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SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW THIAZOLIDINONE DERIVATIVES

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ABSTRACT

A large number of drugs and biologically relevant molecules contain heterocyclic systems. The presence of hetero atoms or groups imparts preferential specificities in their biological responses. Amongst the heterocyclic systems, thiazolidine is a biologically important scaffold. Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds. Thiazolidines are heterocyclic aromatic organic compounds with 5 membered saturated ring with a thioether group and an amine group in 1 and 3 positions respectively. It is a sulfur analogue of Oxazolidine.

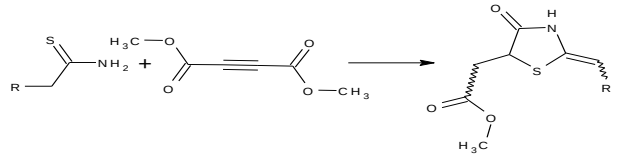
Keywords: Thiazolidinone, Heterocyclic system.

INTRODUCTION

Thiazolidinones with a carbonyl group at position 2, 4, 5 have been subject to extensive study in the recent part. Numerous reports have appeared in literature which highlights their chemistry and use. A comprehensive review has been written on 4-thiazolidinones in 1961 by Brown and in 1980 by Singh et al., Later on, a review article has appeared which deals with the use of Thiazolidinones as stabilizers for polymeric materials. Bis heterocycle compounds exhibit various biological activities. Diverse biological activities such as anti-bacterial, anti-fungal, insecticidal, pesticidal, anti-protozoal, analgesic, anti-inflammatory, anti-covulsant, anti-diabetic etc., have been found to be associated with the thiazolidinone derivatives. Heteroycles containing the thiazole moiety are present in many natural products and conformed as a novel class of potent and selective anti-tumour agents.

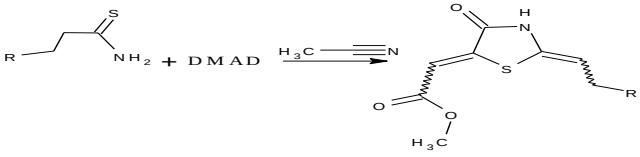
This diversity in the biological response profiles of thiazolidine has attracted the attention of many researchers to explore this skeleton to its multiple potential against several activities. In recent years, interests of researchers have been focused on the heterocyclic systems which contain various heteroatoms such as nitrogen, sulfur and oxygen because of their biological importance.

Reaction of thioamides with dimethyla cetylenedicarboxylate (DMAD) has been shown to occur via the α-situated ester group followed by cyclization leading to a five membered thiazolidinone ring.(fig 1).



[R= -COOEt, -COOMe, -CN, -CONHC$_6$H$_4$-Me-O]

Thioamides of alkyl carboxylic acids reacted with DMAD to afford 2,5-dimethylene thiazolin-4-one or 2-methoxy-2-alkylsubstituted thiazolidinone depending on the solvent which the reaction is carried out.(fig 2)



[R= -CH$_3$, -CH$_2$CH$_3$, -C$_6$H$_5$]

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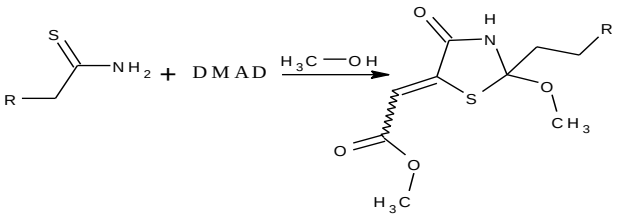
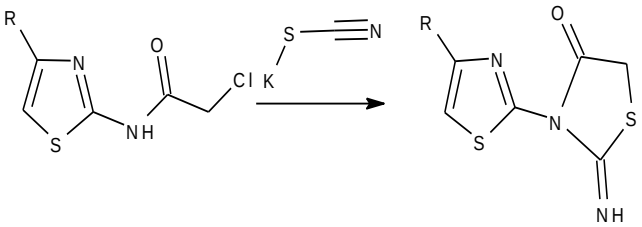


[R= -CH_3, -CH_2CH_3, -C_6H_5]
P/12

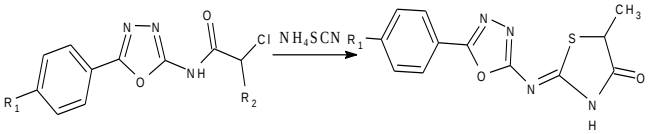
From Thiocyanates[1] :

2-Chloroacetamido-4-arylthiazoles was treated with potassium thiocyanate in refluxing acetone to afford the related 2-amino-3-(4-arylthiazol-2-yl) thiazolidine-4-ones [fig 3].



R=C_6H_5, p-ClC_6H_4, P-$NO_2C_6H_4$, 2,4-$(Cl)_2$-5-F-C_6H_2

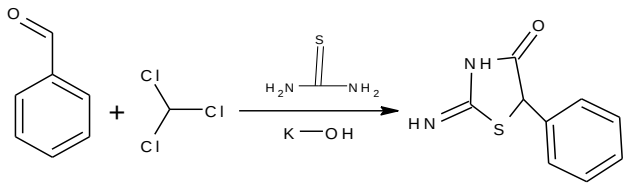
Moreover, 5-aryl-2-(α-chloro-α-phenylacetyl) amino-1,3,4-oxazodiazole [fig 16] when heated with ammonium thiocyanate gave 5-aryl-2-(5-aryl-1,3,4-0xadiazol-2-ylimino)-4-thiazolidinones [fig 4] and its analogues.[2]



[R_1=H, Cl; R_2=CH_3, C_6H_5]

From Thiourea[3]

Ternary condensation of benzaldehyde, chloroform and thiourea under Reeve's conditions (MeOH, KOH, 50^0C) afforded the 2-amino-4-thiazolidinone derivative.(fig 5)
P/13



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From Mercaptosuccinic Acid[4]

Thiazolidinone derivative was prepared by reaction of 3-aminobenzamide, 5-(phenylethyl)-2-thiophenecarboxaldehyde and mercaptosuccinic acid. Also compound was prepared by condensation of methyl-3-aminobenzoate, 4-benzyloxybenzaldehyde and mercaptosuccinic acid. (fig 5)

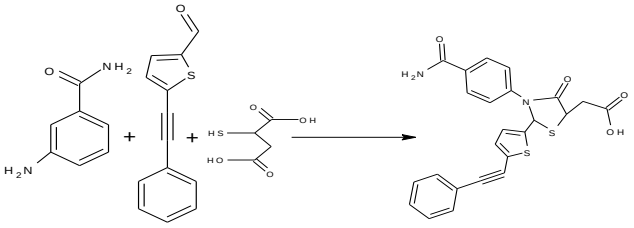

Fig 5

From Dithiocarbamate[5]

2-Thioxo-3-93-triflouromethylphenyl)- 4 - thiazo lidinone was prepared by the reaction of dithiocarbamate [fig 6] with C labeled sodium bromo acetate at room temperature.

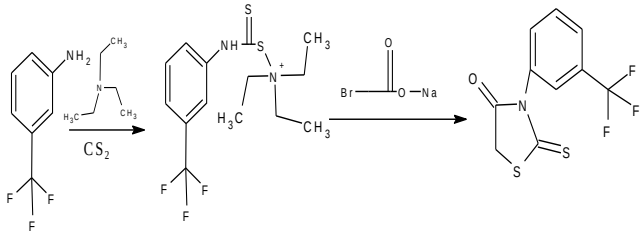

Fig 6

P/14
From Thiosemicarbazone and Thiosemicarbazone derivatives.

Electrophilic substitution on 2-hydroxypyrazine by Ethyl chloroacetate under reflux afforded ethyl (pyrazin-2-yl-oxy) acetate. Which on amination with hydrazine hydrate afforded 2-(pyrazine-2-yl) acetohydrazide [fig 43]. Reaction of with alkyl/aryl isothiocyanate in ethanol gave compound. Condensation of with chloroacetic acid in boiling ethanol containing sodium acetate led to the formation of 4-thiazolidinone derivative. (Fig 7)

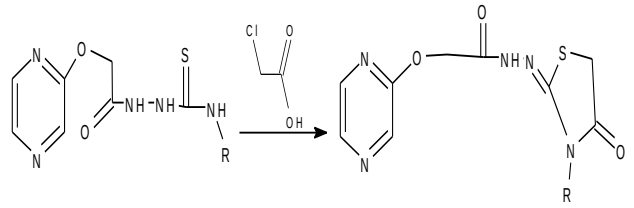

Fig 8. [R=4-chloro-2-nitrophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, n-butyl, t-butyl]
P/16

From a specimen of Chromodoris [6]

Latrunculine A [fig 9] was isolated from a specimen of *chromodoris* sp collected from Indonesian water, and also was determined in extract of the Red Sea sponge.

P/17

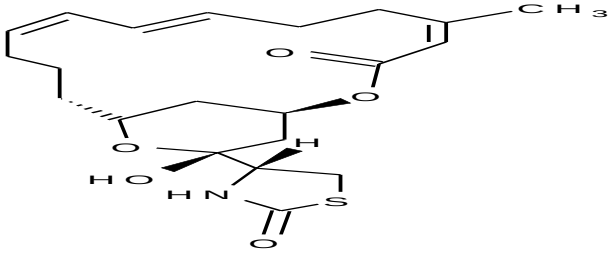

Fig 9 (Latrunculin A)

From Thiolactum Derivatives

Reaction of piperidine-2-thione with α-bromoesters gave the nitrogen bridgehead compounds.

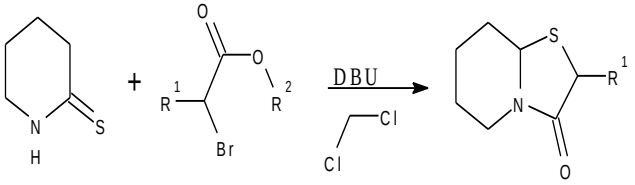

Fig 10 [R^1=Me, n-Pr, n-Bu; R^2=OMe, OEt,; DBU=methyl phenidate derivatives]

P/18

Reactions of 4-Thiazolidinones:

Reactions with Electrophiles

Condensation of the thiazolidinone with aldehydes in ethanol piperidine solution furnished the thiazolidinone derivatives . Besides, treatment of with benzaldehyde in refluxing pyridine afforded the α-benzylidine derivative. On the other hand, repeating this reaction in the presence of ethanol/piperidine yielded the bis benzaldhyde derivatives and also 4-thiazolidinone derivative [fig 23]. Condensation of 2-cyanomethyl-4-thiazolidinone with terephthaldehyde (2:1 molar ratio) in ethanol afforded 1,4-bis(2-cyanomethyl-4,5-dihydro-5-methylidine-4-thiazolonon-5-yl)benzene .

P/19

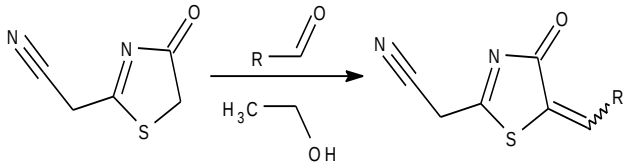

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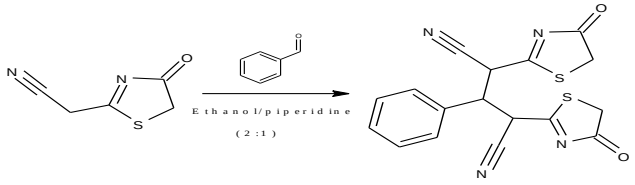
Fig 23 R= p-BrC_6H_4, p-FC_6H_4, $C_6H_4NC_4H_8O$



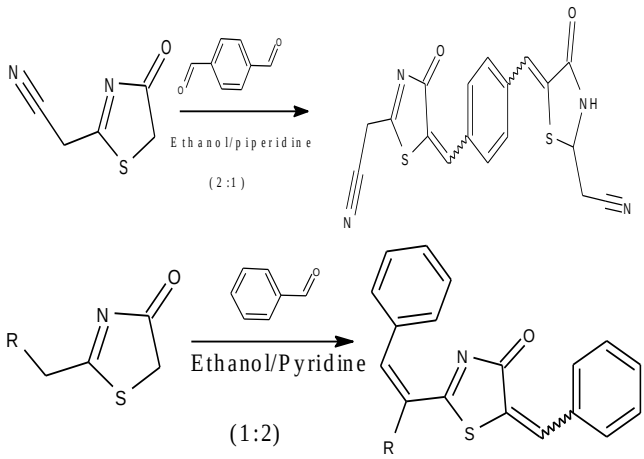


Fig 11[R= -COOEt, -COPh, CN, -CONHNHPh]

P/20

Mannich Reaction

Compound [fig 12] was heated under reflux after the addition of 37% formaldehyde and piperidine /pyrolidine (1:1) to give 5-phenylmethyl-5-piperidino/pyrolidino methyl-2-(5-aryl-1,3,4-oxadiazol-2-yl) imino)-4-thiazolidinones [fig 63], respectively.

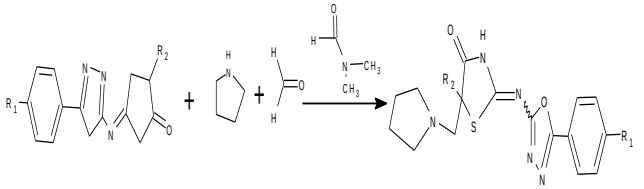
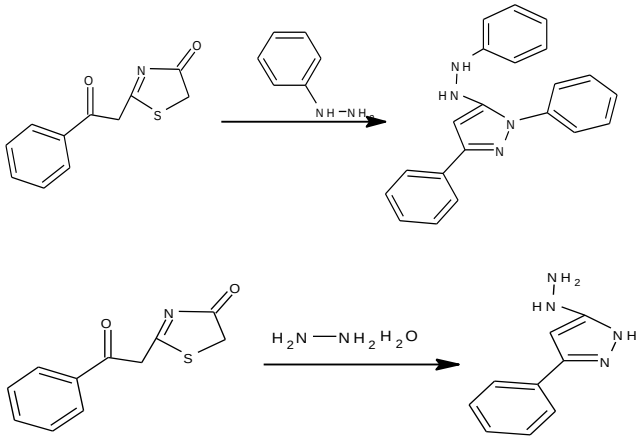


Fig 12 R_1=H, OH R_2=CH_3, NO_2

Ring Cleavage Reaction

When compound is reacted with phenyl hydrazine and hydrazine hydrate in presence of a solvent, the phenyl hydrazinopyrazole derivative and hydrazinopyrazole were formed.



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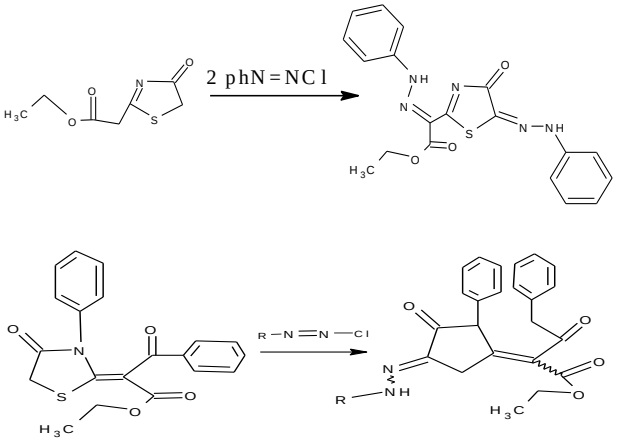
Electrophilic Coupling Reaction

The formation of 4-arylazo-2-(2-arylazo-ethyl acetate)-4-thiazolidinone [fig 66] was achieved by treatment of compound (fig 4a) with benzene diazonium chloride (1:2 molar ratio). Also, the active methylene group of the thiazolidinone [fig 67] was coupled with different diazonium salts to give the corresponding arylazo derivative [fig 13].



67 68

Fig 13 [R=C $_6H_5$, 4-CH_3-C $_6H_4$]

Reactions with Halo compounds

The alkylation of the compound with 2-bromoacetophenones or chloroacetic acid anilides in the presence of potassium carbonate was found to proceed smoothly at the nitrogen atom resulting in 3-(2-aryl-oxoethyl)-2-methylidine-thiazolidin-4-ones and N-aryl-[2-methylidine-4-oxo-thiazolidinyl]acetamides respectively. P/22 Fig 14.

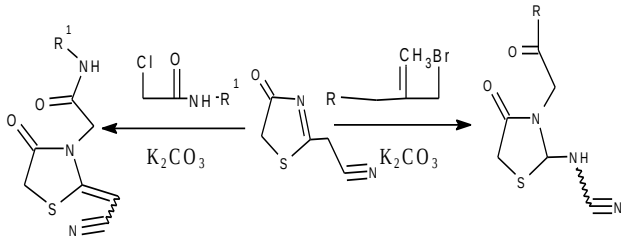


Fig 15 [R=4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$]
[R^1=4-$EtOC_6H_4$, 4-MeC_6H_4, 4-i-PrC_6H_4]

Reaction with Phosphorous Oxychloride Dimethyl formamide Complex.

The formulation of the thiazolones with excess of phosphorous Oxychloride in dimethyl formamide ($POCl_3$/DMF) accomplished the preparation of oxopyrrolo[2,1-b]thiazole system. The pyrrole ring closure is accompanied with the methylene group transformation in to its (dimethyl amino) methylidine derivatives yielded 3-oxopyrrolo[2,1-b]thiazole derivative. Fig 16.

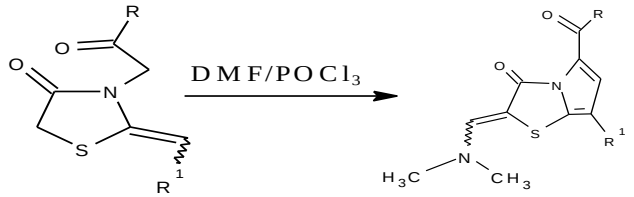


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Fig 16 [R=H, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$; R^1=COOEt, COOMe, CN]

P/23

Reactions with Phenyl Isothiocyanate and Carbon Disulfide

Thioanilide was obtained by treatment of compound with phenyl isothiocyanate in the presence of potassium hydroxide which converted to 2,3-dihydro-1,3,4-thiadiazoles via it's reaction with the appropriate hydrazonoyl halides . Also, methyl carbodithionate was prepared via reaction of with Carbon Disulfide in dimethyl formamide and potassium hydroxide followed by iodomethane.Fig 17

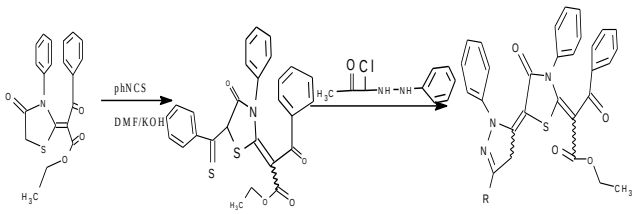

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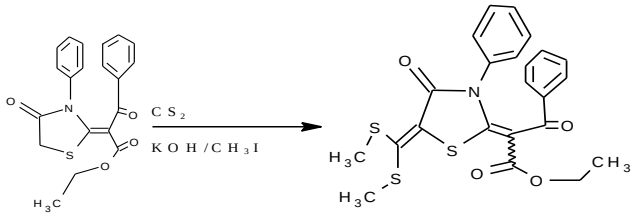
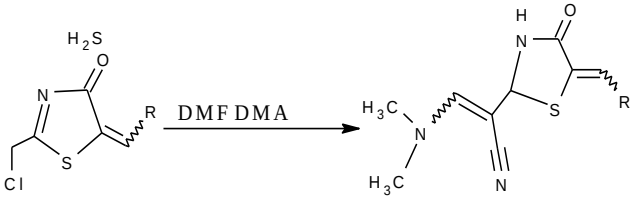
Fig 17 R=OC_2H_5, CH_3, C_6H_5NH;



Reaction with dimethylformamide dimethylacetal and Tryethyl orthoformate

Condensation of compound with dimethylformamide-dimethylacetal (DMF-DMA) and triethyl orthoformate HC $(OEt)_3$, yielde N,N-dimethylamino derivative and ethoxymethylene derivatives respectively.Fig 18.



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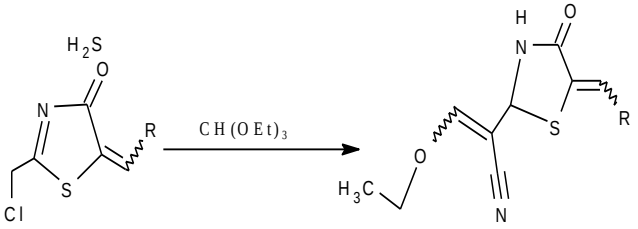
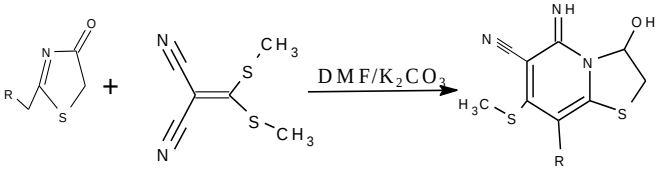


Fig 18

Reaction with Different Arylaldehydes

Bis(methylsulfanyl)methylidene]malononitrile [fig 19] reacts with 1,3-thiazol-4(5H)one derivative in refluxing DMF containing the equivalent amount of K_2CO_3 to yield the 7-methylsulfanylthiazolo-[3,2-a]pyridine derivative .



4 78 79

Fig 19 [R=COOEt, COPh, CONHNHPh, CN]

LITERATURE SURVEY ON BIOLOGICAL ACTIVITY OF 4-THIAZOLIDINONES:

Anticonvulsant activity:

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

Antitubercular activity:

The emergence of multi-drug resistant tuberculosis, coupled with the increasing overlap of AIDS and tuberculosis pandemics has brought tuberculosis to the forefront as a major worldwide health concern.

Ethyl-5- (5-nitro- furan- 2- [2-(2-hydroxy-3-methoxy-2-ylmethyl)-4-thiazolidinonephenyl)5-methyl-4-oxo-thiazolidin-3-yl]3-metyl-butyric acid ethyl ester Turkevich *et al.,* reported few 2-amino-4-thiazolidinone derivatives as possible anti-tubercular compounds. In other study, 5-(5-nitrofurfuryllidene)-3-ethylrhodamine has been found to be a promising tuberculostatic compound. Few derivatives of 2-imino-4-thiazolidinones have also been reported as having anti-tubercular activity with low toxicity. Repeated therapeutic doses were found to possess anti-tubercular activity comparable to streptomycin or phthivazid. A few derivatives were found to inhibit the growth of human tubercle bacilli, H37Rv strain, in a concentration of 12.5 mg/ml. several other derivatives of thiazolidinones have also been found to inhibit the growth of mycobacterium tuberculosis H37Rv strain. 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.

Antiviral activity

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

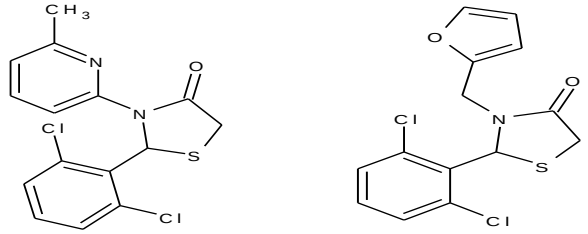


Fig 20-(2,6-Dichloro-phenyl)-3-2-(2,6-Dichloro-phenyl)-3-furan6-methyl-pyridin-2-yl)-2-ylmethyl-4-thiazolidinone 4-thiazolidinone6-methylpyridin-2-yl derivatives, particularly compound 2-(2-6-dichlorophenyl)-3(6-methyl-pyridin-2-yl)4-thiazolidinone, possessed the most promising selectivity index of 6470 and activity with EC50 value of 0/044 mM. In terms of SARs, anti-HIV activity was strongly enhanced by introducing a 2-pyridnyl substituent at the N-3 atom of the thiazolidinone ring and in particular by two chlorine atoms at 2 and 6 positions of the phenyl rings at C-2, 2-(2,6-dichloro-phenyl)-3-furan-2-ylmethyl-4-thiazolidinone, show promising HIV-RT inhibitory activity by determining their ability to inhibit the replication of HIV-1 (IIIB) in MT-4 cells with EC50 value of 0.204 mM.

Anti-inflammatory activity (COX-inhibitor):

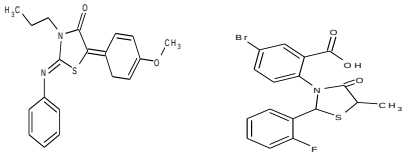


Fig 21 5-(4-methoxyphenylidene)-3-(4-bromo-2-carboxyphenyl)- 2-phenylimino-3-propyl- 2-(fluorophenyl)-

4-thiazolidinone 5-methyl-4-thiazolidinone 5-(4-Methoxyphenylidene)-2-phenylimino-3-propyl-4-thiazolidinone, the most interesting compound, showed promising interaction for COX-2 selectivity at concentration of 1 and10 __ with 35 and 55% inhibition, respectively. In another study, Ashok Kumar et.al., synthesized 3-(4-bromo-2-carboxyphenyl)-2-(fluoro phenyl) -5-methyl-4-thiazolidinone was compared with phenylbutazone for its relative anti-inflammatory potency at three graded oral doses (25, 50, and 100 mg/kg) and were found nearly euipotent, with ED50 $^{1}/_{4}$ 100.00 and 94.9 mg/kg, respectively [6].

Follicle stimulating hormone (FSH) receptor agonist activity:

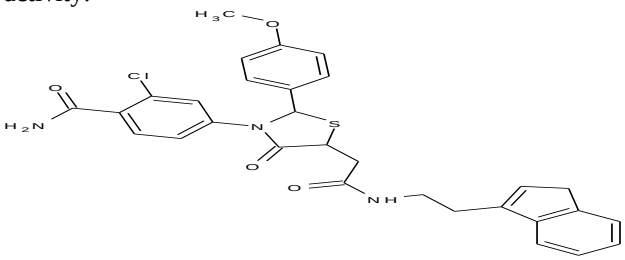


Fig.22. 2-chloro-4-[5-([2-(3H-inden-1-yl)-ethylcarba moyl)] -methyl2-(4-methoxy-phenyl-4-oxo-thiazolidin-3-yl)benzamide

Experimental Procedure

Synthesis of Ethyle-2,4,6-trichloro phenol xyacetate (II) : A mixture of 2,4,6-trichlorophenol (I) (0.01 mol) and ethylchloroacetate (0.01mol) was refluxed in a dry acetone in presence of anhydraous k_2co_3 (0.01 mol) for about 6hrs and then poured on to the crushed ice. Liqid product obtained was isolated by ethanol extraction and then dried. The purity of the compound was checked by TLC. The M.P of the compound was found to be 197^{O}C.

Synthesis of 2,4,6-trichlor opheno xyacetylhydrazide (III) :

A mixture of 2,4,6-trichlorophenoxyacetate (0.01 mol) and hydrazinehydrate (0.01 mole) and absolute alcohol was refluxed for 5hrs. the solution was poured on to the crushed ice. The separated solid was crystallized from ethanol. The purity of the compound was checked by TLC. The M.P of the compound was found to be 155^{o}C

Synthesis of N1[(z)-(phenyl)methylidene]-2-(2,4,6-trichlorophenoxy)acetohydrazide (IV) :

A mixture of 2,4,6-trichloro phenoxy acetylehydrazide (0.001 mol), an appropriate aromatic aldehyde (0.03mol), 30ml of methanol and 0.5ml of glacial acetic acid were added and refluxed for about 2hrs. the reaction mixture was cooled at room temperature then filtered, washed with little amount of methanol and dried. The purity of the compound was checked by TLC. The M.P of the compound was found to be 208^{O}C

Synthesis of *N*-[2-phenyl-4-oxo-1,3-thiazolidin-3-yl]-2-(2,4,6-trichlorophenoxy)acetamide A mixture of compound(IV) (0.001mol) and thioglycolic acid / mercaptopropionicacid (0.004mol) was taken in a round bottom flask containing dimethylformamide and a pinch of anh $ZnCl_2$.the reaction mixture was refluxed for 12hrs and cooled at a room temperature and poured on to the crushed ice. The solid thus separated was filtered, washed with small amount of water, dried and purified by recrystallisation from suitable solvent. As many as 6 compounds have been synthesized by adopting above procedure and physical data presented in Table-1.

MATERIAL AND METHODS

Action on central nervous system gross behavioral studies
Materials: 0.1% Sodium CMC, Test compounds.
Instruments: Sonicator.
Animals: Mice.

Method:

All the compounds tested for acute toxicity studies were also observed for gross behavioural changes, continuously for 5 hours at 1 hour interval after administration of the compounds. There after the observations were recorded intermittently for 24 hours and compared with that of control group.

In the behavioural profile, the animals have been observed for changes in their:

Locomotor activity

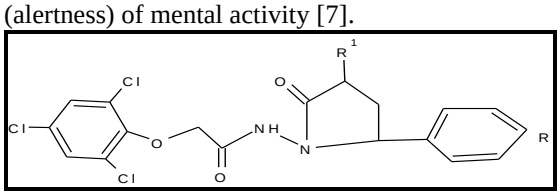
Materials: 0.1% Sodium CMC, Test compounds.
Instruments: Sonicator and Actophotometer.
Animals: Mice.

Method:

The locomotor activity was studied by using actophotometer, which operates on photoelectric cells, which are connected in circuit with a counter. When

Gross behavioral studies:

Animals cut of beam of fight falling on the photocells, count was recorded. Healthy male mice weighing between 20-25 gm were used. Animals were fasted for overnight and divided into groups of six animals each group. The test compounds suspended in 0.1% Sodium CMC are administered at a dose of 100 mg/kg body weight i.p. The control group animal received only vehicle (0/1% sodium CMC). The response (counts) was recorded after 30 minutes of administration of drug or test compounds. Each animal was placed in actophotometer for 10 minutes and scores were recorded (no. of deflections) and compared the results with control. The locomotor activity can be an index of wakefulness (alertness) of mental activity [7].



RESULTS AND DISCUSSION

N-[2-phenyl-4-oxo-1,3-thiazolidin-3-yl]-2-(2,4,6-trichlorophenoxy) acetamidewere schematically synthesized as planned. All the compounds are authentically identified by physical and spectroscopic data.

All the new compounds were screened for gross behavioural studies. The gross behavioural studies of the test compounds revealed that all the test compounds exhibited central nervous system depression in the mice. Table-II pertaining to the gross behavioural studies of N-[2-phenyl-4-oxo-1,3-thiazolidin-3-yl] -2- (2,4,6 - trichlo rophenoxy)acetamide shows that all the compounds did not show alertness. Among the test compounds, Vf showed more depressant activity than the rest of the compounds.

Locomotor Activity

Table-III pertaining to the results of the locomotor activity of the N-[2-phenyl-4-oxo-1,3-thiazolidin-3-yl]-2-(2,4,6-trichlorophenoxy)acetamide in mice shows that all the test compounds reduced the locomotor activity. The locomotor activity was studied by actophotometer. The compound Vf (R=4-OH,3-OCH_3, R1-H) exhibited more effect among all the compounds with 93.80% reduction in the locomotor activity. The compound Vd(R=4-OCH_3, R1=H) reduced the locomotor activity by 92.85% and the compounds Va, Ve, Vb, Vc were next in the order of reduction of locomotor activity.

Table 1. Physical data of *N*-[2-phenyl-4-oxo-1,3-thiazolidin-3-yl]-2-(2,4,6-trichlorophenoxy)acetamide.

S.No	Compound	Substitutions		Mol Formulae	Mol. Weight	M.P(°C)	Yield (%)
		R	R1				
1	Va	4-H	H	$C_{17}H_{13}Cl_3N_2O_3S$	431	210-213	65
2	Vb	4-CL	H	$C_{17}H_{12}Cl_4N_2O_3S$	466	232-235	69
3	Vc	4-$N(CH_3)_2$	H	$C_{19}H_{18}Cl_3N_3O_3S$	474	221-224	67
4	Vd	4-OCH_3	H	$C_{18}H_{15}Cl_3N_2O_4S$	461	243-246	64
5	Ve	2-OH	H	$C_{17}H_{13}Cl_3N_2O_4S$	447	241-246	58
6	Vf	4-OH,3-OCH_3	H	$C_{18}H_{15}Cl_3N_2O_5S$	477	234-236	56

Screening Of *N*-[2-phenyl-4-oxo-1,3-thiazolidin-3-yl]-2- (2,4,6-trichlorophenoxy) acetamide

Table 2. Locomotor activity of N-[2-phenyl-4-oxo-1,3-thiazolidin-3-yl]-2-(2,4,6-trichlorophenoxy)acetamide (Va – Vf)

Compound	Substitutions		Locomotor activity (scores) in 10 minutes, n=6		% Change in activity (↓)
	R	R1	Before administration	After administration	
Va	4-H	H	197	14	92.83
Vb	4-CL	H	212	16	92.41
Vc	4-$N(CH_3)_2$	H	205	22	89.26
Vd	4-OCH_3	H	195	14	92.85
Ve	2-OH	H	211	16	92.43
Vf	4-OH,3-OCH_3	H	195	12	93.80

CONCLUSION

The following conclusions have been drawn from the results of this investigation. Synthetic work of this study have positively undergone as per the planning and as such in all the reactions carried, the expected compounds are obtained. From gross behavioural studies and locomotor activity, all the test compounds showed depression of the central nervous system in mice. Compound with 4-OH,3-OCH_3 substitution on phenyl ring and hydrogen group on thiazolidine ring showed more promising depressant active necessary from the result of preliminary investigations that there is a need for further screening on those test compounds, which had shown promising activity.

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