Synthesis and Characterization of Some New Derivatives of 5-Arylidene-2,4-thiazolidinediones

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A dissertation submitted to the Department of Chemistry,
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2019

“In The Name of ALLAH

The Most Beneficent the Most Merciful”

The Prophet Muhammad (P.B.U.H) said:

"Someone who sets forth in search of knowledge is busy in

the cause of God until he returns from his quest."

Al-Tirmidhi, Hadith 420.

This dissertation is dedicated to

My loving parents

Declaration

This is to certify that this dissertation entitled **"*Synthesis and Characterization of Some New Derivatives of 5-Arylidene-2,4-thiazolidinediones*"** is the result of my original work and has not been copied from anywhere.

Kalsoom Chohan

Acknowledgement

All praises and glory be to Almighty Allah, the only creator of the whole universe, the most benevolent, who created us as a Muslim and blessed us with knowledge to differentiate between right and wrong. Countless salutations upon the Holy Prophet Hazrat Muhammad (P.B.U.H), the source of knowledge and blessings for entire mankind, who exhorted his Ummah to seek for knowledge from cradle to grave.

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I should not forget to acknowledge my brothers and sisters for their continuous support, understanding and good wishes whenever I needed. I am thankful for their love, prayers, care and sacrifices for educating and preparing me for my future. Words become meaningless when I look at my family as icon of strength for being what I'm today.

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May Allah Almighty gift long life and everlasting happiness to those who helped me in any way during the completion of this work.

(Kalsoom Chohan)

Table of Contents

Index of Tables

Index of Schemes

Index of Figures

STANDARD ABBREVIATIONS AND ACRONYMS

ALR	Aldose reductase
b	broad
bs	broad singlet
d	doublet
COX-2	Cyclooxygenase
DMSO	Dimethyl sulphoxide
EAPs	Electro-active polymers
Et_3N	Triethylamine
HIV	Human immune deficiency virus
MEK	Mitogen-activated protein kinase
PPARγ	Peroxisome poliferator activated receptor
PTP1B	Protein tyrosine phosphatase 1B
PI3K-γ	Phosphoinositide 3-kinase
TBAH	Tetrabutylammonium hydroxide

Abstract

Keeping in view the immense biological and pharmacological importance of 5-arylidene-2,4-thiazolidinediones, some new derivatives were synthesized. Initially, 5-arylidene derivatives of 2,4-thiazolidinedione were synthesized. The syntheses were achieved by the condensation of aromatic aldehydes with 2,4-thiazolidinediones. The 3-substituted 5-arylidene-2,4-thiazolidinediones were in turn synthesized by thiocarbohydrazides and benzohydrazides. The thiocarbohydrazide precursor was prepared from carbon disulfide and hydrazine hydrate, that led to the synthesis of 3-substituted 1,2,4-triazole derivatives of 5-arylidene-2,4-thiazolidinediones. Benzohydrazide precursor was synthesized by the reaction of methyl benzoate with hydrazine hydrate, and converted into 3-substituted 1,3,4-oxadiazole derivatives of 5-arylidene-2,4-thiazolidinediones on treatment with acid hydrazides in presence of dehydrating agents. The structures of newly synthesized compounds were established by using available spectroscopic techniques.

Syntheses were carried out by stepwise method successfully. For the synthesis of 5-arylidene derivatives, various conditions (temperatures, solvents and bases) were applied to increase the yield of products and lower the reaction times.

Chapter- 1

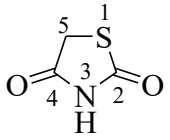
Introduction

Heterocyclic compounds are considered as one of the most imperative classes of organic compounds. Due to their activity in multiple illnesses, heterocyclic compounds are used in many biological fields. These compounds are very important components of pharmaceuticals, electro-active polymers (EAPs), agrochemicals and flavorings, *etc*. Besides, they are abundant in many biologically important natural products (such as vitamins).

Apart from this, substituted five-membered *N*-heterocyclic compounds and their analogues present a broad range of structural diversity. They have been generally used for modulating the immune system (as therapeutic agents), and are very significant structural fragments. Due to the reason, these privileged structures (possessing drug like properties), have been synthesized using various approaches.

1.1 2,4-Thiazolidinediones

2,4-Thiazolidinedione (TZD) is a considerable heterocyclic ring system containing two carbonyl moieties at 2nd and 4th position (sparing behind –NH and methylene) of thiazole ring [1], capable to provide ligands for diverse receptors.



(1)

In different areas of medicinal chemistry, TZDs show a considerable interest due to their enormous pharmacological activities [2] including**:** anti-diabetic [3], anti-inflammatory [4], anti-oxidant [5], anti-tubercular [6], anti-microbial [7], anti-convulsant [8], anti-hyperglycemic [9], anti-cancer [10], anti-arthritic [11], and cytotoxic [12].

2,4-Thiazolidinedione has been considered as a wonder nucleus with a number of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore this skeleton to its multiple potential for several activities.

In view of literature survey, a number of 2,4-thiazolidinedione derivatives have been accounted for by structural variations at -NH and $–CH_2$ positions. This resulted in the development of compounds that are biologically active against a wide range of protein targets, for example, peroxisome poliferator activated receptor (PPARγ), protein tyrosine phosphatase 1B (PTP1B), pimkinase, UDP-*N*-acetylmuramoylalanine, aldose reductase-2 (ALR2), phosphoinositide 3-kinase (PI3K-γ), cyclooxygenase (COX-2), mitogen-activated protein kinase (MEK), and tyrosinases, *etc.* (Figure 1.1) [13]. More importantly, survey articles illustrated the role of TZD core in numerous sickness conditions [14,15], however, our draft is focused on the therapeutic advantages of TZD derivatives.

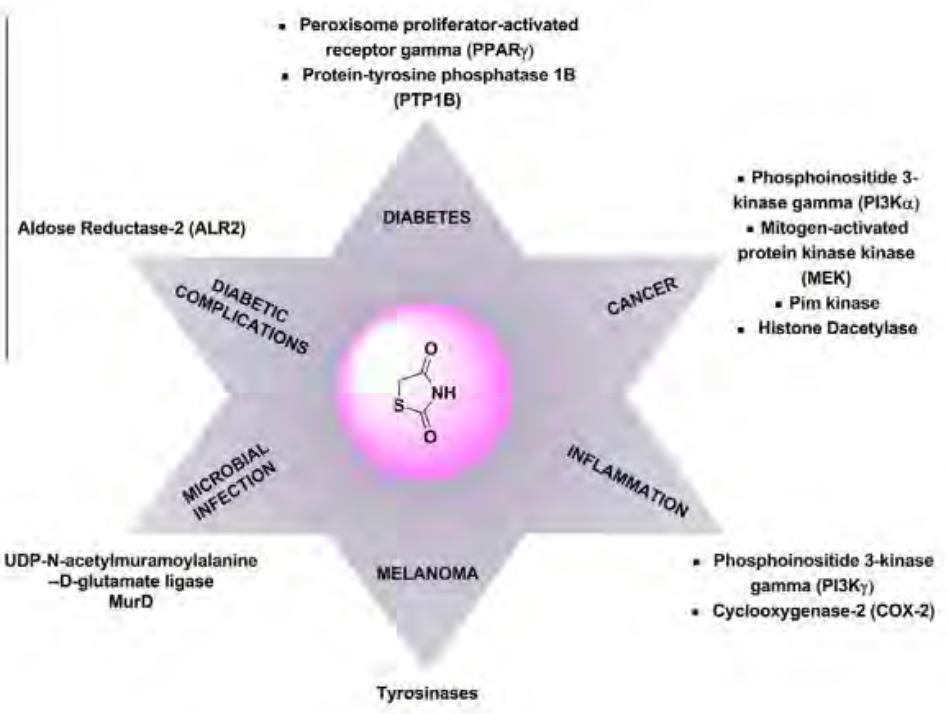


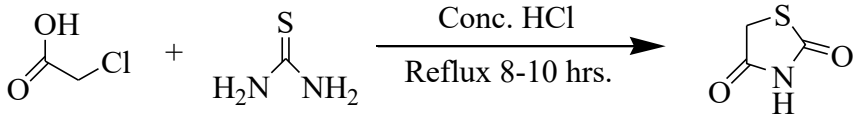
Figure 1.1: Multi-targeted activity of thiazolidine-2,4-diones.

Furthermore, different lines of research are putting resources into the quest for new molecules so as to get progressively particular and less destructive treatment choices for the pathogenesis of atherosclerosis and its hazard factors [16]. Besides, for the investigation of new and profoundly dynamic therapeutic agents, the blend of two pharmacophores into a solitary molecule is an intriguing, viable and generally utilized course in modern medicinal chemistry [17]. At the point for the beneficial treatment of different diseases, it is important that pharmacophores (having distinctive orientations) bind with two different sites on similar molecular target or with different molecular targets at all [18].

1.1.1 Synthetic Strategies for 2,4-Thiazolidinediones

2,4-Thiazolidinediones have been synthesized by various methods.

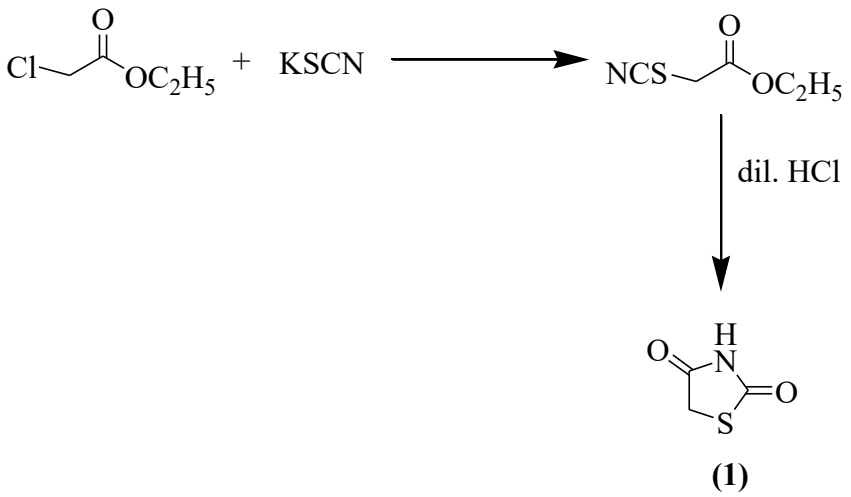
Kekare *et al.* reported the synthesis of 2,4-thiazolidinedione **(1)** by cyclization of chloroacetic acid with thiourea in the presence of concentrated hydrochloric acid [19] (scheme 1.1).



(1)

Scheme 1.1: Synthesis of 2,4-thiazolidinedione from chloroacetic acid and thiourea

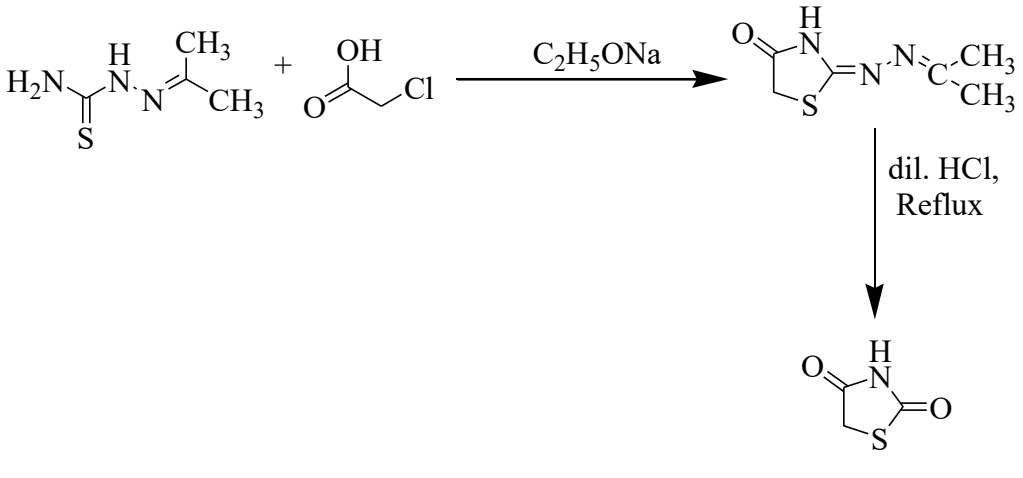
The second protocol to synthesize 2,4-thiazolidinedione nucleus **(1)** involves the reaction of ethyl chloroacetate with potassium thiocyanate to give ethyl 2-thiocyanatoacetate, which is further acidified with dilute hydrochloric acid to obtain the pure product [20] (scheme 1.2).



(1)

Scheme 1.2: Synthesis of thiazolidine-2,4-dione using ethyl chloroacetate and potassium thiocyanate

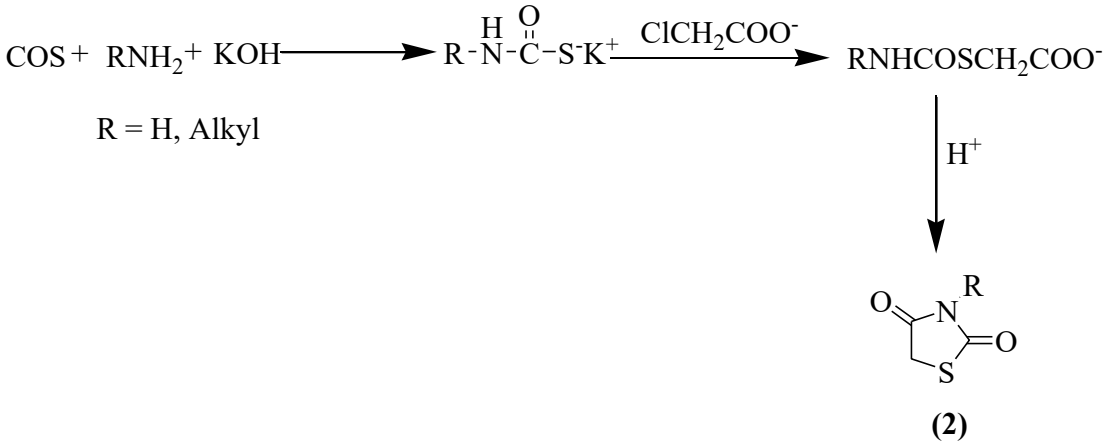
The reaction of thiosemicarbazone with chloroacetic acid in the presence of sodium ethoxide [21] produces 2-hydrazino-4-thiazolidinone, which on reflux in the presence of dil. HCl gives 2,4-thiazolidinedione **(1)** (scheme 1.3).



(1)

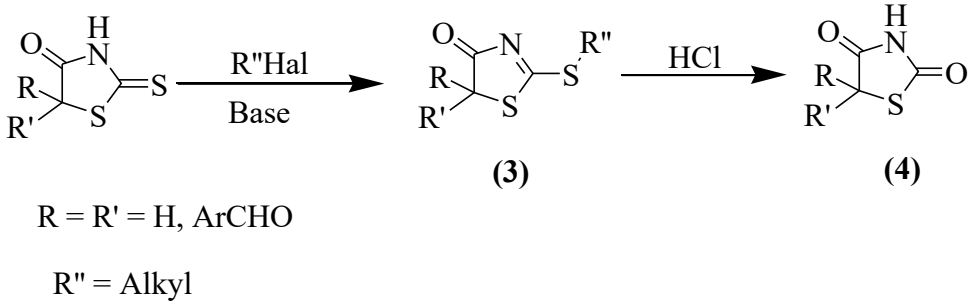
Scheme 1.3: Synthesis of thiazolidine-2,4-dione from thiosemicarbazone and chloroacetic acid

The synthesis of 3-susbstituted 2,4-thiazolidinediones **(2)** has been accomplished by the reaction of ammonia or primary amines with carbon oxysulfide affording ammonium dithiocarbamate, which was made to react with sodium chloroacetate (Scheme 1.4) [22].



Scheme 1.4: Synthesis of 3-alkyl-2,4-thiazolidinediones

Recently, synthesis of 5-substituted 2,4-thiazolidinediones **(4)** was reported by Ginak *et al*. [23] by successful dethionation of corresponding rhodanine derivatives. 5-Substituted rhodanine and its non-substituted derivatives on reaction with alkyl halides in the presence of different bases (KOH, Et_3N, NaOH, K_2CO_3) yielded 2-alkylrhodanines **(3)**, which are hydrolyzed to corresponding 5-substituted 2,4-thiazolidinones **(4)** (scheme 1.5).

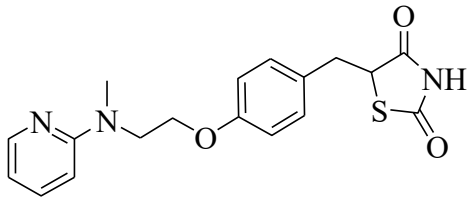


Scheme 1.5: Synthesis of 5-substituted 2,4-thiazolidinediones

1.1.2 Applications of 2,4-Thiazolidinediones

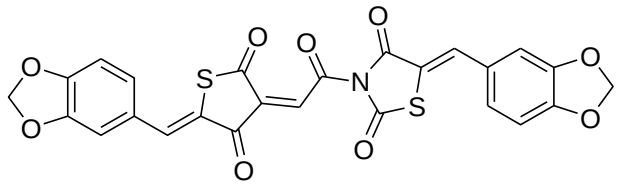
2,4-Thiazolidinedione is present in numerous classes of biologically dynamic compounds. Moreover, synthesis of novel compounds with less side effects and further developed profile than accessible drug molecules are the major focus of consideration for chemists and pharmacologists.

Most promising activity of thiazolidinedione nucleus is anti-diabetic activity. Studies in animal models of Type-2 diabetes have shown that thiazolidinediones prevent deterioration in islet morphology, preserve pancreatic content and β-cell ultrastructure [24]. Juhl *et al*. recently reported that in type-2 diabetic patients, rosiglitazone **(4)** enhances β-cell reaction to glucose, recommending a defensive job for the TZD nucleus on β-cells [25]. Furthermore, treatment with rosiglitazone at early stages of disease can postpone progress to hyperglycemia [24, 26].



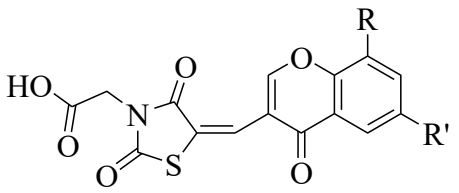
(4)

Novel *(Z)*-5-(benzo[d]dioxo-5-ylmethylene)-3-((*Z*)-2-((*Z*)-5-(benzo[d][1,3]dioxo-5-ylmethylene)-2,4-dioxo-dihydrothiophen-3(2*H*)-ylidene)acetyl)thiazolidine-2,4-dione **(6)** displayed anti-diabetic and anti-hyperlipidemic activity in *in vivo* (using alloxan animal model) [27] as reported by Ahmed *et al*.



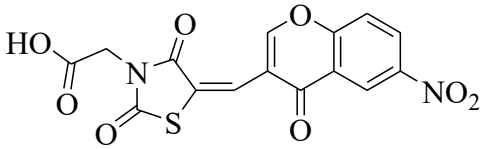
(6)

Bozdağ-Dündar *et al.* synthesized [28] a series of chromonyl-2,4-thiazolidinediones **(7)** in order to reduce complications associated with diabetic disorders particularly having impact on the cataract formation. *In vitro* assay of all synthesized compounds was carried out to check their ability to repress rat kidney aldose reductase. Out of all tested compounds, only compound **8** demonstrated astounding inhibitory activity. They concluded that presence of acetic acid side chain on 2,4-thiazolidinedione may be responsible for the increasing inhibitory effect of compound **7**.



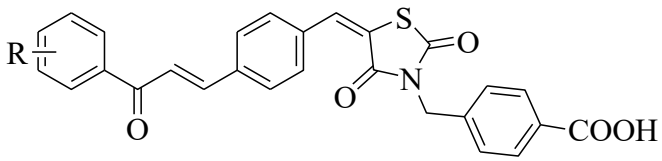
R = H, CH_3, $(CH_3)_2CH$, NO_2
R' = H, CH_3

(7)



(8)

With an intension to synergize the anti-bacterial activity of chalcones and 4-[(2,4-dioxothiazolidin-3-yl)methyl]benzoic acid, several compounds **(9)** possessing these moieties were synthesized as reported by Liu *et al*. [29].



R = H, 2-Cl, 2-Br, 2-OCH_3, 2-OH

(9)

By focusing on the fundamental causes — insulin obstruction and β-cell work — these agents may give a sensible way to deal with treatment and are probably going to have a noticeable job in future diabetes management. However, treatment of type-2 diabetes is moving towards a new era with the presentation of the 2,4-thiazolidinedione class, which likewise offers the opportunity for intervention at the pre-diabetic stage.

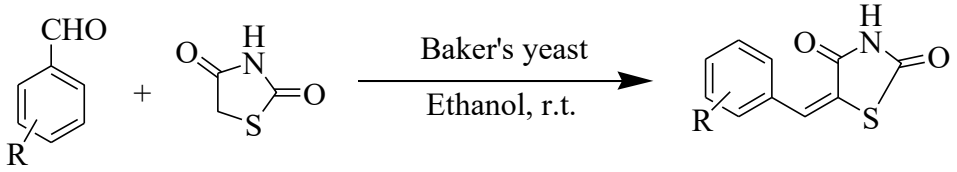
1.2 5-Arylidene-2,4-thiazolidinediones

The 5-arylidene-2,4-thiazolidinediones are significant structural components in medicinal chemistry. 5-Arylidene derivatives of 2,4-thiazolidinedione show anti-inflammatory [30], anti-hypertensive [31], hypoglycemic [32], tyrosine phosphate inhibition [33], aldose reductase inhibition [34], and anti-cancer [35] activities.

1.2.1 Synthetic Strategies for 5-Arylidene-2,4-thiazolidinediones

Derivatization of 2,4-thiazolidinediones has been acquired by introducing substituents at free –NH and $–CH_2$ group of the ring, hence 3-substituted, 5-substituted or 3,5-disubstituted 2,4-thiazolidinediones are possible.

5-Arylidene derivatives may be synthesized via "Knoevenagel condensation", involving the reaction of methylene moiety of 2,4-thiazolidinedione ring with aldehydes or ketones [36]. The Knoevenagel condensation is a fundamental C-C bond forming reaction having great significance in organic synthesis [37]. The Knoevenagel condensation reactions are characteristically catalyzed by base in liquid-phase systems. In view of the literature survey, numerous catalysts have been used in this condensation to impact the response with various aldehydes and the active methylene group. In the wake of having these outcomes, Jones *et al*. synthesized a series of 5-arylidene-2,4-thiazolidinediones by the reaction of 2,4-thiazolidinediones with a number of aryl aldehydes **(10a-l)** [37]. Reaction was carried out at room temperature with the help of Baker's yeast catalyst, which enhance the synthesis of 5-arylidene-2,4-thiazolidinediones **(11a-l)** using ethanol as solvent (scheme 1.6).



(10a-l) **(1)** **(11a-l)**

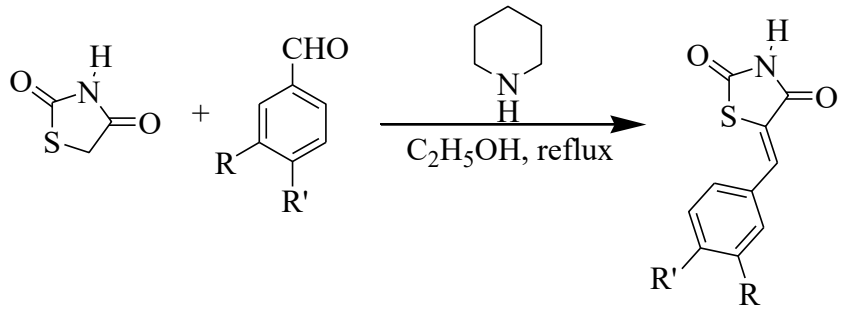
4a: R = H **4b:** R = 3-Cl **4c:** R = 4-Br **4d:** R = 4-Cl

4e: R = 2-OH **4f:** R = 4-OH **4g:** R = 2-Cl **4h:** R = 3,4-diOCH_3

4i: R = 4-F **4j:** R = 2,4-diCl **4k:** R = 4-CH_3 **4l:** R = 4-OCH_3

Scheme 1.6: Knoevenagel condensation of aryl aldehydes with 2,4-thiazolidinedione using Baker's yeast catalyst

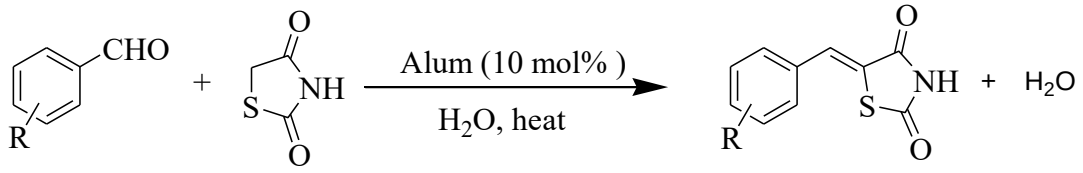
Maccari *et al.* [38] synthesized 5-arylidene-2,4-thiazolidinediones **(12a** and **12b)** by Knoevenagel condensation using commercially available 2,4-thiazolidinedione and appropriate aldehydes using piperidine as base (scheme 1.7).



12a: R = OCH_3, R' = OH **(12a-b)**
12b: R = OH, R' = OCH_3

Scheme 1.7: Knoevenagel condensation of 2,4-thiazolidinedione with aldehydes using piperidine as a base

In another approach, alum [$KAl(SO_4)_2 \cdot 12H_2O$] was used in Knoevenagel condensation as a catalyst for the preparation of 5-aryldene-2,4-thiazolidinediones (scheme 1.8) due to its effectiveness in promoting the reaction. Synthesis can be accomplished by reaction of 2,4-thiazolidinediones with an appropriate aldehyde **(13)** followed by the addition of 10 mol % alum in the presence of water as solvent to afford 5-arylidene-2,4-thiazolidenediones **(14)** in good to excellent yields [39-42] (scheme 1.8).

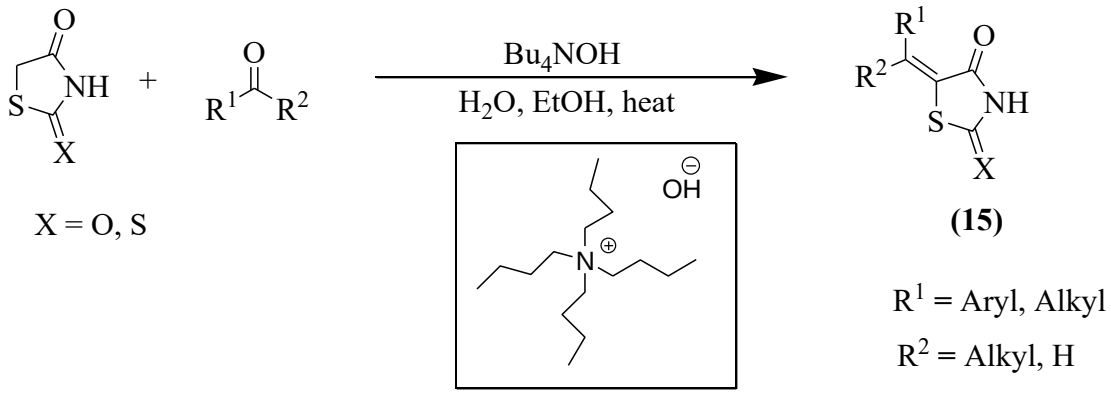


(13a-k) **(1)** **(14a-k)**

14a: R = 3-NO_2 **14b:** R = 4-Cl **14c:** R = 2,4-diCl **14d:** R = 4-OH
14e: R = 2-OH **14f:** R = 4-OMe **14g:** R = 4-CF_3 **14h: R =** 3-OMe
14i: R = 4-OH **14j:** R = 4-NMe_2 **14k:** R = 3,4-diOH

Scheme 1.8: Synthesis of 5-arylidene-2,4-thiazolidinediones using alum as a catalyst

Veisi *et al.* studied another competent synthesis of 5-arylidene-2,4-thiazolidinedione derivatives following the Knoevenagel condensation by the reaction of 2,4-thiazolidinedione with appropriate aromatic aldehydes. Tetrabutylammonium hydroxide/H $_2$O-EtOH [43] was used as a proficient and recyclable catalyst to give the desired product **(15)** in good yield at 50^o C (scheme 1.9).

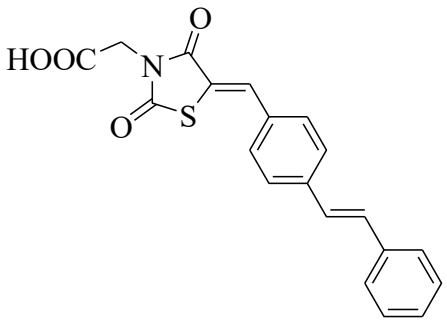


Scheme 1.9: Synthesis of 5-arylidene-2,4-thiazolidinediones using TBAH catalyst

1.2.2 Applications of 5-Arylidene-2,4-thiazolidinediones

5-Arylidene-2,4-thiazolidinediones display a large number of biological activities, hence the 5-substituted derivatives of 2,4-thiazolidinediones are the compounds of current interest.

Ottanà *et al*. reported [44] 5-arylidene-2,4-thiazolidinediones as novel anti-oxidant agents and aldose reductase inhibitors. It was concluded that compounds **(16** and **17)** were best anti-cancer agents and displayed high inhibitory effect against chain-breaking antioxidant α-tocopherol [45], that was used as the reference standard enzymes. It was further reported that these agents balanced the oxidative pressure related to both, diabetic entanglements as well as other pathologies.



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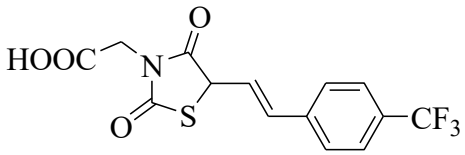
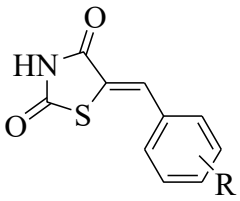
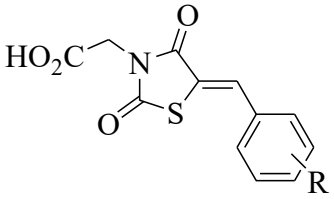


(17)

Rakowitz *et al.* [46] synthesized 5-aryl-2,4-thiazolidinediones **(18a-f** and **19a-f)** and reported the biological evaluation as aldose reductase inhibitors (ARIs). According to this evaluation, *N*-unsubstituted 5-aryl-2,4-thiazolidinediones **(18a-f)** and (5-aryl-2,4-dioxothiazolidin-3-yl)acetic acids **(19a-f)** exhibited moderate-to-high inhibitory action levels. In compound **18a-f**, the occurrence of an additional aromatic ring on the 5-benzyl moiety was found advantageous. Furthermore, substitution at –NH position by the acidic chain essentially upgraded AR inhibitory power, prompting acids **(19a-f)** which were found the best among the tested compounds.



(18a-f)

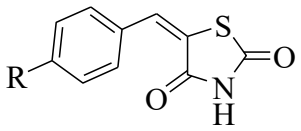


(19a-f)

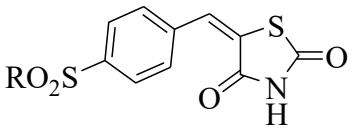
18a: R = 3-OC_6H_5
18b: R = 4-OC_6H_5
18c: R = 4-OH
18d: R = 4-$OCH_2C_6H_5$
18e: R = 3-OCH_3
18f: R = 4-OCH_3

19a: R = 3-OC_6H_5
19b: R = 4-OC_6H_5
19c: R = 4-OH
19d: R = 4-$OCH_2C_6H_5$
19e: R = 3-OCH_3
19f: R = 4-OCH_3

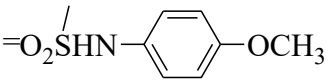
Some Novel derivatives of 5-[4-(substituted)benzylidene]-2,4-thiazolidinediones **(20a-b** and **21a-b)** were reported by Roy *et al*. as oral anti-hyperglycemic agents [47].

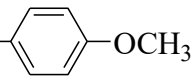


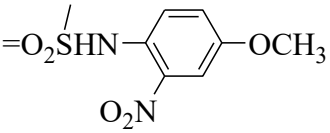
(20a-b)

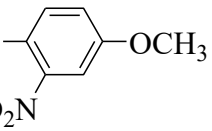


(21a-b)

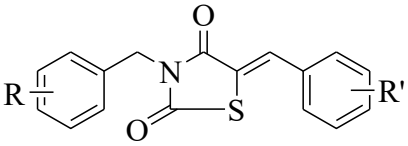
20a: R = 

21a: R = 

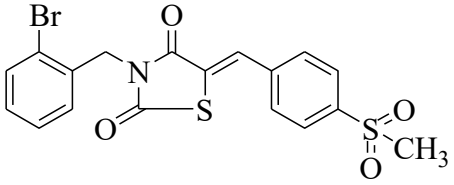
20b: R = 

21b: R = 

Barros *et al*. reported [48] anti-inflammatory activities of 5-arylidene-3-benzyl-thiazolidine-2,4-diones bearing different halo substituted benzyl rings **(22)** and 3-(2-bromobenzyl)-5-(4-methanesulfonylbenzylidene)-thiazolidine-2,4-dione **(23)**. The compound **23** displayed an anti-inflammatory activity of 73.3 %, which was slightly higher than the standard drug rosiglitazone (72.0 %).



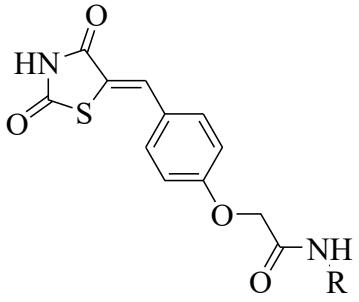
(22)



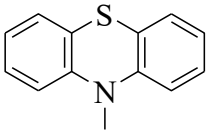
(23)

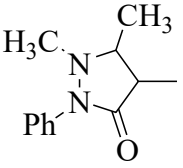
R = 3-Cl, 2-Br, 2-Cl, 6-F
R' = 5-Br, 2-OCH_3, 4-SO_2CH_3, 4-C_6H_5,
4-OCH_3, 3-Br, 2-F, 2,4-diCl

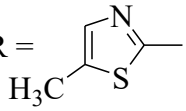
Ten derivatives of 5-benzylidene-2,4-thiazolidinediones **(24a-j)** have been synthesized and evaluated by Patil *et al*. [49] for their anti-proliferative activities in seven cancer cell lines. These compounds displayed varying degrees of cytotoxicity in the veteran cell lines. Most noticeable effect was observed in nasopharyngeal cancer cell lines, MCF7 (breast cancer cell lines) and K562 (leukemia cancer cell lines).

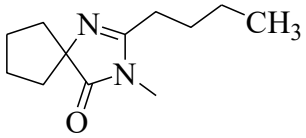


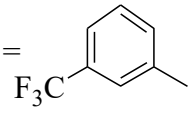
(24a-j)

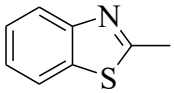
24a: R = 

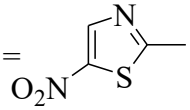
24b: R = 

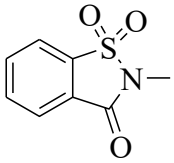
24c: R = 

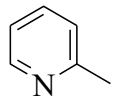
24d: R = 

24e: R = 

24f: R = 

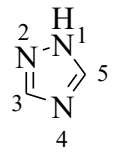
24g: R = 

24h: R = 

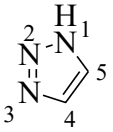
24i: R = 

1.3 1,2,4-Triazoles

Triazoles (also called pyrrodiazoles), constitute one of the significant classes of heterocyclic compounds consisting of a five-membered diunsaturated ring made up of two carbon and three nitrogen atoms. Over the most recent couple of decades, triazoles have been examined widely for their biological activities. Triazole core exists in two isomeric structures: 1,2,3-triazole and 1,2,4-triazole.



1,2,4-Triazole



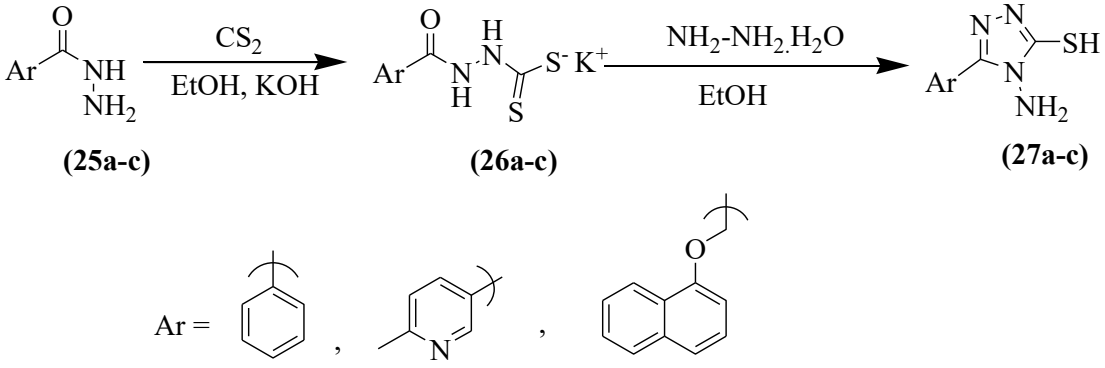
1,2,3-Triazole

1,2,4-Triazoles have wide scope of pharmacological activities and this assorted variety in the pharmacological activities has attracted the attention of many researchers to explore triazole structure for its wide potential. 1,2,4-Triazole derivatives procure an incredible significance in the field of medicinal chemistry due to their unique structure. 1,2,4-Triazole and its derivatives show a broad spectrum of biological activities including**:** anti-bacterial [50-52], anti-oxidant [53], anti-fungal [54], anti-convulsant [55,56], anti-inflammatory [57,58], anti-cancer [59-62], anti-viral [63,64], anti-tubercular [65-67], anti-corrosive [68], hypoglycemic [69], analgesic [70], and anti-HIV [71].

1.3.1 Synthetic Strategies for 1,2,4-Triazoles

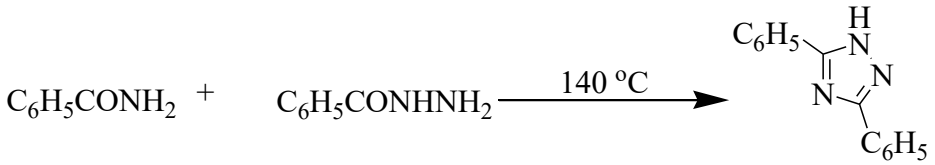
Triazole scaffold has an inherent tendency for the treatment of many challenging diseases. Therefore, there are numerous synthetic strategies available for the synthesis of 1,2,4-triazole derivatives. Some important methods are being presented here:

4-Amino-3-aryl-1,2,4-triazole-5-thiols **(27a-c)** have been synthesized from aryl acid hydrazides **(25a-c)** following a multi-step synthetic strategy [72, 73] (scheme 1.10), in which acid hydrazides react with carbon disulphide and potassium hydroxide in absolute EtOH to give potassium salts **(26a-c)**. These salts, in the presence of hydrazine hydrate, undergo ring closure to afford corresponding triazoles **(27a-c)**.



Scheme 1.10: Synthetic route for 4-amino-3-aryl-1,2,4-triazole-5-thiols

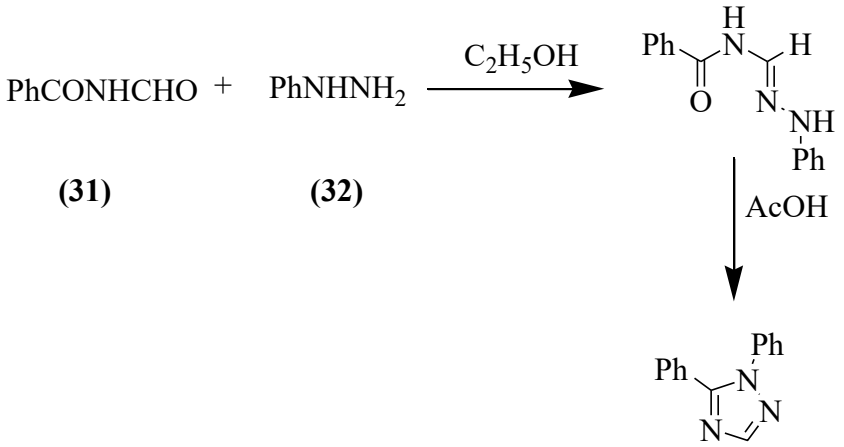
A well known method for the synthesis of 1,2,4-triazole derivatives is "Pellizzari Reaction" involving the coupling of amide and acyl hydrazide to give 1,2,4-triazole derivatives. Al-Khuzaie *et al*. [74] reported the synthesis of 3,5-diphenyl-1,2,4-triazole **(30)** by the reaction of benzamide **(29)** with benzoyl hydrazide **(28)** at 140° C (scheme 1.11).



(28) **(29)** **(30)**

Scheme 1.11: Synthesis of 1,2,4-triazole derivative by Pellizzari Reaction

Hanif *et al.* [75] synthesized 1,2,4-triazole derivatives by a known reaction called "Einhorn-Burnor Reaction". In this method mono-substituted hydrazines and diacylamines reacts in the presence of weak acid to give 1,2,4-triazole by elimination of a water molecule, *e.g.*, *N*-formyl benzamide **(31)** and phenyl hydrazine **(32)** gave 1,5-diphenyl-1,2,4-triazole **(33)** (scheme 1.12).

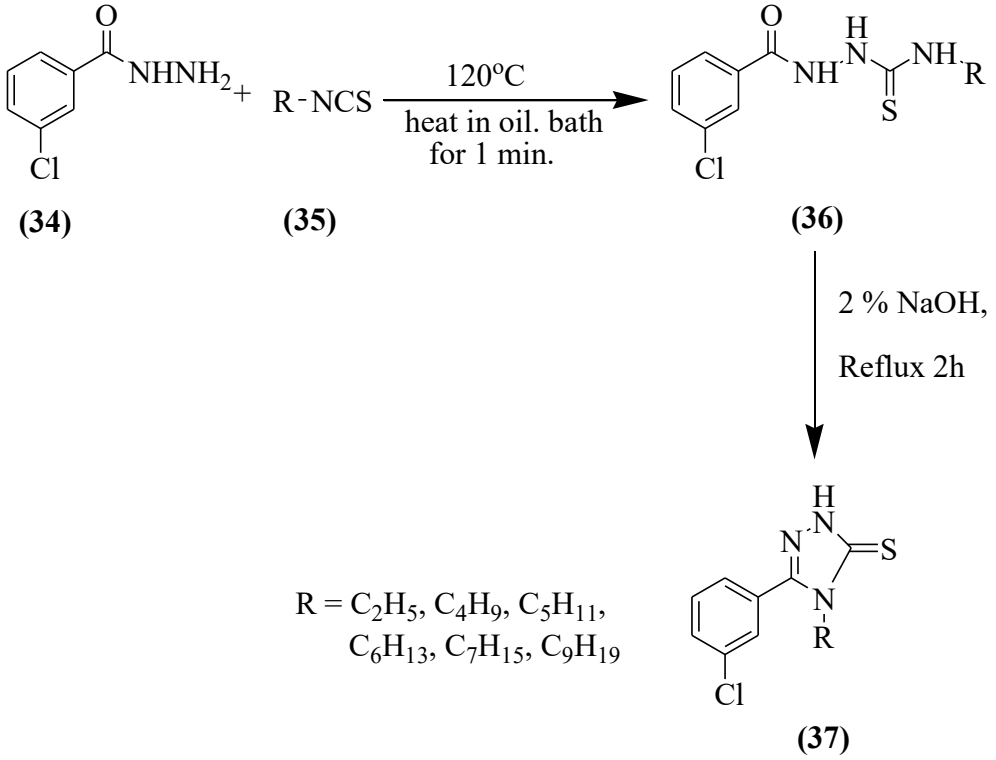


(31) **(32)** **(33)**

Scheme 1.12: Synthesis of 1,2,4-triazole derivatives by Einhorn-Burnor reaction

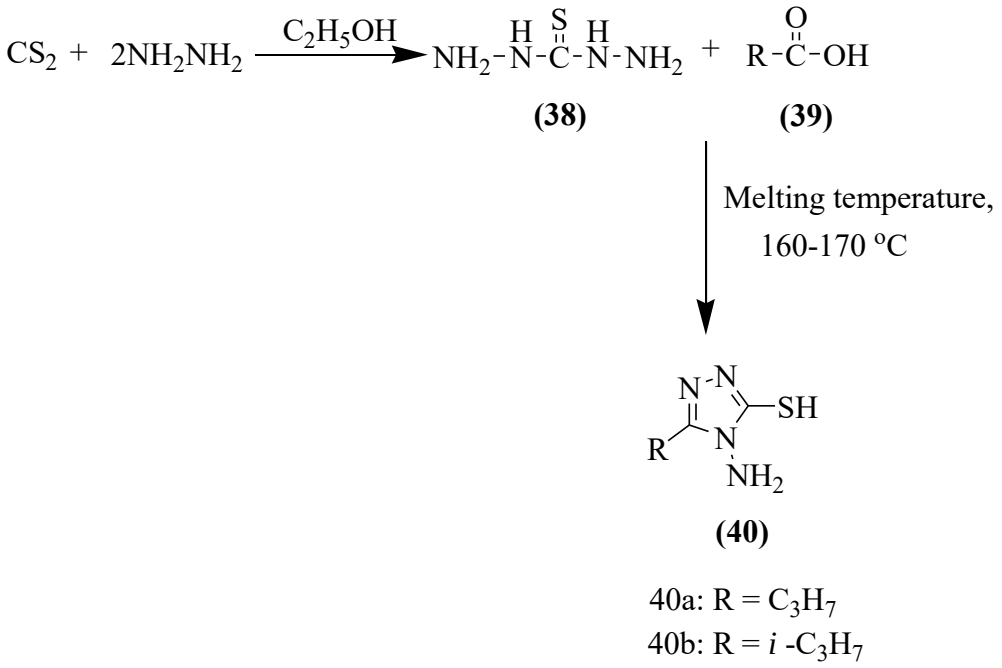
Another successful synthesis of 1,2,4-triazole derivatives has been accomplished by Jain and co-workers [76]. The method reports the heating of an equimolar mixture of

3-chlorobenzhydrazide **(34)** and alkyl isothiocyanate **(35)** at 120°C for 1 minute to get 4-alkyl-1-(3-chlorobenzoyl)thiosemicarbazides **(36)**. This intermediate was then dissolved in 2% NaOH followed by 2 hours of reflux. After cooling to room temperature, the reaction mixture was neutralized with 3M HCl to afford the successful precipitation of the target compound **(37)** (scheme 1.13).



Scheme 1.13: Synthesis of 1,2,4-triazole derivatives using 3-chlorobenzhydrazide and alkyl isothiocyanates

The synthesis of 3-substituted 4-amino-1,2,4-triazole-5-thiols **(40a-b)** has been accomplished by the reaction of hydrazine hydrate with carbon disulfide affording thiocarbohydrazide **(38)** [77]. The product was made to react with substituted carboxylic acids **(39a-b)** followed by fusion reaction [78] to give 3-alkyl-2,4-thiazolidinediones (scheme 1.14).

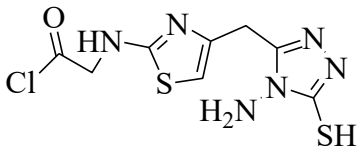


Scheme 1.14: Synthesis of 3-substituted-4-amino-1,2,4-triazole-5-thiols

1.3.2 Applications of Triazoles

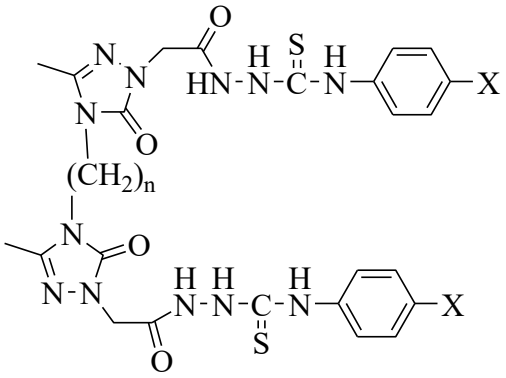
According to the literature survey, heterocyclic frameworks consisting of 1,2,4-triazole nucleus have a broad spectrum of pharmacological applications [79]. The triazole scaffold is tremendously versatile and has been included in various clinically utilized medications, highlighting the significance of this core.

Novel thiazolyl triazole derivative **(41)** has been reported by Shiradkar *et al*. [80] and evaluated for anti-microbial and anti-mycobacterial activity. The purpose of this synthesis was to develop a new molecule with enhanced potency for treating mycobacterium tuberculosis infections.



(41)

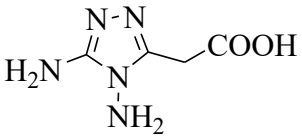
Düğdü *et al.* synthesized 1,2,4-triazole-possessing thiosemicarbazides **(42a-c)** as potent anti-fungal and anti-bacterial agents [81]. According to the report, thiosemicarbazide groups present in the triazole compounds are important pharmacophores for the formation of lead compounds.



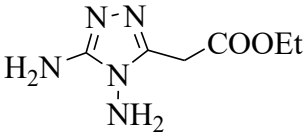
(42a-c)

42a: X = F
42b: X = Br
42c: X = CH_3

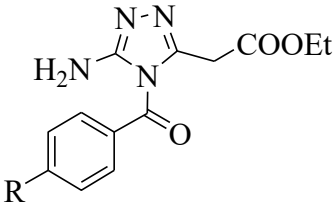
Kasahara *et al.* synthesized and evaluated anti-inflammatory [82] activities of 1,2,4-triazole-3-acetic acid derivatives **(43-46)** against carrageenan-induced rat paw edema.



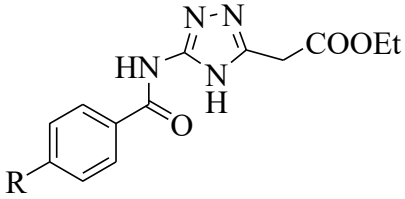
(43)



(44)



(45a-e)

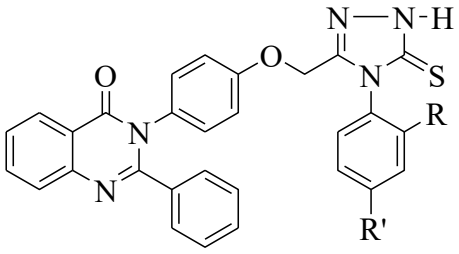


(46a-e)

45a: R = H
45b: R = Cl
45c: R = Br
45d: R = OCH_3
45e: R = NO_2

46a: R = H
46b: R = Cl
46c: R = Br
46d: R = OCH_3
46e: R = NO_2

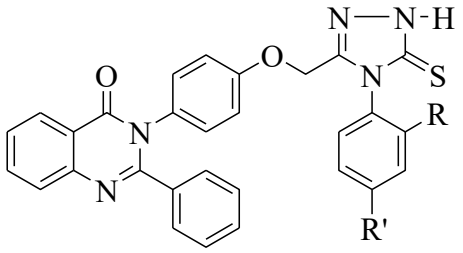
A series of novel 3-[4-(substituted phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazole-3-ylmethoxy)phenyl]-2-phenyl-3*H*-quinazoline-4-ones **(47a-c)** was synthesized and evaluated for anti-fungal activity by Havaldar *et al*. The compound 3-[4-{nitrophenyl-5-thioxo-4,5-dihydro-1*H*-(1,2,4)triazole-3-ylmethoxy}phenyl]-2-phenyl-3*H*-quinazolin-4-one **(47c)** displayed potent activity against aspergillus niger [83].



(47a-c)

47a: R = H, R' = H
47b: R = H, R' = F
47c: R = H, R' = NO_2

The compound 3-[4-{nitrophenyl-5-thioxo-4,5-dihydro-1*H*-(1,2,4)triazole-3-ylmethoxy}phenyl]-2-phenyl-3*H*-quinazolin-4-one **(47c)** displayed potent activity against aspergillus niger [83].

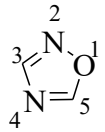


(47a-c)

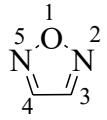
47a: R = H, R' = H
47b: R = H, R' = F
47c: R = H, R' = NO_2

1.4 1,3,4-Oxadiazoles

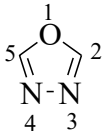
Oxadiazole is a five-membered heterocyclic ring comprising of one oxygen and two nitrogen atoms besides two carbon atoms. It is derived by the substitution of two methylene groups (=CH) of furan with two pyridine type nitrogens (-N=) [84]. Depending on the position of these two nitrogen atoms, oxadiazoles exhibit four possible isomeric forms. Out of these four isomers, three stable isomers include**:**1,2,4-oxadiazole **(48)**, 1,2,5-oxadiazole **(49)**, and 1,3,4-oxadiazole **(50)**, however the fourth isomer, 1,2,3-oxadiazole **(51)**, is unstable and returns to the diazoketone tautomer.



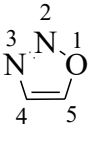
1,2,4-oxadiazole **(48)**



1,2,5-oxadiazole **(49)**



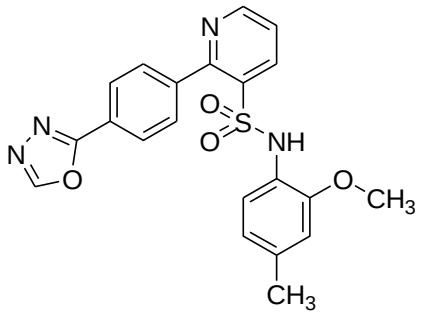
1,3,4-oxadiazole **(50)**



1,2,3-oxadiazole **(51)**

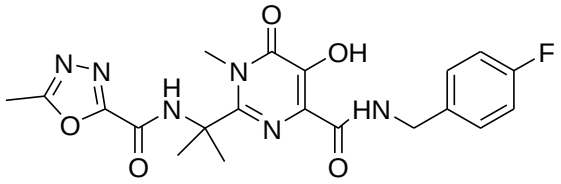
1,3,4-Oxadiazole derivatives have a wide-ranging spectrum of pharmacological activities including**:** anti-diabetic, anti-bacterial, anti-cancer, anti-fungal, anti-inflammatory, analgesic, anti-viral, anti-convulsant, anti-hypertensive and ulcerogenic [85].

Among different heterocyclic compounds, 1,3,4-oxadiazole has turned into a significantly developed motif for the preparation of novel drugs. Some currently used drugs containing 1,3,4-oxadiazole moiety are zibotentan **(52)**, which acts as an anti-cancer agent [86] andraltegravir **(53)**, an anti-retroviral drug [87].



Zibotentan

(52)



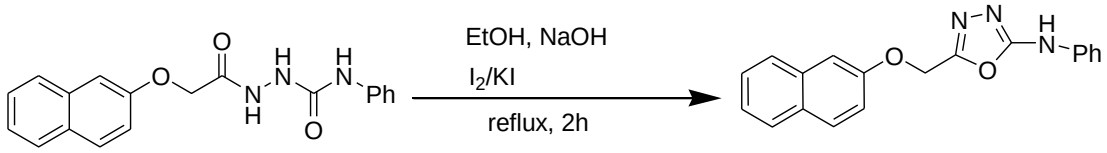
Raltegravir

(53)

1.4.1 Synthetic Strategies for 1,3,4-Oxadiazoles

The privileged structure of 1,3,4-oxadiazoles has made them vital for designing bio-active molecules because of their vast biological potential. Therefore, many synthetic approaches have been reported for 1,3,4-oxadizole compounds.

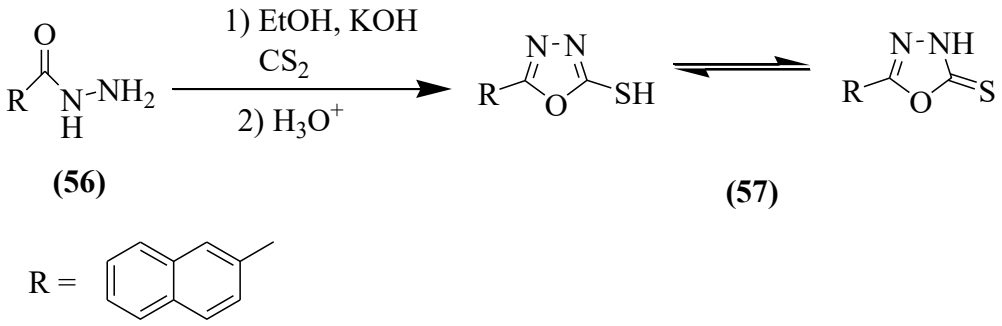
Recently, El-Sayed and co-workers [88] synthesized 5-[(naphthalen-2-yloxy)methyl]-*N*-phenyl-1,3,4-oxadiazol-2-amine (**55**) by heating 1-[2-(naphthalene-2-yloxy)acetyl]-4-phenylsemicarbazide **(54)** in ethanol in the presence of NaOH using iodine as an oxidizing agent (scheme 1.15).



(54) **(55)**

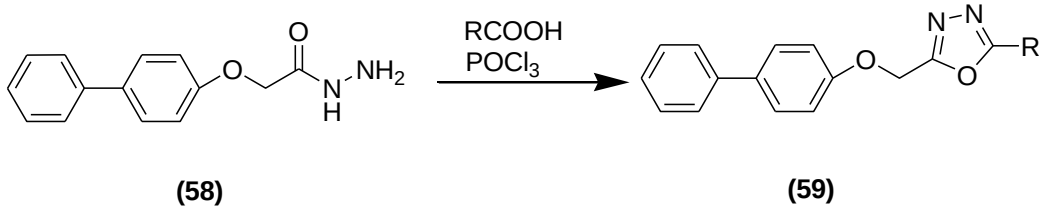
Scheme 1.15: Synthesis of 1,3,4-oxadiazol-2-amines from cyclization reaction of acyl thiosemicarbazides in presence of iodine

A useful method for preparing certain 5-substituted 1,3,4-oxadiazole-2-thiol(thione)s **(57)** involves the reaction of an acyl hydrazide **(56)** with carbon disulfide in a basic alcoholic solution, followed by acidification of the reaction mixture. Compound **(57)** exhibits thiol-thione tautomerism in which one of the structures generally prevails [89] (scheme 1.16).



Scheme 1.16: Synthesis of 5-substituted 1,3,4-oxadiazole-2-thiol(thione)s

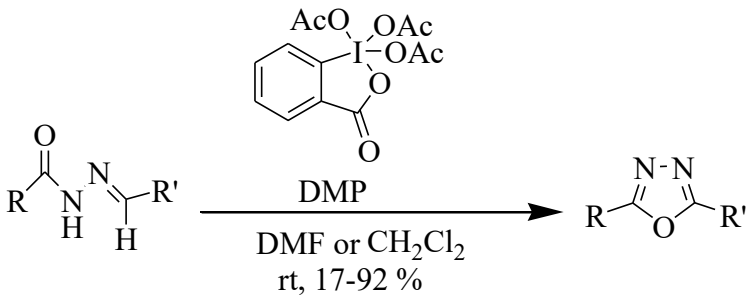
The reaction of 2-(biphen-4-yloxy)acetic acid hydrazide **(58)** with a suitable aromatic acid in the presence of phosphorus oxychloride affords 5-[(biphen-4-yloxy)-methyl]-2-substituted- 1,3,4-oxadiazoles **(59a-h)** as reported by Kumar *et. al.*[90] (scheme 1.17).



59a: R = C_6H_5
59b: R = 4-FC6H4
59c: R = 2-ClC_6H_4
59d: R = 4-ClC_6H_4
59e: R = 4-BrC_6H_4
59f: R = 2,4-diClC_6H_3
59g: R = 2,4-di$CH_3C_6H_3$
59h: R = n-butyl

Scheme 1.17: Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles

Dobrotã *et al.* [91] synthesized 2,5-disubstituted 1,3,4-oxadiazoles **(61)** by oxidative cyclization of *N*-acyl hydrazones **(60)** through utilization of an excess of Dess-Martin periodinane under mild reaction conditions (scheme 1.18).



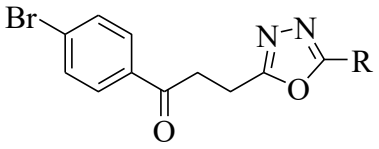
(60) **(61)**

61a: R = Ph, R' = Ph
61b: R = 4-ClC_6H_4, R' = 4-BrC_6H_4
61c: R = 4-$NO_2C_6H_4$, R' = 4-BrC_6H_4
61d: R = 2-furyl, R' = 2-furyl
61e: R = 4-pyridyl, R' = 4-pyridy

Scheme 1.18: Oxidative cyclization of *N*-acyl hydrazones using Dess-Martin periodinane

1.4.2 Applications of 1,3,4-Oxadiazoles

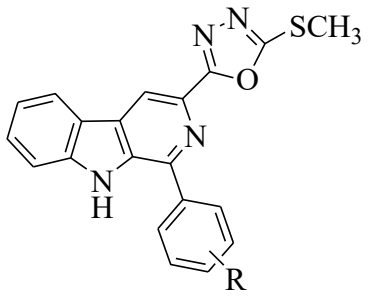
1,3,4-Oxadiazole scaffold due to its privileged structure, is present in many classes of biologically active compounds. Husain *et al*. explored a novel progressive series of 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles **(62a-k)** with the purpose to get better analgesic and anti-inflammatory activities with minimum or without side effects [92].



(62a-k)

62a: R = C_6H
62b: R = 2-ClC_6H_4
62c: R = 4-ClC_6H_4
62d: R = 2-OHC_6H_4
62e: R = 4-$NO_2C_6H_4$
62f: R = 4-FC_6H_4
62g: R = 4-$CH_3C_6H_4$
62h: R = 4-$OCH_3C_6H_4$
62i: R = 3,4-di$OCH_3C_6H_3$
62j: R = -$CH_2C_6H_5$
62k: R = -CH_2-O-C_6H_5

Anti-tumor properties of 1,3,4-oxadiazoles have also been displayed by their (2-substituted 1,3,4-oxadiazole-5-yl)β-carboline derivatives. Formagio *et al.* [93] reported the synthesis and anti-tumor properties of novel 2-substituted 1,3,4-oxadiazole-5-yl bearing β-carboline derivatives **(62a-h)**. Biological evaluation was carried out against eight human tumor cell lines *i.e.,* leukemia cancer cell line, melanoma cancer cell line, breast cancer cell line, prostate cancer cell line, lung cancer cell line, ovarian cancer cell line, colon and renal cancer cell lines.



(63a-h)

63a: R = H
63b: R = 4-OCH_3
63c: R = 4-OH
63d: R = 3-NO_2
63e: R = 4-NO_2
63f: R = 3-OCH_3
63g: R = 4-$N(CH_3)_2$
63h: R = 4-Cl

Anti-HIV activity of 1,3,4-oxadiazole derivatives was reported by Iqbal *et al.* [94]. Biological evaluation for compounds **63a-c** and **64a-c** was done against the human immunodeficiency virus HIV-1 using the cell proliferation assay (XTT) on MT-4 cells. The results showed that compound **64c** was the most active among all evaluated compounds. Compounds **63a-c** displayed non-significant anti-viral activity.

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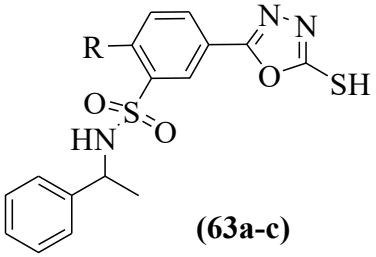
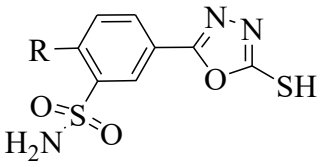


(63a-c)

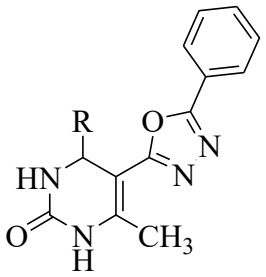


(64a-c)

63a: R = H
63b: R = OCH_3
63c: R = Cl

64a: R = H
64b: R = OCH_3
64c: R = Cl

Two 1,3,4-oxadiazole derivatives **(65a** and **65b)** were synthesized by Mishra *et al.* and reported their anti-microbial activities. The synthesized compounds were evaluated in comparison with standard drugs, levofloxacin and ofloxacin [95]. Compound **65a** was most active in this series and displayed most potent broad spectrum anti-bacterial activity against Gram-positive bacteria (*i.e., Streptococcus pneumonia*) and compound **65b** showed high anti-bacterial activity against Gram-negative bacteria, *i.e., Escherichia coli,* as compared to the standard drugs



(65a-b)

65a: R = 4-$OCH_3C_6H_5$
65b: R = 4-$NO_2C_6H_5$

Due to various possibilities of chemical derivatization of 2,4-thiazolidinedione ring, 2,4-thiazolidinedione-based compounds will probably remain a privileged scaffold in drug discovery. To explore the enhancement in biological activities as well as to discover new pharmacological activities, synthesis of some new 3,5-disubstituted 2,4-thiazolidinedione, a promising template for drug discovery, is desirable.

1.5 Plan of Work

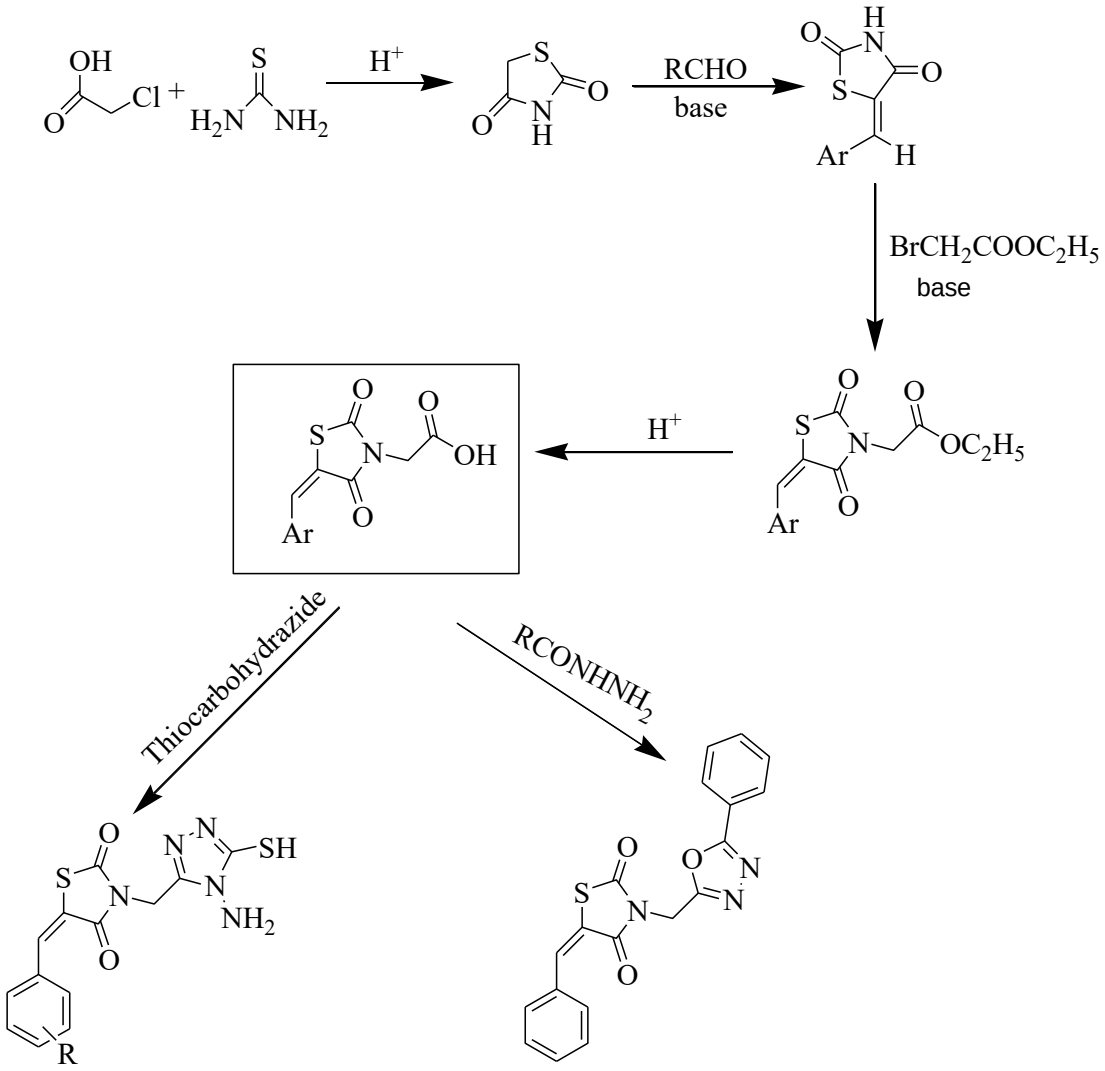
2,4-Thiazolidinedione and its derivatives have been widely studied over half a century due to their diverse biological applications. 2,4-Thiazolidinedione derivatives are widely used as anti-diabetic drugs for type-2 diabetes patients and are highly selective agonists for peroxisome proliferator-activated receptors [96,97]. Also, its derivatives have caught renewed attention recently due to their interesting biological and pharmacological activities like anti-cancer [98,99], anti-hyperglycemic [100], Pan-pim kinases inhibition [101], anti-inflammatory [30], and anti-hypertensive [31].

2,4-Thiazolidinedione is a methylene active heterocycle. More versatility may be brought about by varying the nature of substituents on the ring. By introducing substitution at 3 and/or 5 positions, its pharmacological activities may be varied.

As discussed earlier, 1,3,4-oxadiazole and 1,2,4-triazole moieties have found numerous applications in medicinal field. Therefore, keeping in view the hitherto importance of these two moieties, 5-arylidene-2,4-thiazolidinedione ring possessing either of these moieties was acknowledged as target molecules to explore their biological activities.

According to the planned synthetic strategy, chloroacetic acid and thiourea may be converted into the 2,4-thiazolidinedione and then this nucleus may be converted into 5-arylidene-2,4-thiazolidinediones by treatment with appropriate aldehydes in the presence of a base. The 5-arylidene-2,4-thiazolidinediones, on treatment with ethyl bromoacetate under basic conditions, are supposed to afford ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates. The esters on hydrolysis will yield the corresponding acids. This acid may be used as a common intermediate in the synthesis of 1,2,4-triazole derivatives, on cyclization using thiocarbohydrazide, and 1,3,4-oxadiazole derivatives on treatment with acid hydrazides in presence of some dehydrating agents.

The following synthetic route was devised for the synthesis of target molecules:



Scheme 1.19: Synthesis of 1,2,4-triazole and 1,3,4-oxadiazole derivatives from 5-arylidene-2,4-thiazolidinediones

The synthesized compounds will be characterized using available modern spectroscopic techniques- IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry.

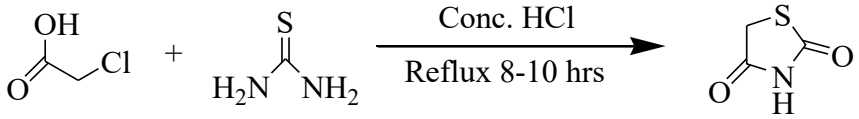
Chapter-2

Results and Discussion

5-Arylidene-2,4-thiazolidinedione derivatives have been studied by many researchers all over the world because they constitute a recurring scaffold of many bioactive compounds, and their importance is further underlined by their use in the treatment of diabetic disorders [102]. A variety of substituents on 2,4-thiazolidinedione nucleus when combined with other heterocyclic rings, display wide array of biological activities including: anti-cancer [10], anti-microbial [103], anti-hyperglycemic [9], anti-inflammatory [4], anti-tubercular [6], cytotoxicity [12], and anti-oxidant [5]. Because of such vast pharmacological and biological potential of 2,4-thiazolidinedione, some new derivatives of 5-arylidene-2,4-thiazolidinediones were synthesized as outlined in scheme 1.19.

2.1 Synthesis of 2,4-Thiazolidinedione (1)

2,4-Thiazolidinedione **(1)** was synthesized by the reaction of chloroacetic acid with thiourea dissolved in water in the presence of concentrated hydrochloric acid [19]. The synthesized 2,4-thiazolidinedione was recrystallized from ethanol (scheme 2.1).



(1)

Scheme 2.1: Synthesis of 2,4-thiazolidinedione **(1)**

2,4-Thiazolidinedione was obtained in an excellent purified yield of 88 %. This compound melted in the range 124-126 ºC which is comparable to its literature melting point (123-125 ºC) [19]. The R_f value of the compound was found to be 0.8 in chloroform : methanol (8:2) solvent system on aluminium precoated silica gel 60 F_{254}.

The formation of 2,4-thiazolidinedione was indicated in its IR spectrum by the appearance of absorption band at 1687 cm^{-1} assigned to carbonyl group present between two electronegative

(sulphur and nitrogen) atoms. Another absorption band at 1738 cm^{-1} corresponded to carbonyl group directly attached to only one electronegative (nitrogen) atom. Two factors, resonance and inductive effect, are responsible for increase in absorption frequency to 1738 cm^{-1} (normal value for acetone/cyclohexanone is 1715 cm^{-1}). The absorption band at 3126 cm^{-1} corresponds to N-H functionality. The C-S functionality was observed as an absorption peak at 680 cm^{-1}. IR spectral data for 2,4-thiazolidinedione is tabulated in table 2.1.

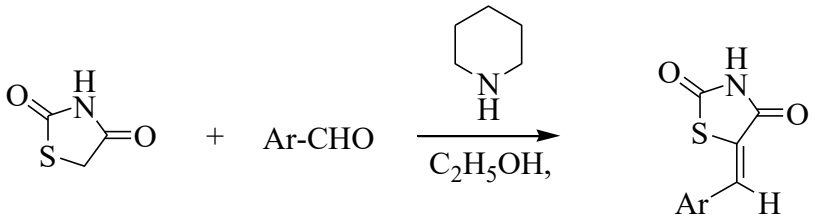
Table 2.1: IR spectral data of 2,4-thiazolidinedione **(1)**

Functional group	**$\bar{\upsilon}$ (cm^{-1})**
N-H Str. (secondary)	3126
C=O Str.	1738, 1687
C-S Str.	680

In ^{1}H-NMR spectrum, appearance of a broad singlet in deshielded region at 8.47 ppm, integrating to one proton and assigned to NH proton, confirmed the synthesis of 2,4-thiazolidinedione (1). The two methylene protons resonated at 4.12 ppm.

2.2 Synthesis of 5-Arylidene-2,4-diones (66a-f)

Synthesis of 5-arylidene derivatives of 2,4-thiazolidinedione **(1)** was carried out by refluxing 2,4-thiazolidinedione with corresponding aromatic aldehydes in the presence of piperidine as a base and ethanol as a solvent at ambient temperature [104, 105] (scheme 2.2).



(1) **(66a-f)**

66a: Ar = C_6H_5 **66b:** Ar = 4-$CH_3C_6H_4$ **66c:** Ar = 4-$OCH_3C_6H_4$

66d: Ar = 4-ClC_6H_4 **66e:** Ar = 2-$OCH_3C_6H_4$ **66f:** Ar = C_4H_3O (furfuryl)

Scheme 2.2: Synthesis of 5-arylidene-2,4-thiazolidinediones **(66a-f)**

The reaction was carried out by applying two reaction conditions, bases and solvents in order to minimize reaction time and to optimize the yield of 5-arylidene-2,4-thiazolidinediones.

Initially piperidine was used as a base. It was observed that when piperidine was used as a base, the time of reaction was too long (about 24 hours) and yields were moderate. Also, due to poisonous nature of piperidine, its use was avoided. However, with the use of equimolar quantities of acetic acid and ammonium acetate instead of piperidine, reaction completed in 6-8 hours and yields were good. Therefore, it remained the best choice throughout the experiments. The synthesized products were purified by recrystallization from ethanol affording pure products **(66a-f)**. The physical data of synthesized products **(66a-f)** is tabulated in table 2.2.

Table 2.2: Physical data of 5-arylidene-2,4-thiazolidinediones **(66a-f)**

Compd.	Ar	Physical Appearance	m.p. (°C)	R_f*	Yield (%)
66a	C_6H_5	Off-white solid	237-239	0.6	90
66b	4-$CH_3C_6H_4$	White solid	173-176	0.5	86
66c	4-$OCH_3C_6H_4$	Off-white solid	216-219	0.4	86
66d	4-ClC_6H_4	Light green solid	237-240	0.6	80
66e	2-$OCH_3C_6H_4$	Yellow solid	213-215	0.4	88
66f	C_4H_3O (furfuryl)	Beige coloured solid	241-244	0.7	90

*chloroform:methanol (9:1) for 66a, *n*-hexane:ethyl acetate (7:3) for 66b and 66c, *n*-hexane:ethyl acetate (1:1) for 66d, *n*-hex:EtOAc (6:4) for 66e and 66f; all on aluminium precoated silica gel 60 F_{254}

The synthesized 5-arylidene-2,4-thiazolidinediones **(66a-f)** were characterized by their spectral data. IR spectra indicates characteristic absorption bands in the region of 1679-1660 cm^{-1} corresponded to exocyclic C=C methylene linkage. Absorption band for aromatic rings appeared in the region 1598-1427 cm^{-1}. Strong absorptions in the region 1788-1635 cm^{-1} corresponded to C=O stretching vibrations. N-H peak appeared in the region 3208-3125 cm^{-1}. The IR spectral data for compounds **66a-f** is presented in table 2.3.

Table 2.3. IR spectral data of 5-arylidene-2,4-thiazolidinediones **(66a-f)**

Compd.	Ar	$\bar{\upsilon}$ (cm^{-1})			
		N-H	C=O	C=C (Ar)	C=C
66a	C_6H_5	3208	1709, 1651	1439, 1427	1679
66b	4-$CH_3C_6H_4$	3160	1728, 1650	1461, 1450	1665
66c	4-$OCH_3C_6H_4$	3125	1788, 1635	1548, 1538	1660
66d	4-ClC_6H_4	3144	1743, 1648	1458, 1450	1675
66e	2-$OCH_3C_6H_4$	3133	1732, 1673	1582, 1577	1670
66f	C_4H_3O (furfuryl)	3165	1776, 1653	1608, 1598	1669

The formation of 5-arylidene-2,4-thiazolidinediones **(66a-e)** was confirmed in the ^{1}H NMR spectra by appearance of a singlet for one benzylidene proton in the region of 7.64-7.90 ppm and absence of the methylene signal of 2,4-thiazolidinedione molecule. The chemical shift of benzylidene protons is displaced towards higher frequency (deshielded region) due to decrease in electron density at C-6 as a result of resonance associated with the α,β-unsaturated carbonyl-linkage (involving C-4, C-5 and C-6) as shown in figure 3.1. Aromatic protons of all the synthesized derivatives showed characteristic patterns in the region of 7.22-7.61 ppm.

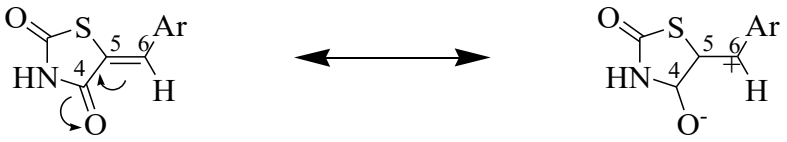
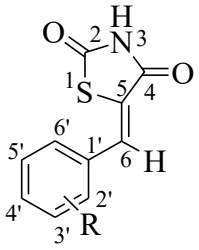


Figure 2.1: Resonance involved in the α,β-unsaturated carbonyl linkage affecting electron density at position 6

The ^{1}H NMR spectral data for compounds **66a-e** is tabulated in table 2.4.

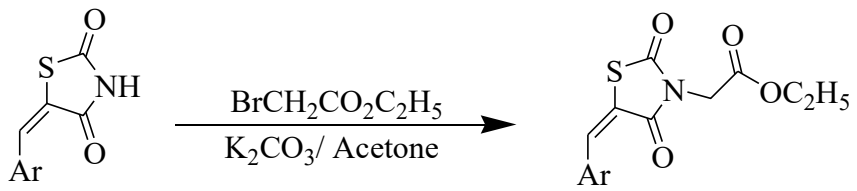
Table 2.4: ^{1}H NMR spectral data of 5-arylidene-2,4-thiazolidinediones **(66a-e)**



Protons	δ (ppm), Integration and multiplicity				
	66a **R = H**	**66b** **R = 4-CH$_3$**	**66c** **R = 4-OCH$_3$**	**66d** **R = 4-Cl**	**66e** **R = 2-OCH$_3$**
NH	12.6 (1H, s)	12.5 (1H, s)	11.21 (1H, s)	10.69 (1H, s)	11.30 (1H, s)
R	----	2.91 (s, 3H)	4.29 (3H, s)	----	3.85 (3H, s)
H-4'	7.47-7.61 (5H, m)	----	----	----	7.51 (1H, s)
H-2'		7.47-7.50 (2H, d)	7.38-7.40 (2H, d)	7.53-7.56 (2H, d)	----
H-6'					7.79 (1H, s)
H-3'		7.32-7.35 (2H, d)	7.22-7.25 (2H, d)	7.47-7.50 (2H, d)	6.88 (1H, s)
H-5'					7.09 (1H, s)
H-6	7.79 (1H, s)	7.75 (1H, s)	7.64 (1H, s)	7.72 (1H, s)	7.90 (1H, s)

2.3 Synthesis of Ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates (67a-f)

5-Arylidene-2,4-thiazolidinediones **(66a-f)** and potassium carbonate were refluxed in acetone followed by the addition of ethyl bromoacetate [106] affording ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates **(67a-f)** (scheme 2.3).



(66a-f) **(67a-f)**

Scheme 2.3: Synthesis of ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates

The reaction mixture was dissolved in chloroform followed by rotary evaporation to give solid product. The synthesized products **67a-f** were purified by recrystallization from methanol, pure crystals of ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates **(67a-f)** were obtained in moderate to good yields (%). The physical data of synthesized products **(67a-f)** is tabulated in table 2.5.

Table 2.5: Physical data of ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates **(67a-f)**

Compd.	Ar	Physical Appearance	m.p. (ºC)	R_f*	Yield (%)
67a	C_6H_5	Light green crystals	75-77	0.9	78
67b	4-$CH_3C_6H_4$	Off-white crystals	119-121	0.8	76
67c	4-$OCH_3C_6H_4$	Orange crystals	88-90	0.8	75
67d	4-ClC_6H_4	White crystals	120-122	0.7	72
67e	2-$OCH_3C_6H_4$	Off-white crystals	87-89	0.7	79
67f	C_4H_3O (furfuryl)	Orange crystals	130-133	0.8	80

**n*-hexane: ethyl acetate (6:4); on aluminium precoated silica gel 60 F_{254}

In IR spectra, the formation of ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates **(67a-e)** was identified by the appearance of a sharp peak at 1745-1735 cm^{-1} assigned to the carbonyl group of the ester compounds. The disappearance of NH stretch in the

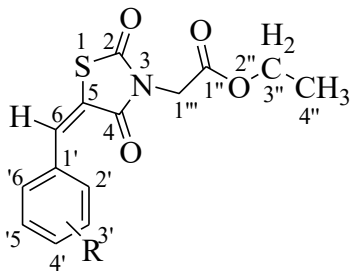
region 3208-3125 cm^{-1} observed in the starting 5-arylidene-2,4-thiazolidinediones **(66a-e)** provided additional evidence for successful conversion to ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates **(67a-e)**. Imide bond show characteristic C=O absorption bands in the region 1678-1588 cm^{-1}. The IR spectral data for compounds **67a-e** is presented in table 2.6.

Table 2.6: IR data of ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates **(67a-e)**

Compd.	Ar	$\bar{\upsilon}$ (cm^{-1})			
		C=O (Ester)	C=O	sp^3 C-H Stretch (N-CH_2)	sp^3 C-H Stretch
67a	C_6H_5	1735	1676, 1602	2984	2944, 2842
67b	4-$CH_3C_6H_4$	1745	1677, 1591	2982	2943, 2845
67c	4-$OCH_3C_6H_4$	1735	1678, 1590	2981	2941, 2843
67d	4-ClC_6H_4	1735	1674, 1588	2990	2940, 2841
67e	2-$OCH_3C_6H_4$	1735	1677, 1591	2985	2943, 2845

The formation of ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates **(67a-e)** was confirmed in the ^1H NMR spectra by appearance of a singlet in the region 4.50-4.3.76 ppm for two methylene protons adjacent to imide functionality. These two methylene protons appeared in slightly downfield region because of presence of neighbouring NH and C=O functionalities, which decreases electron density at methylene carbon and displaced these protons towards higher frequency (deshielded region). The disappearance of signal for NH proton in the region 11.22-12.6 ppm observed in the starting 5-arylidene-2,4-thiazolidinediones **(66a-f)** provided additional evidence for the formation of ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates **(67a-e)**. Signal for methyl group appeared in the region 1.22-1.34 ppm. The methylene protons directly attached to oxygen atom appeared in the region 3.92-4.29 ppm. The ^1H NMR spectral data for compounds **67a-e** is tabulated in table 2.7.

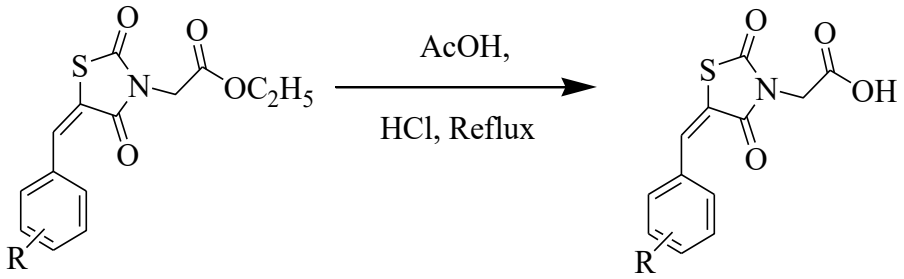
Table 2.7: ^{1}H NMR spectral data for ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl) acetates **(67a-e)**



Protons	δ (ppm), Integration and multiplicity				
	67a R=H	**67b R= 4-CH$_3$**	**67c R= 4-OCH$_3$**	**67d R= 4-Cl**	**67e R= 2-OCH$_3$**
R	----	2.91 (3H, s)	4.32 (3H, s)	----	3.88 (3H, s)
H-4'	7.28-7.55 (5H, m)	----	----	----	7.53 (1H, s)
H-2'		7.45-7.49 (2H, d)	7.33-7.36 (2H, d)	7.40-7.44 (2H, d)	----
H-6'					7.82 (1H, s)
H-3'		7.30-7.34 (2H, d)	7.24-7.28 (2H, d)	7.34-7.38 (2H, d)	6.93 (1H, s)
H-5'					7.12 (1H, s)
H-6	7.95 (1H, s)	7.87 (1H, s)	7.74 (1H, s)	7.79 (1H, s)	7.93 (1H, s)
H-3''	4.22-4.29 (2H, s)	4.18-4.21 (2H, s)	3.92-3.96 (2H, s)	4.19-4.23 (2H, s)	3.99-4.15 (2H, s)
H-4''	1.28-1.33 (3H, s)	1.22-1.28 (3H, s)	1.27-1.32 (3H, s)	1.31-1.34 (3H, s)	1.26-1.29 (3H, s)
H-1'''	4.41-4.49 (2H, s)	4.40-4.46 (2H, s)	3.77-3.82 (2H, s)	4.43-4.49 (2H, s)	3.92-3.98 (2H, s)

2.4 Synthesis of 2-(5-Arylidene-2,4-dioxothiazolidin-3-yl)acetic acids (68a-f)

A mixture of ethyl 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetates **(67a-f)**, glacial acetic acid and hydrochloric acid was refluxed for four hours to give pure 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids **(68a-f)** [107] as depicted in scheme 2.4.



(67a-f) **(68a-f)**

Scheme 2.4: Synthesis of 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids **(68a-f)**

The synthesized compounds **68a-f** were purified by recrystallization from methanol providing pure products. All compounds formed in moderate to good yields (%). Physical appearance of all synthesized compounds was different and exhibited wide range of melting points. The physical data of synthesized products **67a-f** is presented in table 2.8.

Table 2.8: Physical data of 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids **(68a-f)**

Compd.	R	Physical Appearance	m.p. (°C)	R_f*	Yield (%)
68a	C_6H_5	Light green solid	70-74	0.2	76
68b	4-$CH_3C_6H_4$	White solid	110-113	0.5	73
68c	4-$OCH_3C_6H_4$	Orange coloured solid	79-82	0.9	72

Continued...

Table 2.8: Continuation.

Compd.	R	Physical Appearance	m.p. (°C)	R_f*	Yield (%)
68d	4-ClC_6H_4	White solid	110-113	0.7	68
68e	2-$OCH_3C_6H_4$	Off-white solid	67-70	0.7	78
68f	C_4H_3O (furfuryl)	Orange solid	111-115	0.7	80

*chloroform:methanol (9:1) for 68a, 68c and *n*-hexane:ethyl acetate (7:3) for 68b, 68d, 68e, 68f; all on aluminium precoated silica gel 60 F_{254}

These synthesized compounds were characterized by their spectral data. In the IR spectra, appearance of a broad OH band in the region 3540-2658 cm^{-1} indicates the formation of corresponding acid group. Carbonyl stretching vibrations for acid group appeared in the region 1740-1735 cm^{-1}. Peaks for other carbonyl groups appeared in the region 1681-1589 cm^{-1}. The disappearance of stretching vibrations for ethyl group in the region 2944-2841 cm^{-1} provided further evidence for successful conversion to 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids **(68a-f).** The IR spectral data for compounds **68a-e** is presented in table 2.9.

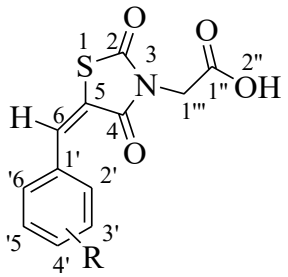
Table 2.9: IR data of 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids **(68a-e)**

Compd.	Ar	$\bar{\upsilon}$ (cm^{-1})			
		C=O Acid	C=O	Sp^3 C-H Stretch ($N-CH_2$)	OH Broad band
68a	C_6H_5	1737	1680, 1595	2952	3536-2663
68b	4-$CH_3C_6H_4$	1736	1678, 1593	2950	3530-2659
68c	4-$OCH_3C_6H_4$	1736	1679, 1591	2953	3534-2662
68d	4-ClC_6H_4	1736	1680, 1589	2951	3535-2661
68e	2-$OCH_3C_6H_4$	1736	1681, 1590	2947	3540-2658

The formation of 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids **(68a-e)** was confirmed in the ^1H NMR spectra by the appearance of a broad signal for OH of the carboxylic acid in the region 12.4-13.9 ppm. The disappearance of signals of ethyl protons further confirms the synthesis of

2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids **(68a-e)**. The two methylene protons adjacent to imide functionality appeared in the region 3.98-4.45 ppm. Aromatic protons of all synthesized derivatives show characteristic patterns in the region of 6.91-7.58 ppm. The ^{1}H NMR spectral data for compounds **68a-e** is tabulated in table 2.10.

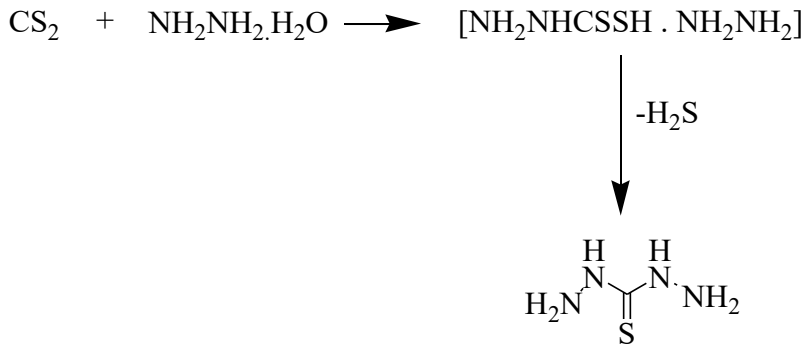
Table 2.10: ^{1}H NMR spectral data for 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids **(68a-e)**



Protons	δ (ppm), Integration and multiplicity				
	68a **R=H**	**68b** **R= 4-CH_3**	**68c** **R= 4-OCH_3**	**68d** **R= 4-Cl**	**68e** **R= 2-OCH_3**
R	----	2.98 (3H, s)	4.68 (3H, s)	----	3.89 (3H, s)
H-4'	7.51-7.67 (5H, m)	----	----	----	6.91 (1H, s)
H-2'		7.55-7.58 (2H, d)	7.39-7.43 (2H, d)	7.41-7.43 (2H, d)	----
H-6'					7.82 (1H, s)
H-3'		7.33-7.38 (2H, d)	7.30-7.36 (2H, d)	7.37-7.41 (2H, d)	6.93 (1H, s)
H-5'					7.12 (1H, s)
H-6	8.00 (1H, s)	7.89 (1H, s)	7.85 (1H, s)	7.84 (1H, s)	7.94 (1H, s)
H-1'''	4.39 (2H, s)	4.45 (2H, s)	4.1 (2H, s)	3.99 (2H, s)	3.98 (2H, s)
OH	13.4 (1H, b, s)	13.00 (1H, b, s)	13.2 (1H, b, s)	12.9 (1H, b, s)	13.3 (1H, b, s)

2.5 Synthesis of Thiocarbohydrazide (69)

Carbon disulfide was treated with three-molar excess of aqueous hydrazine hydrate at low temperature to form hydrazinium dithiocarbazinate (a water-soluble salt) in nearly quantitative yield (%). This salt was then heated to form desired product **(69)** with the elimination of hydrogensulfide [108-110] (scheme 2.4).



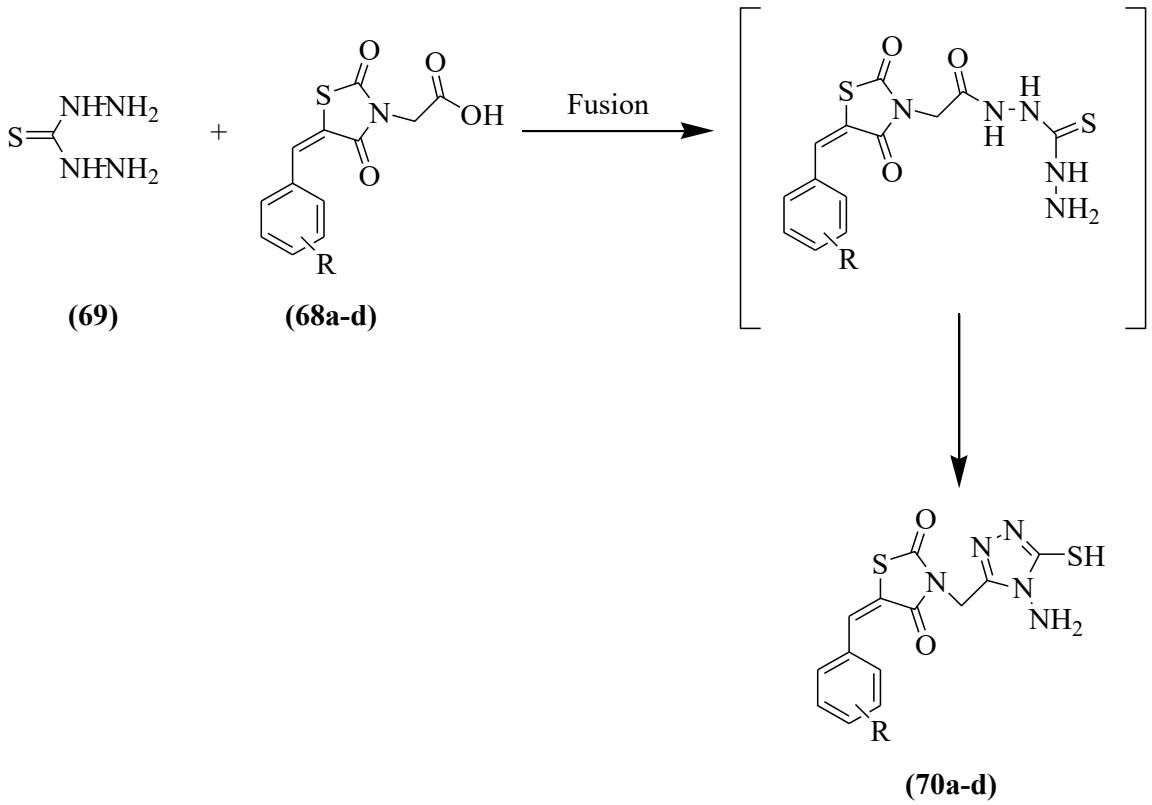
(69)

Scheme 2.5: Synthesis of thiocarbohydrazide **(69)**

Thiocarbohydrazide was obtained in an excellent purified yield of 88 %. The physical appearance of thiocarbohydrazide was crystalline needles. This compound melted in the range 172-175 ºC which is comparable to its literature melting point (171-174 ºC) [108-110]. The R_f value of the compound was found to be 0.6 in *n*-hexane : ethyl acetate (8:2) solvent system on aluminium precoated silica gel 60 F_{254}.

2.6 Synthesis of 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones (70a-d)

Equimolar amounts of thiocarbohydrazide was reacted with various 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids at their respective melting points to afford simultaneous cyclization giving 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)** [111] as depicted in scheme 2.5.



(69) **(68a-d)** **(70a-d)**

Scheme 2.6: Synthesis of 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)**

The synthesized compounds **70a-d** were purified by recrystallization from ethanol affording pure products. All compounds showed moderate yields and displayed a wide melting point range. The physical appearance of two compounds was orange solid and two compounds showed light brown colour. The physical data of synthesized products **70a-d** is presented in table 2.11.

Table 2.11: Physical data of 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)**

Compd.	R	Physical Appearance	m.p. (°C)	R_f^*	Yield (%)
70a	C_6H_5	Orange Solid	210-212	0.7	70
70b	4-$CH_3C_6H_4$	Orange solid	181-184	0.8	72
70c	4-$OCH_3C_6H_4$	Light brown solid	206-209	0.8	67
70d	4-ClC_6H_4	Light brown solid	173-178	0.6	63

*n-hexane:ethyl acetate (6:4); on aluminium precoated silica gel 60 F_{254}

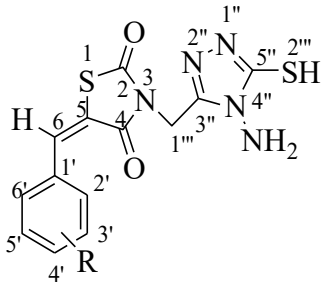
The characterization of the synthesized compounds **(21-24)** was done by their spectral data. In IR spectra, Imide bond show characteristic C=O absorption bands in the region 1746-1671 cm^{-1}. Appearance of C=N stretching vibrations in the region 1611-1609 cm^{-1} indicates the formation of new 1,2,4-triazole moiety. The primary NH peak appeared in the region 3330-3310 cm^{-1} which was another indication for the synthesis of compounds **70a-d.** The disappearance of the carbonyl stretching vibrations in the region 1737-1735 cm^{-1} and OH band in the region 3540-2658 cm^{-1} observed in the starting 2-(5-arylidene-2,4-dioxothiazolidin-3-yl)acetic acids **(68a-e)** provided further evidence of successful conversion to 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)**. The IR spectral data for compounds **70a-d** is presented in table 2.12.

Table 2.12: IR spectral data of 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)**

Compd.	Ar	$\bar{\upsilon}$ (cm^{-1})			
		C=O	Sp^3 C-H Stretch	C=N Stretch	N-H Str. (Primary)
70a	C_6H_5	1745, 1679	2950	1607	3325
70b	4-$CH_3C_6H_4$	1746, 1675	2944	1611	3330
70c	4-$OCH_3C_6H_4$	1743, 1676	2951	1609	3315
70d	4-ClC_6H_4	1742, 1671	2950	1606	3311

The synthesis of 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)** was confirmed in ^{1}H NMR by appearance of a singlet in deshielded region (12.8-13.1 ppm) for SH proton. A singlet in the region 5.59-5.64 ppm assigned to two NH_2 protons which was another confirmation for the newly synthesized 1,2,4-triazole moiety. The disappearance of signal for OH proton observed in the starting compounds **(68a-d)** provided additional confirmation of successful conversion to 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)**. The ^{1}H NMR data of synthesized compounds **70a-d** is tabulated in table 2.13.

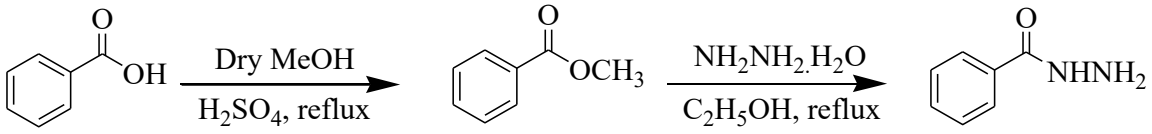
Table 2.13: ^{1}H NMR spectral data of 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)**



Protons	δ (ppm), Integration and multiplicity			
	70a **R=H**	**70b** **R= 4-CH_3**	**70c** **R= 4-OCH_3**	**70d** **R= 4-Cl**
R	----	2.98 (3H, s)	4.72 (3H, s)	----
SH	13.1 (1H, s)	13.00 (1H, s)	12.8 (1H, s)	12.9 (1H, s)
NH_2	5.64 (2H, s)	5.59 (2H, s)	5.61 (2H, s)	5.63 (2H, s)
H-4'	7.51-7.67 (5H, m)	----	----	----
H-2'		7.56-7.59 (2H, d)	7.41-7.45 (2H, d)	7.43-7.47 (2H, d)
H-6'				
H-3'		7.36-7.40 (2H, d)	7.36-7.39 (2H, d)	7.39-7.45 (2H, d)
H-5'				
H-6	7.99 (1H, s)	7.87 (1H, s)	7.82 (1H, s)	7.80 (1H, s)
H-1'''	4.91 (2H, s)	4.63 (2H, s)	4.66 (2H, s)	4.22 (2H, s)

2.7 Synthesis of Benzohydrazide (73)

Benzoic acid was treated with sulphuric acid in dry distilled methanol to produce its methyl ester in a quantitative yield (%). This ester on further reaction with hydrazine hydrate (on heating in ethanol), gave a high yield of benzohydrazide using a reported procedure [112, 113] (scheme 2.6).



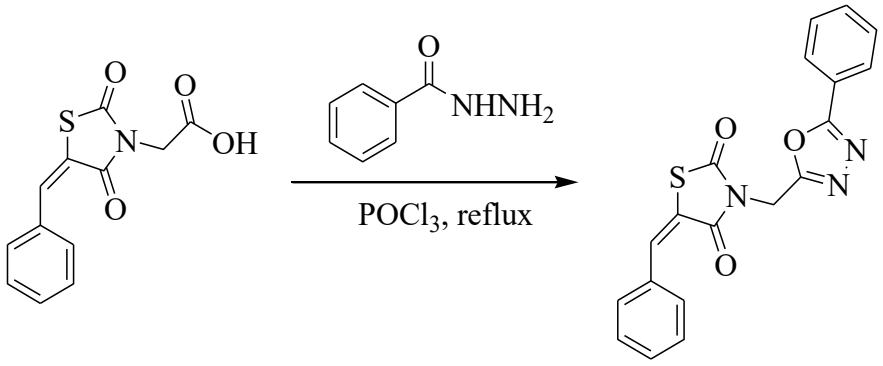
(71) **(72)** **(73)**

Scheme 2.7: Synthesis of benzohydrazide **(73)**

Benzohydrazide **(73)** was obtained in an excellent purified yield of 68 %. The physical appearance of benzohydrazide was white crystals. This compound melted in the range 113-115 ºC which is comparable to its literature melting point (115 ºC) [114]. The R_f value of the compound was found to be 0.2 in *n*-hexane : ethyl acetate (6:4) solvent system on aluminium precoated silica gel 60 F_{254}.

2.8 Synthesis of 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione (74)

5-Benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)** was prepared by treatment of benzohydrazide with 2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)acetic acid **(68a)** in the presence of phosphorus oxychloride. The reaction mixture was refluxed for 6-8 hours and poured onto crushed ice to afford the precipitation, followed by filteration and recrystallization from ethanol [90] as depicted in scheme 2.7.



(68a) **(74)**

Scheme 2.8: Synthesis of 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)**

5-Benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)** was obtained in an excellent purified yield of 85 %. This compound melted in the range 168-172 ºC. The compound appeared as reddish brown solid and R_f value of the compound was found to be 0.5 in *n*-hexane : ethyl acetate (7:3) solvent system on aluminium precoated silica gel 60 F_{254}.

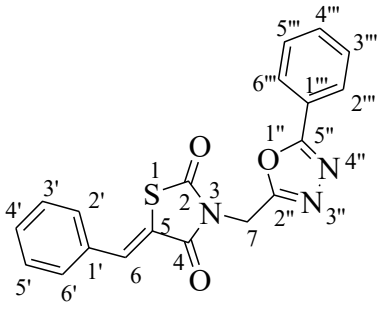
The synthesized compound, 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74),** was characterized by its spectral data. In the IR spectrum, appearance of C=N stretching vibrations at 1603 cm^{-1} indicates the formation of oxadiazole ring. Strong absorptions in the region 1100-1090 cm^{-1} corresponded to C-O-C stretching vibrations. The disappearance of a broad OH band and C=O peak (for carboxylic acid group) observed in the starting 2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)acetic acid **(68a)** provided additional evidence for the synthesis of new 1,3,4-oxadiazole moiety. Carbonyl stretching vibrations appeared in the region 1760-1680 cm^{-1}. The IR spectral data for the compound **74** is presented in table 2.14.

Table 2.14: IR spectral data of 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)**

Functional group	$\bar{\upsilon}$ (cm^{-1})
C=N Str.	1603
C=O Str.	1747, 1682
C-O-C Str.	1140

The synthesis of 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)** was confirmed in ^{1}H NMR spectrum by appearance of more protons in the aromatic region (7.52-7.99 ppm) which confirms the synthesis of new 1,3,4-oxadiazole moiety on 5-arylidene-2,4-thiazolidinedione ring. A singlet for two protons at 5.22 ppm assigned to methylene group present adjacent to imide functionality. The disappearance of a singlet at 13.4 ppm which was due to OH group of starting 2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)acetic acid **(68a),** provided further confirmation for the synthesis of 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)**. The benzylic proton appeared as singlet at around 8.02 ppm. The ^{1}H NMR data of synthesized compound **74** is tabulated in table 2.15.

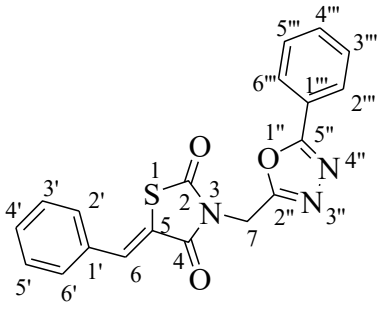
Table 2.15: ^{1}H NMR data of 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)**



Protons	**Chemical shifts δ (ppm), Integration, Multiplicity**
CH2	5.22 (2H, s)
CH	8.02 (1H, s)
C-H Aromatic	7.52-7.99 (10H, m)

The formation of the product **(74)** was also confirmed in ^{13}C NMR spectrum by appearance of two signals for newly formed heterocyclic ring in deshielded region. Appearance of some more signals in the aromatic region further confirmed the synthesis of 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)**. The disappearance of signal corresponded to carboxylic acid group was another evidence for the synthesis of 1,3,4-oxadiazole moiety. The methylene carbon adjacent to imide functionality resonated at around 36.26 ppm. Signals for carbonyl groups appeared in the region 165.2-167.2 ppm. The ^{13}C NMR data of synthesized compound **74** is presented in table 2.16.

Table 2.16. ^{13}C NMR data of 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)**



Carbons	Chemical shifts (δ, ppm)
C-2	167.27
C-4	165.25
C-2"	165.11
C-5"	161.59
$\underline{C}H_2$	36.26
Aromatic carbons	121.17-134.44

Conclusions

The chemical modification at 3 and 5 position of the core structure 2,4-thiazolidinedione lead to different series of 3-substituted 5-arylidene-2,4-thiazolidinediones which were synthesized and characterized by available modern spectroscopic techniques.

The synthesized 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)** and 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione **(74)** will be subjected to different biological activities.

Chapter-3

Experimental

4.1 Experimental Notes

4.1.1 Instrumentation

Melting points of all the synthesized compounds were determined in open-glass capillaries using Gallenkamp melting point apparatus (MP-D) and are uncorrected. Infrared (IR) spectra were recorded on Shimadzu Fourier Transform Infra-Red Spectrophotometer model 270 using ATR (Attenuated total reflectance) facility. Only the strongest and most significant peaks are listed. NMR spectra were acquired on a Bruker Avance 300 MHz spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded either in $CDCl_3$ or DMSO-d_6. The chemical shift values were referenced to TMS. Spectral data were consistent with proposed structures. The Progress of all the reactions were monitored by thin layer chromatography (TLC) using silica gel protected aluminium sheets (silica gel-60 F_{254}) purchased from Merck (Germany). The spots were detected by disclosure to UV-lamp at wavelength (λ) of 254 nm for a few seconds.

4.1.2 Substrates and Reagents

Ethanol, chloroform, methanol, ethyl acetate and acetone were obtained from commercial sources. Dichloromethane, diethyl ether and petroleum ether were the products of Riedel de Haen. The compounds *p*-toulaldehyde, *p*-anisaldehyde, 4-chlorobenzaldehyde, 2-methoxybenzaldehyde, furfuryl, benzoic acid, phosphorus oxychloride, carbon disulfide, hydrazine hydrate and glacial acetic acid were purchased from Sigma-Aldrich. The reagents used were of high purity grade, while the solvents were purified, whenever required.

4.2 Synthesis of 2,4-Thiazolidinedione (1)

The mixture of chloroacetic acid (0.6 mol) and thiourea (0.6 mol) was dissolved in 60 mL of water and stirred for fifteen minutes. White precipitates were formed upon

Cooling at room temperature. Hydrochloric acid (60 mL) was added dropwise to the contents of flask, and reaction mixture was then refluxed for 8-10 hours at 100-110 ºC. On cooling to room temperature, a cluster of white needles formed in the reaction mixture. The precipitates were filtered and washed with water to remove traces of hydrochloric acid. The product was purified by recrystallization from ethyl alcohol [17].

2,4-Thiazolidinedione (1). White crystals; Yield: 88 %; m.p.: 124-126 ºC (lit. m.p. 123-125 ºC); R_f : 0.8 ($CHCl_3$: MeOH; 8:2); **IR** (neat, cm^{-1}): 1738, 1687 (C=O), 3126 (N-H), 680 (C-S-C); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 8.47 (1H, s), 4.1-4.28 (2H, s).

4.3 General Procedure for the Synthesis of 5-Arylidene-2,4-thiazolidinediones (66a-f)

A mixture of 2,4-thiazolidinedione (20 mmol), aldehyde (20 mmol), piperidine (16 mmol) and EtOH (150 mL) was refluxed for 24 hours. After completion of the reaction, the precipitates formed were filtered off and washed with water, followed by acidification with acetic acid to give solid product. The solid obtained was recrystallized from methanol to give pure product [94,95].

5-Benzylidene-2,4-thiazolidinedione (66a) Off-white solid; Yield: 90 %; m.p.: 237-239 ºC; R_f : 0.6 ($CHCl_3$: MeOH; 9:1); **IR** (neat, cm^{-1}): 1709, 1651 (C=O), 3208 (N-H), 789 (C-S-C); 1439, 1427 (Aromatic C=C); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 12.6 (1H, s, NH), 7.79 (1H, s, H-6), 7.47-7.61 (5H, m, H-2', H-3', H-4', H-5', H-6').

5-(4-methylbenzylidene)-2,4-thiazolidinedione (66b) White solid; Yield: 86 %; m.p.: 173-176 ºC; R_f : 0.5 (*n*-hex : EtOAc 7:3); **IR** (neat, cm^{-1}): 1728, 1650 (C=O), 3160 (N-H), 790 (C-S-C); 1461, 1450 (Aromatic C=C); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 12.5 (1H, s, NH), 7.75 (1H, s, H-6), 7.47-7.50 (2H, d, H-2', H-6'), 7.32-7.35 (2H, d, H-3', H-5'), 2.91 (s, 3H, CH_3).

5-(4-Methoxybenzylidene)-2,4-thiazolidinedione (66c) Off-white solid; Yield: 86 %; m.p.: 216-219 ºC; R_f : 0.4 (*n*-hex : EtOAc 7:3); **IR** (neat, cm^{-1}): 1788, 1635 (C=O), 3125 (N-H), 788 (C-S-C); 1548, 1538 (Aromatic C=C); **^{1}H-NMR ($CDCl_3$):**

δ (ppm) = 11.21 (1H, s, NH), 7.64 (1H, s, H-6), 7.38-7.40 (2H, d, H-2', H-6'), 7.22-7.25 (2H, d, H-3', H-5'), 4.29 (3H, s, OCH_3).

5-(4-Chlorobenzylidene)-2,4-thiazolidinedione (66d) Light-green solid; Yield: 80 %; m.p.: 237-240 ºC; R_f : 0.6 (*n*-hex : EtOAc 1:1); **IR** (neat, cm^{-1}): 1743, 1648 (C=O), 3144 (N-H), 792 (C-S-C); 1458, 1450 (Aromatic C=C); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 10.69 (1H, s, NH), 7.72 (1H, s, H-6), 7.53-7.56 (2H, d, H-2', H-6'), 7.47-7.50 (2H, d, H-3', H-5').

5-(2-Methoxybenzylidene)-2,4-thiazolidinedione (66e) Yellow solid; Yield: 88 %; m.p.: 213-215 ºC; R_f : 0.4 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1732, 1673 (C=O), 3133 (N-H), 741 (C-S-C); 1582, 1577 (Aromatic C=C); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 11.30 (1H, s, NH), 7.90 (1H, s, H-6), 3.85 (3H, s, OCH_3), 7.51 (1H, s, H-4'), 7.79 (1H, s, H-6'), 6.88 (1H, s, H-3'), 7.09 (1H, s, H-5').

5-(Furan-2-ylmethylene)-2,4-thiazolidinedione (66f) Beige coloured solid; Yield: 90 %; m.p.: 241-244 ºC; R_f : 0.7 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1776, 1653 (C=O), 3165 (N-H), 785 (C-S-C).

4.4 General Procedure for the Synthesis of Ethyl-2-(5-arylidene-2,4- dioxothiazolidin-3-yl)acetates (67a-f)

A mixture of 5-arylidene-2,4-thiazolidinediones (10 mmol), ethyl bromoacetate (20 mmol) and potassium carbonate (20 mmol) was refluxed in acetone (120 mL) for 24 hours. After cooling to room temperature, the residues were filtered off and the solvent was evaporated under reduced pressure and the solid was recrystallized from methanol affording pure acetate.

Ethyl-2-(5-benzylidene-2,4-dioxothiazolidin-3-yl)acetate (67a) Light green crystals; Yield: 78 %; m.p.: 75-77 ºC; R_f : 0.9 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1735 (C=O of ester), 1676, 1602 (C=O), 2984 (sp^3 C-H Stretch, N-CH_2), 2944, 2842 (sp^3 C-H Stretch, CH_2 and CH_3); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 4.22-4.29 (2H, s, O-CH_2), 1.28-1.33 (3H, s, CH_3), 4.41-4.49 (2H, s, N-CH_2), 7.95 (1H, s, H-6), 7.28-7.55 (5H, m, H-2', H-3', H-4', H-5', H-6').

Ethyl-2-[5-(4-methylbenzylidene-2,4-dioxothiazolidin-3-yl)]acetate (67b) Off-white crystals; Yield: 76 %; m.p.: 119-121 ºC; R_f : 0.8 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1745 (C=O of ester), 1677, 1591 (C=O), 2982 (sp^3 C-H Stretch, N-CH_2), 2943, 2845 (sp^3 C-H Stretch, CH_2 and CH_3); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 4.18-4.21 (2H, s, O-CH_2), 1.22-1.28 (3H, s, CH_3), 4.40-4.46 (2H, s, N-CH_2), 7.87 (1H, s, H-6), 7.45-7.49 (2H, d, H-2', H-6'), 7.30-7.34 (2H, d, H-3', H-5'), 2.91 (3H, s, CH_3).

Ethyl-2-[5-(4-methoxybenzylidene-2,4-dioxothiazolidin-3-yl)]acetate (67c) Orange crystals; Yield: 75 %; m.p.: 88-90 ºC; R_f : 0.9 (*n*-hex : EtOAc 6:4); **IR** (neat, .comcm^{-1}): 1735 (C=O of ester), 1678, 1590 (C=O), 2981 (sp^3 C-H Stretch, N-CH_2), 2941, 2843 (sp^3 C-H Stretch, CH_2 and CH_3); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 3.92-3.96 (2H, s, O-CH_2), 1.27-1.32 (3H, s, CH_3), 3.77-3.82 (2H, s, N-CH_2), 7.74 (1H, s, H-6), 7.33-7.36 (2H, d, H-2', H-6'), 7.24-7.28 (2H, d, H-3', H-5'), 4.32 (3H, s, OCH_3).

Ethyl-2-[5-(4-chlorobenzylidene-2,4-dioxothiazolidin-3-yl)]acetate (67d) White crystals; Yield: 72 %; m.p.: 120-122 ºC; R_f : 0.7 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1735 (C=O of ester), 1674, 1588 (C=O), 2990 (sp^3 C-H Stretch, N-CH_2), 2940, 2841 (sp^3 C-H Stretch, CH_2 and CH_3); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 4.19-4.23 (2H, s, O-CH_2), 1.31-1.34 (3H, s, CH_3), 4.43-4.49 (2H, s, N-CH_2), 7.79 (1H, s, H-6), 7.40-7.44 (2H, d, H-2', H-6'), 7.34-7.38 (2H, d, H-3', H-5').

Ethyl-2-[5-(2-methoxybenzylidene-2,4-dioxothiazolidin-3-yl)]acetate (67e) Off-white crystals; Yield: 79 %; m.p.: 87-89 ºC; R_f : 0.7 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1735 (C=O of ester), 1677, 1591 (C=O), 2985 (sp^3 C-H Stretch, N-CH_2), 2943, 2845 (sp^3 C-H Stretch, CH_2 and CH_3); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 3.99-4.15 (2H, s, O-CH_2), 1.26-1.29 (3H, s, CH_3), 3.92-3.98 (2H, s, N-CH_2), 7.93 (1H, s, H-6), 6.93 (1H, s, H-3'), 7.53 (1H, s, H-4'), 7.12, (1H, s, H-5'), 7.82 (1H, s, H-6'), 3.88 (3H, s, OCH_3).

Ethyl-2-[5-(furan-2-ylmethylene)-2,4-dioxothiazolidin-3-yl]acetate (67f) Orange crystals; Yield: 80 %; m.p.: 130-133 ºC; R_f : 0.8 (*n*-hex : EtOAc 6:4).

4.5 General Procedure for the Synthesis of 2-(5-Arylidene-2,4-dioxothiazolidin-3-yl) acetic acid (68a-f)

A mixture of ester (10 mmol), glacial acetic acid (120 mL) and hydrochloric acid (30 mL) was refluxed for 4 hours. After rotary evaporation, the crude solid was washed with water and recrystallized from methanol affording pure acid.

2-(5-Benzylidene-2,4-dioxothiazolidin-3-yl) acetic acid (68a) Light green solid; Yield: 76 %; m.p.: 70-74 ºC; R_f : 0.2 ($CHCl_3$: MeOH 9:1)**; IR** (neat, cm^{-1}): 1737 (C=O of Acid), 1680, 1595 (C=O), 2952 (sp^3 C-H Stretch), 3536-2663 (OH band); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 13.4 (1H, b, s, OH), 4.39 (2H, s, CH_2), 8.00 (1H, s, H-6), 7.51-7.67 (5H, m, H-2', H-3', H-4', H-5', H-6').

2-[5-(4-Methylbenzylidene-2,4-dioxothiazolidin-3-yl)]acetic acid (68b) White solid; Yield: 73 %; m.p.: 110-113 ºC; R_f : 0.5 (*n*-hex : EtOAc 7:3); **IR** (neat, cm^{-1}): 1736 (C=O of Acid), 1678, 1593 (C=O), 2950 (sp^3 C-H Stretch), 3530-2659 (OH band); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 13.00 (1H, b, s, OH), 4.45 (2H, s, CH_2), 7.89 (1H, s, H-6), 7.55-7.58 (2H, d, H-2', H-6'), 7.33-7.38 (2H, d, H-3', H-5').

2-[5-(4-Methoxybenzylidene-2,4-dioxothiazolidin-3-yl)]acetic acid (68c) Orange coloured solid; Yield: 72 %; m.p.: 79-82 ºC; R_f : 0.9 ($CHCl_3$: MeOH 9:1); **IR** (neat, cm^1): 1736 (C=O of Acid), 1679, 1591 (C=O), 2953 (sp^3 C-H Stretch), 3534-2662 (OH band); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 13.2 (1H, b, s, OH), 4.1 (2H, s, CH_2), 7.85 (1H, s, H-6), 7.39-7.43 (2H, d, H-2', H-6'), 7.30-7.36 (2H, d, H-3', H-5').

2-[5-(4-Chlorobenzylidene-2,4-dioxothiazolidin-3-yl)]acetic acid (68d) White solid; Yield: 68 %; m.p.: 110-113 ºC; R_f : 0.7 (*n*-hex : EtOAc 7:3); **IR** (neat, cm^{-1}): 1736 (C=O of Acid), 1680, 1589 (C=O), 2951 (sp^3 C-H Stretch), 3535-2661 (OH band); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 12.9 (1H, b, s, OH), 3.99 (2H, s, CH_2), 7.84 (1H, s, H-6), 7.31-7.43 (2H, d, H-2', H-6'), 7.37-7.41 (2H, d, H-3', H-5').

2-[5-(2-Methoxybenzylidene-2,4-dioxothiazolidin-3-yl)]acetic acid (68d) Off-white solid; Yield: 78 %; m.p.: 67-70 ºC; R_f : 0.7 (*n*-hex : EtOAc 7:3); **IR** (neat, cm^{-1}): 1736 (C=O of Acid),

1681, 1590 (C=O), 2947 (sp^3 C-H Stretch), 3540-2658 (OH band); **^{1}H-NMR ($CDCl_3$):** δ (ppm) = 13.3 (1H, b, s, OH), 3.98 (2H, s, CH_2), 7.94 (1H, s, H-6), 6.93 (1H, s, H-3'), 6,91 (1H, s, H-4'), 7.12, (1H, s, H-5'), 7.82 (1H, s, H-6'), 3.89 (3H, s, OCH_3).

Ethyl-2-[5-(furan-2-ylmethylene)-2,4-dioxothiazolidin-3-yl]acetic acid (68e) Orange solid; Yield: 80 %; m.p.: 111-115 ºC; R_f : 0.7 (*n*-hex : EtOAc 7:3).

4.6 Synthesis of Thiocarbohydrazide (69)

Carbon disulfide was treated with three-molar excess of aqueous hydrazine hydrate at relatively low temperature to form hydrazinium dithiocarbazinate (a water-soluble salt) in nearly quantitative. This salt was then heated to form desired product **(69)** with the elimination of hydrogen sulfide [98-100].

Thiocarbohydrazide (69) Crystalline needles; Yield: 88 %; m.p.: 171-174 ºC; R_f : 0.6 (*n*-hex : EtOAc 8:2); **^{1}H-NMR (DMSO-d_6):** δ (ppm) = 4.47 (s, 4H, NH2), 8.68 (d, 2H, NH).

4.7 General Procedure for the 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones (70a-d)

Equimolar amounts of thiocarbohydrazide (0.1 mol) and various acids **68a-d** (0.1 mol) were reacted at their respective melting points to afford simultaneous cyclization giving 3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-arylidenethiazolidine-2,4-diones **(70a-d)** [101].

3-[(4-Amino-5-mercapto-1,2,4-triazol-3-yl)methyl]-5-benzylidenethiazolidine-2,4-dione (70a) Orange solid; Yield: 70 %; m.p.: 210-212 ºC; R_f : 0.7 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1745, 1679 (C=O), 2950 (sp^3 C-H Stretch), 1607 (C=N), 3325 (N-H Str.); **^{1}H-NMR (DMSO-d_6):** δ (ppm) = 13.1 (1H, s, SH), 5.64 (2H, s, NH_2), 4.91 (2H, s, CH_2), 7.99 (1H, s, H-6), 7.51-7.67 (5H, m, H-2', H-3', H-4', H-5', H-6').

5-(4-Methylbenzylidene)-3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]thiazolidine-2,4-dione (70b) Orange solid; Yield: 72 %; m.p.: 181-184 ºC; R_f : 0.8 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1746, 1675 (C=O), 2944 (sp^3 C-H Stretch), 1611 (C=N), 3329 (N-H Str.); **^{1}H-NMR (DMSO-d_6):** δ (ppm) = 13.00 (1H, s, SH), 5.59 (2H, s, NH_2), 4.63 (2H, s, CH_2),

7.87 (1H, s, H-6), 7.56-7.59 (2H, d, H-2', H-6'), 7.36-7.40 (2H, d, H-3', H-5').

5-(4-Methoxybenzylidene)-3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]thiazolidine-2,4-dione (70c) Light brown solid; Yield: 67 %; m.p.: 206-209 ºC; R_f : 0.8 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1743, 1676 (C=O), 2951 (sp^3 C-H Stretch), 1609 (C=N), 3324 (N-H Str.); **^{1}H-NMR (DMSO-*d*$_6$):** δ (ppm) = 12.8 (1H, s, SH), 5.61 (2H, s, NH_2), 4.66 (2H, s, CH_2), 7.82 (1H, s, H-6), 4.72 (3H, s, OCH_3), 7.41-7.45 (2H, d, H-2', H-6'), 7.36-7.39 (2H, d, H-3', H-5').

5-(4-Chlorobenzylidene)-3-[(4-amino-5-mercapto-1,2,4-triazol-3-yl)methyl]thiazolidine-2,4-dione (70d) Light brown solid; Yield: 63 %; m.p.: 173-178 ºC; R_f : 0.6 (*n*-hex : EtOAc 6:4); **IR** (neat, cm^{-1}): 1742, 1671 (C=O), 2950 (sp^3 C-H Stretch), 1606 (C=N), 3323 (N-H Str.); **^{1}H-NMR (DMSO-*d*$_6$):** δ (ppm) = 12.9 (1H, s, SH), 5.63 (2H, s, NH_2), 4.22 (2H, s, CH_2), 7.80 (1H, s, H-6), 7.43-7.47 (2H, d, H-2', H-6'), 7.39-7.45 (2H, d, H-3', H-5').

4.8 Synthesis of Benzohydrazide (73)

Benzoic acid (0.02 mol) was treated with sulphuric acid in dry distilled methanol to produce its methyl ester. The mixture of methyl benzoate (1.35 mL, 0.01 mol) and hydrazine hydrate (0.58 mL, 0.012 mol) was taken in a round bottom flask and refluxed for 4 hours [112,113]. The reaction mixture was cooled to room temperature to afford precipitation. The precipitates formed were filtered and washed carefully with water.

Benzohydrazide (73) White Crystals; Yield: 86 %; m.p.: 113-115 ºC; R_f : 0.2 (*n*-hex : EtOAc 6:4).

General Procedure for the Synthesis of 5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione (74)

A mixture of benzohydrazide (0.001 M) was treated with 0.001 M of 2-(5-arylidene-2,4-dioxothiazolidin-3-yl) acetic acid in the presence of phosphorus oxychloride (10 mL). The reaction mixture was refluxed for 6-8 hours. After completion of reaction, the reaction mixture was slowly poured over crushed ice and kept overnight.

The precipitates formed were filtered, treated with dilute NaOH, washed with water and recrystallized from ethanol [86].

5-benzylidene-3-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]thiazolidine-2,4-dione (74) Reddish brown solid; Yield: 85 %; m.p.: 168-172 ºC; R_f : 0.5 (*n*-hex : EtOAc 7:3); **IR** (neat, cm^{-1}): 1747, 1682 (C=O), 1603 (C=N), 1140 (C-O-C); **^{1}H-NMR (DMSO-d_6):** δ (ppm) = 5.22 (2H, s, CH_2), 8.02 (1H, s, H-6), 7.52-7.99 (10H, m, H-2', H-3', H-4', H-5', H-6', H-2''', H-3''', H-4''', H-5''', H-6'''); **^{13}C-NMR (DMSO-d_6):** δ (ppm) = 167.27, 165.25 (C=O), 165.11, 161.59 (N=C-O), 36.27 (CH_2), 121.17-134.44 (C-1', C-2', C-3', C-4', C-5', C-6', C-1''', C-2''', C-3''' C-4''', C-5''', C-6''').

Chapter-4

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