Chemistry and Biological Activities of 1,3-Thiazolidin-4-ones

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Abstract: 1,3-Thiazolidin-4-ones are an important group of heterocyclic compounds that are used in the field of medicinal chemistry. The utility of 1,3-thiazolidin-4-ones as synthons for various biological compounds has given impetus to these studies. In recent years, 1,3-thiazoldin-4-ones have been among the most extensively studied compounds. This review aims to review the work reported on the chemistry and biological activities of 1,3-thiazolidin-4-ones during the past few years.

INTRODUCTION

There are numerous biologically active molecules with five-membered rings, containing two hetero atoms. Thiazolidinone is an important scaffold known to be associated with several biological activities. A comprehensive review has been written on 4-thiazolidinones in 1981 [1].

1,3-Thiazolidin-4-ones are heterocycles that have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 4 (Fig. **1**). Substituents in the 2-,3-, and 5-position may be varied, but in this review we focused only modifications in the positions 2 and 3. Numerous methods for the synthesis of thiazolidinones and also their diverse reactions offer enormous scope in the field of medicinal chemistry. We present here the chemistry and biological properties of this heterocyclic ring since 2000.

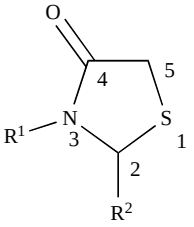

Fig. (1). General structure of 1,3-thiazolidin-4-ones.

Synthesis of 1,3-thiazolidin-4-ones

The main synthetic route to prepare 1,3-thiazolidin-4-ones involve three components (an aldehyde or ketone, an amine and a mercapto-acid), either in a one- or two-step process. The reactions proceed by initial formation of an imine (the nitrogen of amine attacks the carbonyl of aldehyde or ketone), which undergoes attack by sulfur nucleophile, followed by intramolecular cyclization on elimination of water (Fig. **2**). The latter step seems to be critical for obtaining high yields of 1,3-thiazolidin-4-ones. The most common protocol to remove the water is by azeotropic distillation. Srivastava *et al.* reported an improved protocol wherein *N*,*N*-dicyclohexyl carbodiimide (DCC) is used as a dehydrating agent to accelerate the intramolecular cyclization resulting in faster reaction and improved yields [2]. The same results were found when 2-(1*H*-benzotriazo-1-yl)-1,1,3,3-tetramethyl uraniumhexafluorophosphate (HBTU) was used [3]. Iyengar *et al.* also reported the use of the anhydrous γ-ferrite as desiccant agent [4,5]. The efficient combination of an ionic liquid system and microwave dielectric heating for the preparation of a small library of 1,3-thiazolidin-4-ones with low reaction times and moderate yields was reported by Fraga-Dubreuil *et al.* [6].

Ma *et al.* reported the synthesis of some ferrocene derivatives. The 4-ferrocenyl-2-thiazolamine condenses with benzaldehyde to give the imine **1** in poor yield (30%) that cyclizes with mercaptoacetic acid using a Dean-Stark apparatus to produce compound **2** (Scheme **1**) [7].

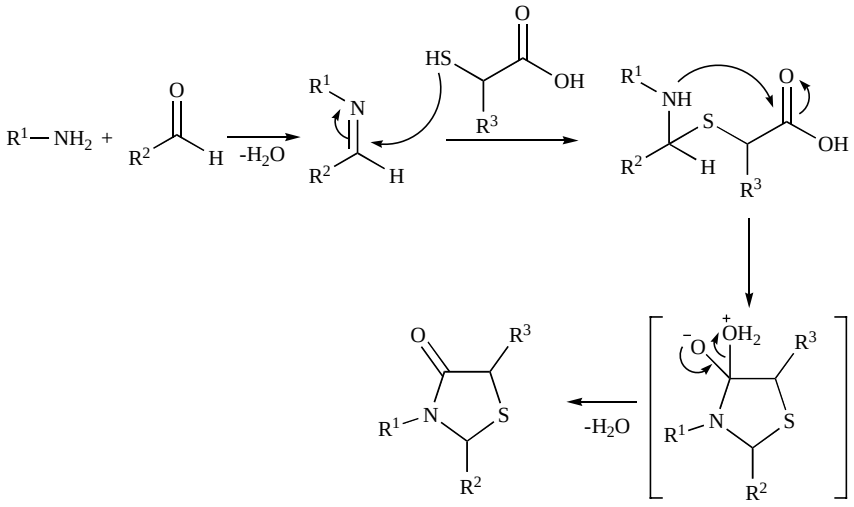

Fig. (2). Mechanism of formation of 1,3-thiazolidin-4-ones from aldehyde.

Kato *et al.* described the improvement on the synthesis of cardioprotective drug CP-060S (**3**) [8]. The initial synthetic route is not economical enough for providing sufficiently quantity of the 1,3-thiazolidin-4-one intermediate and the authors developed an im-

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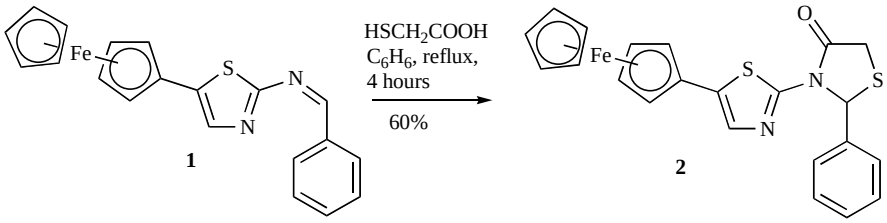
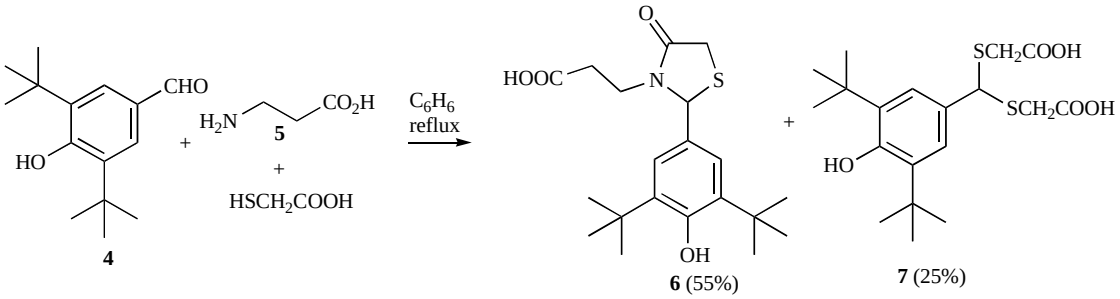
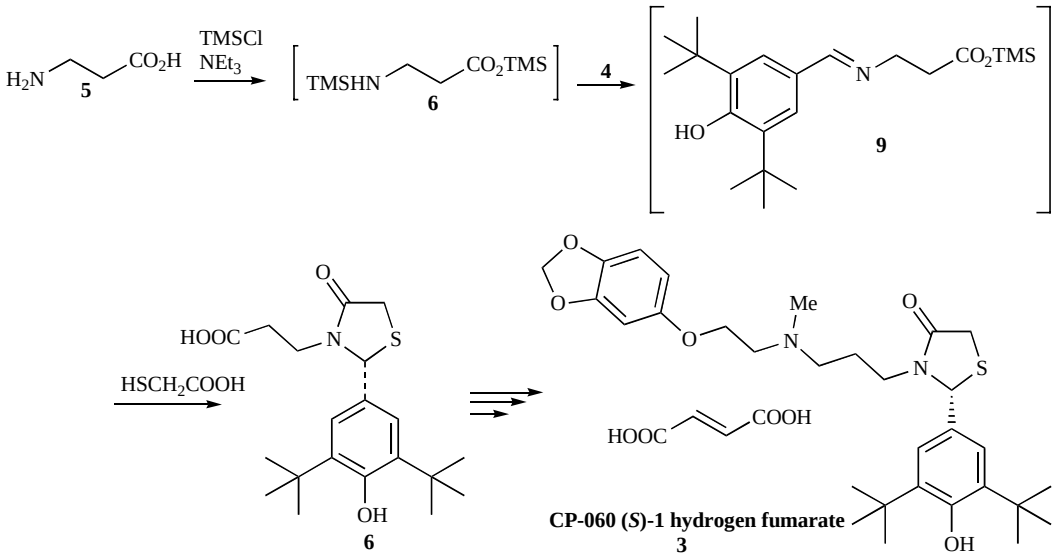


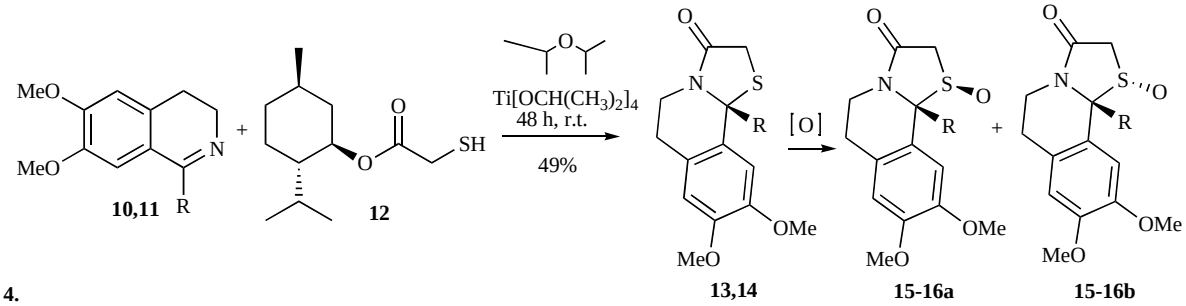
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

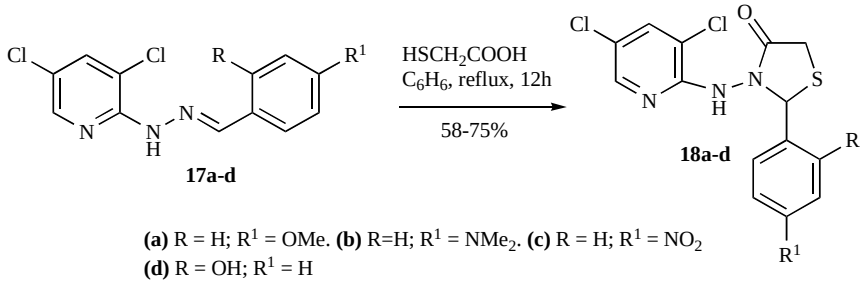
provement by protection of β-alanine with chloro trimethylsilane (TMSCl). The direct condensation of aldehyde **4**, alanine **5** and mercaptoacetic acid give the desired thiazolidinone **6** along with the dithioacetal **7** as the major byproduct (Scheme **2**).

Treatment of alanine with TMSCl and triethylamine in toluene gave the intermediate **8,** which was treated with aldehyde **4** to give the imine **9**. Further treatment of this imine with mercaptoacetic acid afforded the desired thiazolidinones carboxylic acid without formation of **7** (Scheme **3**).

Rozwadowaska *et al.* described the asymmetric synthesis of thiazolidinones **13** and **14** from imines (**10** and **11**) and (-)-menthyl thioglycolate **12** (synthesized by condensation of mercaptoacetic acid with (-)-menthol) (Scheme **4**) [9]. The authors also studied the oxidation of thiazoisoquinolines **13** and **14**, using four peroxy agents: *meta*-chloroperbenzoic acid (*m*CPBA) at 0°C, 30% hydrogen peroxide at r.t., 30% hydrogen peroxide at reflux and oxone at 0°C [10]. As a result, the mixture of two diastereoisomeric sulfoxides were produced with diastereoselectivity depending on the oxidation system used (Table **1**).

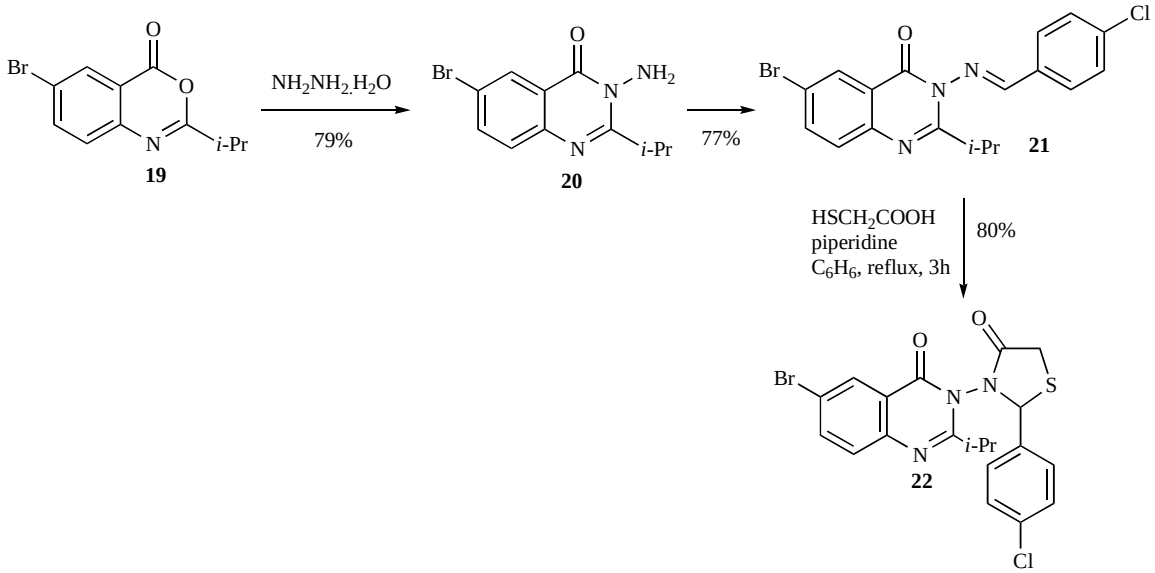
Table 1. Reaction Conditions for Oxidation of Thiazolidinones 13 and 14

Sulfide		Oxidant	Reaction Time	Sulfoxide	
Comp.	R			Yield (%)	Dominating
13	H	*m*CPBA, CH_2Cl_2, 0°C	0.5 h	91	**15b**
13	H	30% H_2O_2, $CHCl_3/CH_3OH$ (2:1), r.t.	6 h	71	**15a**
13	H	30% H_2O_2, $CHCl_3/CH_3OH$ (2:1), reflux	2-2.5 h	75	**15b**
13	H	Oxone, $CHCl_3/CH_3OH$ (2:1), 0°C	3 h	71	**15a**
14	CH_3	*m*CPBA, CH_2Cl_2, 0°C	0.5 h	94	**16b**
14	CH_3	30% H_2O_2, $CHCl_3/CH_3OH$ (2:1), r.t.	3 days	96	**16b**
14	CH_3	Oxone, $CHCl_3/CH_3OH$ (2:1), 0°C	1.5 h	97	**16a**



(a) R = H; R^1 = OMe. **(b)** R=H; R^1 = NMe_2. **(c)** R = H; R^1 = NO_2
(d) R = OH; R^1 = H

Scheme 5.

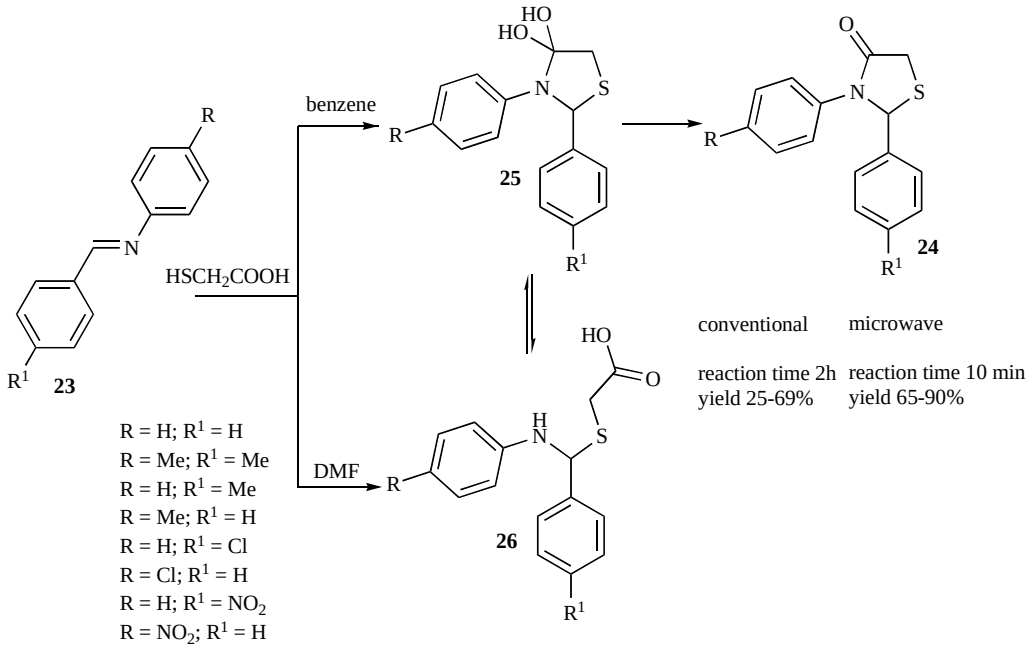


Scheme 6.

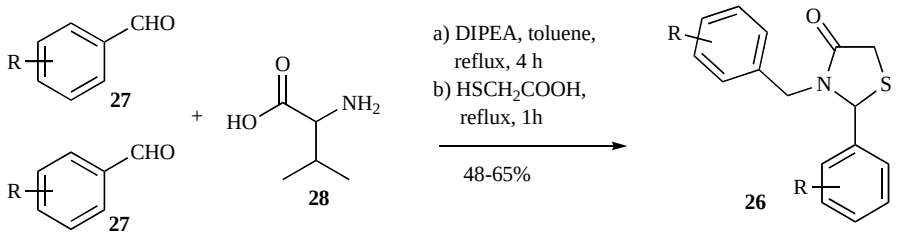
The reaction of hydrazones **17a-d** with mercaptoacetic acid gives the 1,3-thiazolidin-4-ones **18a-d** in good yields (Scheme **5**) [11]. The best yields were achieved by refluxing the reagents in benzene for 12 hours with a molar ratio of hydrazones **17a-d** to mercaptoacetic acid of 1:2 to 1:2.5 in the presence of 3-5 weight % of zinc chloride. In the absence of $ZnCl_2$ the yield of the thiazolidinones did not exceed 40-45%.

6-Bromo(4*H*)-3,1-benzoxazin-4-one **19** was synthesized and converted into 3-amino-4(3*H*) quinazolinone **20** by reaction with hydrazine hydrate. This compound was used as precursor on synthesis of diverse heterocyclic systems including the thiazolidinone **22** (Scheme **6**) [12].

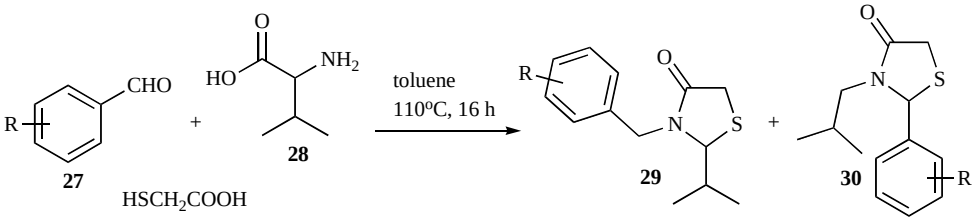
Bolognese *et al.* studied the mechanism of the reaction of imines **23** with mercaptoacetic acid under microwave irradiation and conventional heating [13]. While the reactions in microwave showed very high yields (65-90%), the reaction in conventional heating required longer times and gave much lower yields (25-69%). The reaction studied by ^{1}H NMR has shown that 1,3-thiazolidin-4-one **24** are directly formed from the starting materials under microwave irradiation. Under conventional heating, two intermediate species in equilibrium, the *gem*-diol **25** and the sulfanyl acetic acid **26**, have been detected. The nature of the solvent determines the formation mechanism. In benzene, **25** was the first product formed, while in DMF, **26** was the first one (Scheme **7**).



Scheme 7.



Scheme 8.



Scheme 9.

Cunico *et al.* described the unexpected formation of 2-aryl-3-benzyl-1,3-thiazolidin-4-ones (**26**) from reaction of 2 equivalents of areneldehydes **27**, 1 equivalent of valine **28**, 1 equivalent of diisopropylethylamine (DIPEA), excess of mercaptoacetic acid in toluene using a Dean-stark apparatus (Scheme **8**) [14]. The structure was confirmed by x-ray diffraction [15]. Recently, the authors studied this reaction using microwave irradiation with better yields and very low reaction times [16].

In order to explore this reaction in more details, the authors reported the formation of two novel 1,3-thiazolidin-4-ones **29** and **30** (Scheme **9**) [17]. These heterocycles were synthesized when the reaction was carried out in 1:1:3 mole ratio of valine-arenealdehyde-mercaptoacetic acid in absent of DIPEA in order to minimize the formation of thiazolidinone **26**. The strong withdrawing group NO_2 present on nitrobenzaldehydes (**27b-d**), promotes the selective formation of thiazolidinones **29b-d** in good yields (entry 2-4), whereas the methoxy and fluoro groups did not showed good selectivity as shown in Table **2**. The structure of compounds **29b** and **29d** were confirmed by x-ray diffraction [18].

Cunico *et al.* also studied the application of 5-amino-1,2,3-thiadiazole **31** as precursor on synthesis of 1,3-thiazolidin-4-ones **32** [19], because of its versatility in synthetic chemistry. The synthesis of compounds **32** was carried out by the reaction of an arenealdehyde (**27**) with an equimolar amount of amine **31** and excess of mercaptoacetic acid in refluxing toluene for 24 hours (Scheme **10**).

Antiretroviral Activity

There are several works in the literature describing the thiazolidinones highly active as non-nucleoside reverse transcriptase inhibitor (NNRTI) with minimal cytotoxicity (Fig. **3**). The biological activity of 1,3-thiazolidin-4-ones is associated with the ability to assume a conformation "butterfly-like" shape. From the SAR point of view, the anti-HIV activity is strongly influenced by the nature of the substituent at 2 and 3 position of the thiazolinone nucleus. The presence of the two halogen atoms at 2 and 6 position restricted the rotation of the phenyl ring (at 2-position on thiazolidinone ring) and allowed the molecules to assume the characteristic butterfly-like conformation. The rings 2-pyridinyl and 2-pyrimidinyl attached at N-3 atom enhances the HIV activity (Table **3**) [20-24]. The replacement of these heterocycles for a phenyl [25], a furfuryl [26], a thiazol or a thiadiazol [27], moiety reduce the HIV-RT inhibitory activity. The replacement of the carbonyl group with the isostere thiocarbonyl group negatively influences the activity with appreciably decreases [28].

Table 2. Yields and GC-Analysis of Compounds 29 and 30

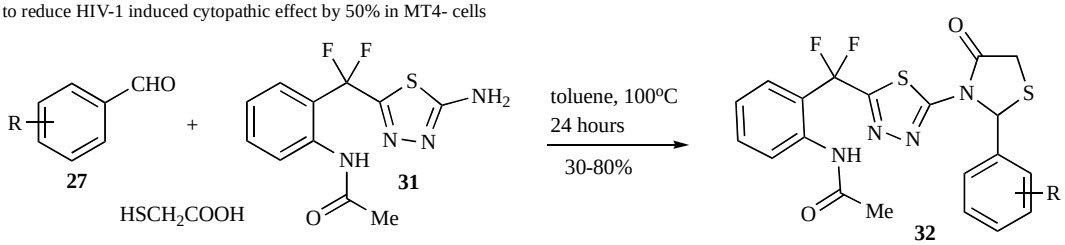
Entry		R	Yield Mixture (%)[a]	GC-Analyses (%)	
				29	30
1	**a**	H	76	35	27
2	**b**	2-NO_2	83	77	-
3	**c**	3-NO_2	68	73	12
4	**d**	4-NO_2	89	92	3
5	**e**	2-F	74	65	12
6	**f**	3-F	71	40	25
7	**g**	4-F	76	34	32
8	**h**	2-OMe	64	27	36
9	**i**	3-OMe	69	34	28
10	**j**	4-OMe	72	27	40

[a] – isolated mixture

Table 3. HIV Activity of Thiazolidinones 33

X	R	R^1	R^2	R^3	R^4	R^5	EC_{50} (μM)[a]	Ref.
CH	H	H	Me	H	Cl	Cl	0.044	[20]
CH	H	H	Me	H	F	F	0.082	[20]
CH	H	H	Me	H	Cl	F	0.053	[21]
CH	H	H	Br	H	F	F	0.030	[21]
CH	H	H	Br	H	OMe	OMe	0.045	[22]
CH	H	H	Br	H	OMe	F	0.034	[22]
CH	H	H	Me	Me	Cl	F	0.050	[22]
N	Me	H	H	H	Cl	Cl	0.044	[23]
N	Me	H	Me	H	Cl	Cl	0.017	[23]
N	Me	H	Me	H	Cl	F	0.038	[23]
N	Me	H	OMe	H	Cl	Cl	0.024	[23]
N	Me	Me	Me	H	Cl	Cl	0.03	[24]
N	Me	Me	Me	H	Cl	F	0.02	[24]

[a] – Concentration to reduce HIV-1 induced cytopathic effect by 50% in MT4- cells



Scheme 10.

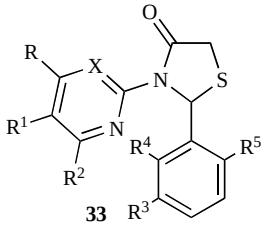


Fig. (3). Thiazolidinones as inhibitors of HIV non-nucleoside reverse transcriptase.

Antimicrobial Activity

The pharmacological properties of thiazolidinones have stimulated researchers to synthesize several compounds containing this moiety. Thiazolidinones with C-2 and N-3 substituted positions, presenting diverse degrees of inhibition against gram-positive and gram-negative bacteria and fungal (Fig. **4**) [29-32].

Kavitha *et al.* obtained the most promising results. The MIC and inhibitory zone of various compounds synthesized (**34** and **35**)

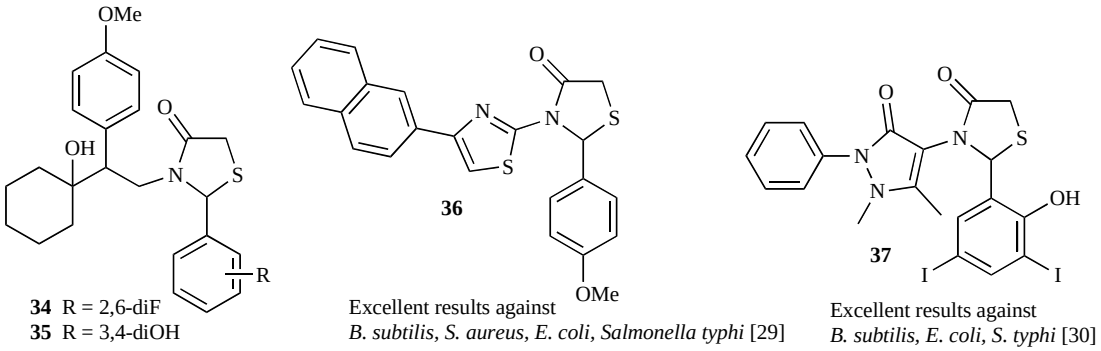


Fig. (4). Thiazolidinones with antimicrobial activity.

Table 4. The Minimal Inhibitory Concentration for Compounds 34 and 35 Against Several Bacteria and Fungal Strains

	Minimal Inhibitory Concentration (MIC) (µg/ml)				
	Bacillus subtilis	***Escherichia coli***	***Pseudomonas fluorescens***	***Xanthomonas campestris pvs***	***Xanthomonas oryzae***
34	10	9	6	5	7
35	12	11	9	8	9
streptomycin	25	19	17	-	-
tetracycline	-	-	-	13	19
	Minimal Inhibitory Concentration (MIC) (µg/ml)				
	Aspergillus niger	***Aspergillus flavus***	***Fusariaum oxysporum***	***Trichoderma species***	***Fusariam monaliforme***
34	15	14	16	12	15
35	19	18	21	17	20
nystatin	29	34	36	30	32

against bacterial and fungal strains were better than that showed by reference drugs tested indicating that these compounds deserve further investigation to develop more potent antimicrobial agents for therapeutic use (Table **4**) [31].

Antimalarial Activity

Solomon *et al.* reported the synthesis of chloroquine analogues having a 1,3-thiazolidin-4-one nucleus at the terminal side chain amino group of 4-aminoquinoline. All compounds were evaluated for their antimalarial activity against *P. falciparum in vitro* and some compounds that have shown activity comparable to standard drug, were also evaluated against *P. yoelli in vivo*. The best compound (**38**, IC_{50} = 0.039µM) posses superior *in vitro* activity compared to chloroquine (IC_{50} = 0.106µM) (Fig. **5**). The biochemical studies confirm that the mechanism of action of those compounds is similar to that of chloroquine, as most of the compounds form an association complex with hematin and thereby inhibit hemazoin formation [33].

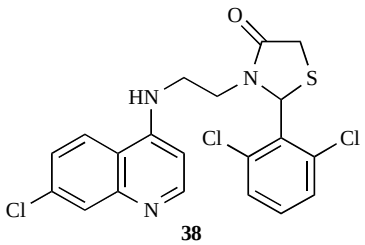


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Fig. (5). Thiazolidinone chloroquine analogue **38**.

Antidiarrhoeal Activity

Several 1,3-thiazolidin-4-ones were synthesized and screened for antidiarrhoeal activity in mice. Although the results showed that the compounds were 15- to 80-fold less active than the reference loperamide, they were much less toxic, ≥ 1000 mg/Kg and 108.8 mg/Kg, respectively. The most active compound was the 2-phenyl-3-{2-[(4-phenyl-4-cyano)piperidino]ethyl}-1,3-thiazolidin-4-one (**39**) (Fig. **6**) [34].

Anti-Yellow Fever Virus Activity

Sriram *et al.* described the synthesis of 1,3-thiazolidin-4-ones bearing diaryl ring at C-2 and N-3 positions. The compounds were evaluated for their inhibitory effects on the replication on yellow fever virus in green monkey kidney, by means of a cytopathic effect reduction assay. Among these compounds, the 2-(4-chlorophenyl)-3-(4-fluorophenyl)-1,3-thiazolidin-4-one (**40**) emerged as the most promissory anti-yellow fever virus agent with EC_{50} of 6.9 µM and CC_{50} more than 100 µM making it more potent than standard ribavirin (Fig. **7**) [35].

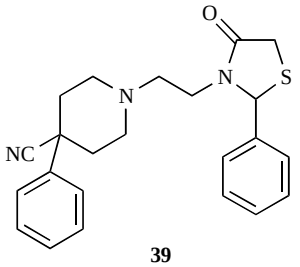

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Fig. (6). Thiazolidinone with antidiarrhoeal activity.

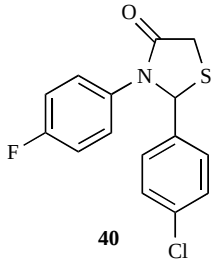

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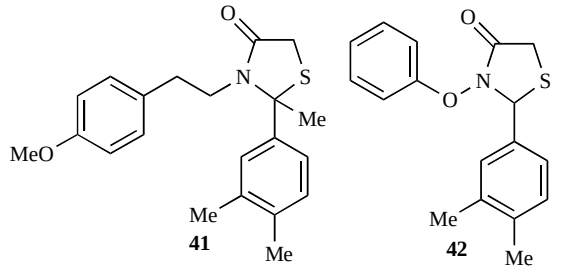
Fig. (7). Structure of 2-(4-chlorophenyl)-3-(4-fluorophenyl)-1,3-thiazolidin-4-one **40**.

Antiarrhythmic Activity

Atrial flutter and atrial fibrillation are the most common cardiac arrhythmias and they are associated with an increase in heart failure, stroke, and mortality. Blockade of the Kv1.5 ion channel is potentially atrial-selective avenue for the treatment of atrial fibrillation and atrial flutter. Jackson *et al.* described the synthesis and biological evaluation of thiazolidinone-based blockers of Kv1.5. The 3,4-dimethyl derivatives **41** (IC_{50} = 0.069μM) and **42** (IC_{50} = 0.270μM) were the most potent compounds of this series (Fig. **8**) [36].



41 **42**

Fig. (8). Thiazolidinones with antiarrhythmic activity.

Anticancer Activity

Gududuru *et al.* described the synthesis and biological evaluation against prostate cancer cells of new 2-aryl-4-oxo-thiazolidin-3-yl amides. The antiproliferative effects of synthesized compounds were examined in five human prostate cancer cell lines (DU-145, PC-3, LNCaP, PPC-1, and TSU). Three potent compounds have been detected (**43**, **44** and **45)**, which are effective in killing prostate cancer cells with improved selectivity compared to serine amide phosphates (SAPs) (Fig. **9**) [37].

The compound **46** (Fig. **10**) was screened against nine types of human cancer cells and showed significant cytotoxic activity in the case of lung cancer, melanoma and renal cancer, where the reduction in growth was found to be 75%, 97% and 84%, respectively, at the concentration of 1.0 x 10^{-4}M [38].

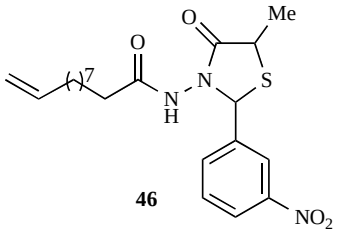


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Fig. (10). Structure of thiazolidinone **46**.

Anticonvulsant Activity

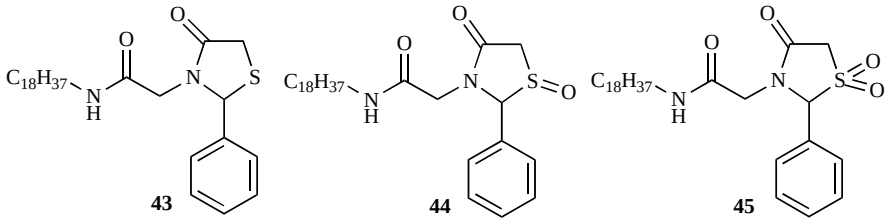
Several 5-[(2-phenyl-4-oxothiazolidin-3-yl)amino]-2-oxo-thiobarbituric acids (**47** and **48**) [39] and 3-({4-[2-alkylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-monosubstituted-quinazolin-4(3*H*)-one (**49**) [40] have been synthesized and screened *in vivo* for their anticonvulsant activity at a dose of 30 mg/kg and an acute toxicity studies.

Considering the results of compounds of those series, it may be concluded that *p*-methoxyphenyl-substituted and *m*-methoxy-*p*-hydroxyphenyl-substituted in thiazolidinone moieties have shown more potent response in comparison to other substituted derivatives. The compounds **47, 48** and **49** were found to be the most potent compounds (Fig. **11**).

Antiinflammatory Activity

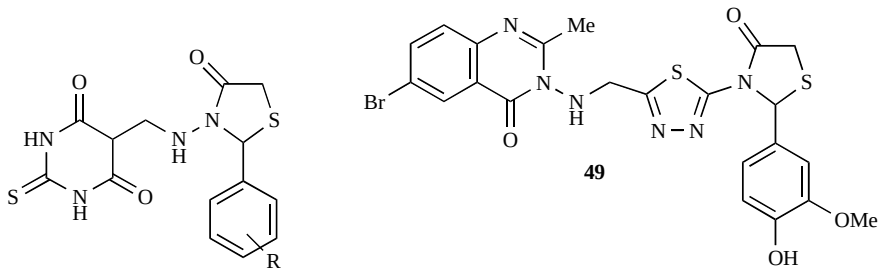
The compound **50** and the phenylbutazone (standard drug) exhibited nearly equipotent activity, however, compound **50** was found to be less ulcerogenic when compared to the standard drug (Fig. **12**) [41]. Bisthiazolidinones were also synthesized and the compound **51** had good antiinflammatory activity and also produce gastric damage lower than the reference drugs (Fig. **12**) [42].

Kumar *et al.* studied the cyclooxygenase activity of thiazolidiones **52** and **53** indicating that these compounds reduce inflammatory response by inhibition of prostaglandins (Fig. **13**) [43]. The compound **53** was found to be the most potent derivative being more active than standard drugs phenylbutazone and indomethacin with COX-II inhibitory action of 90% at 50 mg/kg p.o [44]. The study was also extended to 2-phenyl-3-naftyl-1,3-thiazolidin-4-ones derivatives with good results [45].



43 **44** **45**

Fig. (9). Thiazolidinones as anticancer agents.

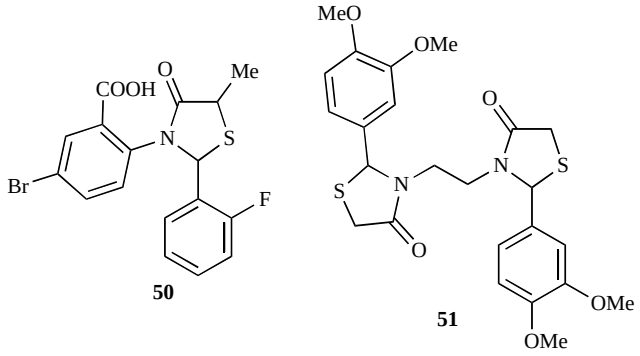


47 - R = *p*-OCH_3
48 - R = *m*-OCH_3, *p*-OH

49

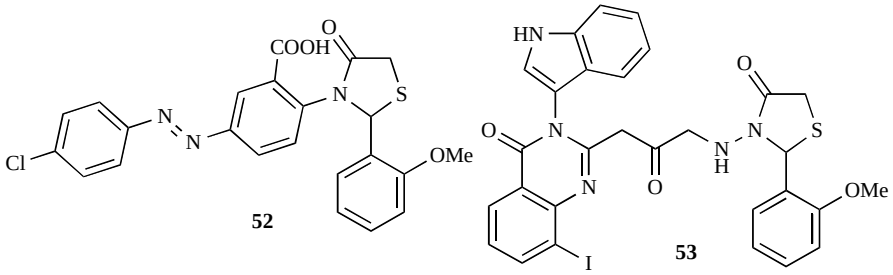
47 - 90% inhibition, acute toxicity > 2000mg/Kg p.o.
48 - 80% inhibition, acute toxicity > 2000mg/Kg p.o.
49 - 80% inhibition, acute toxicity > 1000mg/Kg i.p.

Fig. (11). Thiazolidinones with anticonvulsant activity.



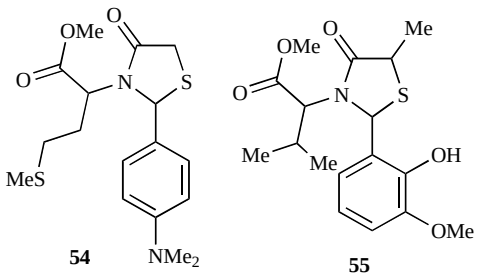
50 **51**

Fig. (12). Thiazolidinones with antiinflammatory activity.



52 **53**

Fig. (13). Structure of thiazolidinones **52** and **53**.



54 **55**

Fig. (14). Structure of thiazolidinones **54** and **55**.

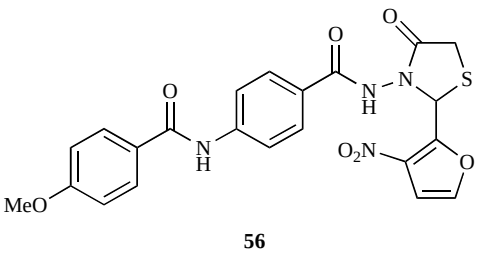
Antitubercular Activity

Babaoglu *et al*. reported the activity of 1,3-thiazolidin-4-ones against *Mycobacterium tuberculosis* by inhibition of dTDP-rhamnose synthesis, an emerging target to combat tuberculosis disease (Fig. **14**) [46]. The authors proposed a hypothesis that the thiazolidinone scaffold can act as a diphosphate mimetic. The compound **54,** the most potent RmlC inhibitor of the library (90% of inhibition at 20 μM), showed no activity versus whole cells (MIC >200 μg/ml). The reason for this is unclear but may be due to poor *M. tuberculosis* cell permeability or inactivation by the cellular enzymes. The 1,3-thiazolidin-4-one **55** showed moderated activity (MIC 25 μg/ml).

Küçükgüzel *et al.* reported that 5-nitrofuryl derivative at C-2 position and {[4-(4-methoxybenzoylamino)benzoyl]amino} derivative at N-3 position (**56**) showed good activity against *M. tuberculosis* (MIC >6.25 μg/ml) (Fig. **15**). This compound also showed good results against several bacteria and fungi tested, especially, *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus pneumoniae*, *S. pyogenes*, *Bacillus* sp and *E. coli* [47].

CONCLUSION

In this work, we review the recently literature data of synthesis and biological activities of thiazolidinones. The ability to join three classes of building block families in synthesis will allow for the generation of significant diversity which should find broad application in drug discovery. Thus, 1,3-thiazolidin-4-one scaffold is not only synthetically important but also possesses a wide range of promising biological activities, including insecticidal activity [48]. Some thiazolidinones have better activity than standard drugs and could become a new drug on the market in the future. Especially, the compound **34**, as antimicrobial agent, the commpound **38**, as antimalarial agent and the compound **50**, as antiinflammatory agent. Future investigations could give some more encouraging results.



56

Fig. (15). Structure of thiazolidinone **56**.

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