesized and evaluated for its antimicrobial properties. Compound XVII (a) was found to have 92% growth inhibition, against S. aureus and was most potent among the series, XVII (b), XVII (c), XVII (d) was effective against C. albicans and shown to 85% inhibition activity was observed in this case [25].



XVI (c)

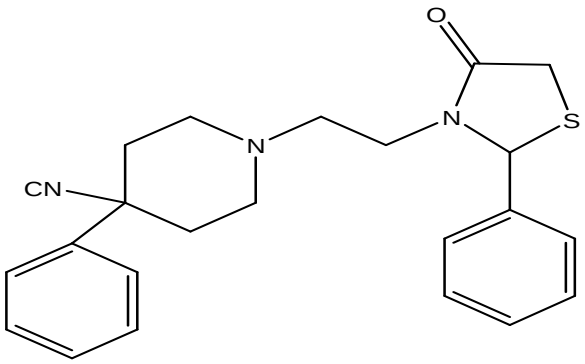


XVII a) R=H
b) R=$N(CH_3)_2$
C) R=4-Cl
D) R=2-Cl

Some Other Aspects

Antidiarrhoeal Activity

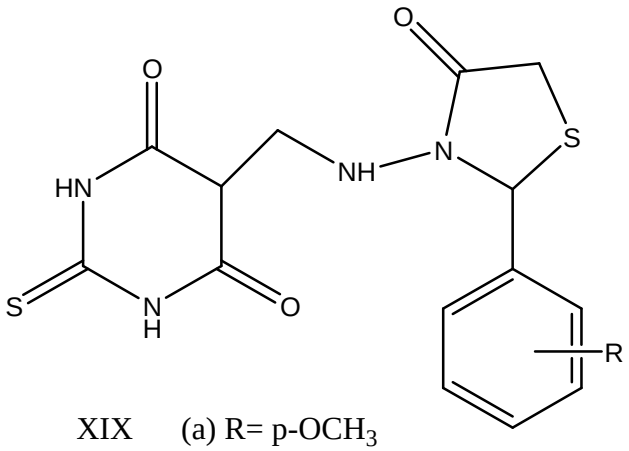
Mazzoni et al synthesized several derivatives of 1,3-thiazolidin-4-ones and screened for antidiarrhoeal activity.The most active compound was the 2-phenyl-3-{2-[(4-phenyl-4-cyano)piperidino]ethyl}-1,3-thiazolidin-4-one **(XVIII)** [26].



XVIII

Oxo-thiobarbituric acid Fused Derivatives

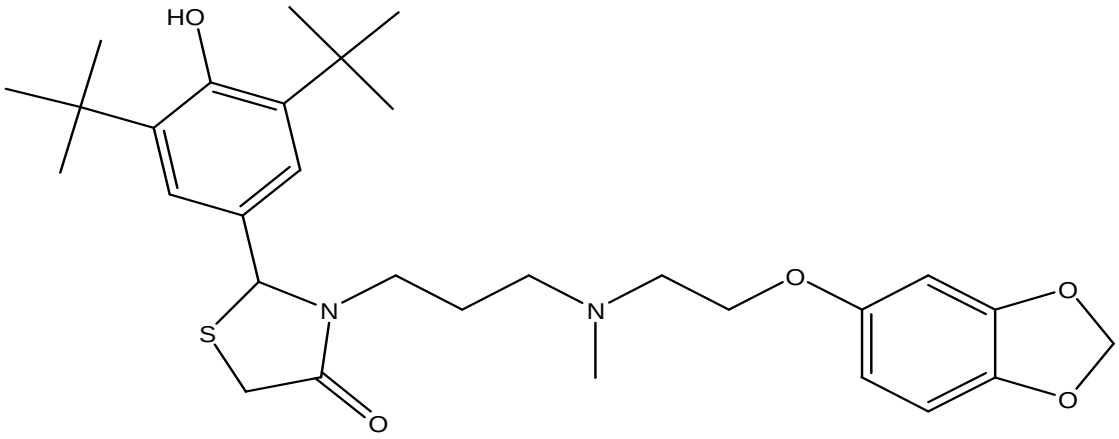
Agarwal et al synthesized Several derivatives of 5-[(2-phenyl-4-oxothiazolidin-3-yl)amino]-2-oxo-thiobarbituric acids [27], and 3-({4-[2-alkylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-monosubstituted-quinazolin-4(3H)-one derivatives were synthesized by Archana et al and screened them in vivo for their anticonvulsant activity at a dose of 30 mg/kg for acute toxicity studies[28]. They concluded that p-methoxyphenyl-substituted and m-methoxy-phydroxyphenyl substituted in thiazolidinone moieties have shown more potent response in comparison to other substituted derivatives. The compounds XIX (a), XIX (b), XIX (c) were found to be the most potent.



XIX (a) R= p-OCH_3
(b)R = m-OCH_3,
(c) p-OH

Antioxidant Activity

A series of 2-(3, 5-di-tert-butyl-4-hydroxyphenyl)-3-(aminopropyl)thiazolidinones was synthesized by Kato et al in order to explore novel calcium antagonists with potent anti-ischemic activity. These compounds were designed in such a way to have both Ca_2+ antagonistic and antioxidant activity in one molecule. Among them 2-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-[3-[N-methyl-N-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one **(I)** was found to be highly potent and possessed a well-balanced combination of these activites *in-vitro* [29].

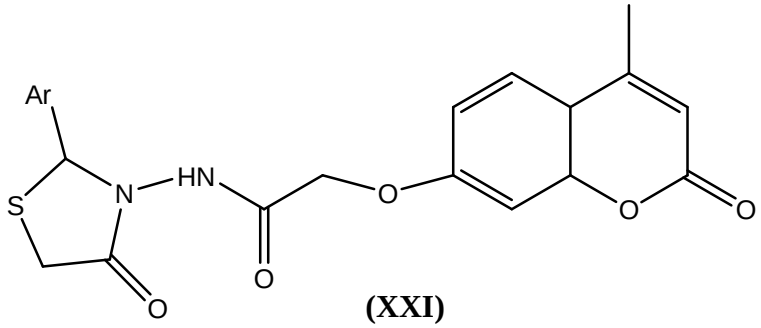


2-(3,5-di-tert-butyl-4-hydroxyphenyl)-3-[3-[N-methyl-N-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one

XX

Coumarine derivatives and thiazolidinone

Milan et al synthesized various derivatives of N-(2-aryl-4-oxo-thiazolidine-3-yl)-2-(4-methyl-2-oxo-2H-chromen-7-yloxy)-acetamides **(XXI)** and evaluated it for its antioxidant property by phosphomolybdenum method. Three of 1, 3-thiazolidine-4-ones **XXI (**a), **XXI (**b), **XXI (**c) proved to have better antioxidant activity in comparison with ascorbic acid [30].



(XXI)

Ar
a)2,3-dihydroxyphenyl
b)2,4-dihydroxyphenyl
c)2,5-dihydroxyphenyl

CONCLUSION

The literature survey revealed that 4- Thiazolidinone has diverse spectrum of biological activities and have taken attention of the chemist, pharmacologists and researchers working in field of medicinal chemistry. Beside this Some of the new biological activities associated with thaizolidinone has been explored such as antioxidant activity, anticonvulsant activity, FSH (Follical Stimulating Harmone) agonistic activity. At the present scenario it can be concluded that 4-Thiazolidinone have a great biological potential to be used as important scaffold in medicinal chemistry.

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