Ain Shams University
Faculty of Science
Chemistry Department

Synthesis of heterocyclic compounds containing nitrogen atom of expected biological activity

A Thesis submitted for the degree of Master of Science
as a Partial fulfillment for requirement of the Master of Science

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Approval Sheet

"Synthesis of heterocyclic compounds containing nitrogen atom of expected biological activity"

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Finally, deep thanks to my family, my friends and for all people who helped me to finish this work.

Mina Girgis

Aim of the work

The research aims to achievement of the following goals.

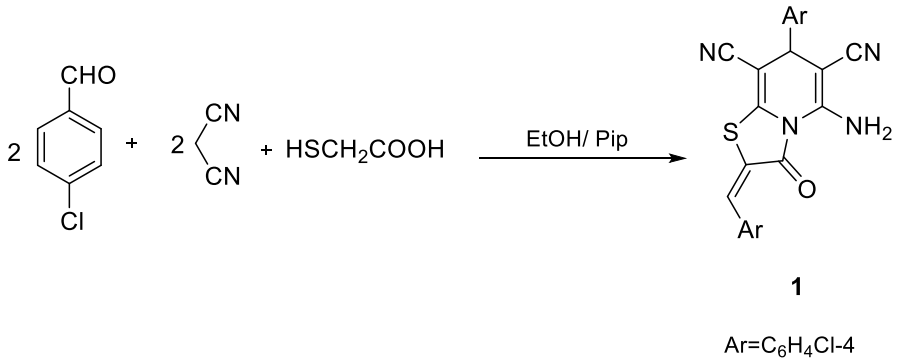
1. Synthesize of 5-amino-2-(4-chlorobenzylidene)-7-(4-chlorophenyl) -3-oxo-2, 3-dihydro-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile.
2. Using of thiazolo[3,2-a]pyridine-6,8-dicarbonitrile derivative as a key starting material for synthesis of new heterocyclic compounds.
3. Study the reactivity of 5-amino-2-(4-chlorobenzylidene)-7-(4-chlorophenyl)-3-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile towards different electrophilic and nucleophilic reagents.
4. Elucidation of the structural features of the synthesized compounds *via* elemental analysis and spectrometric methods such as IR., MS.and ^{1}H-NMR Spectra.
5. Evaluation the biological activity of the synthesized compounds as anticancer activity.

Keywords: Thiazolopyridine, thiazolopyridopyrimidine, isoxazolo thiazolopyridine, Pyrano thiazolopyridine and pharmacological activities.

Summary

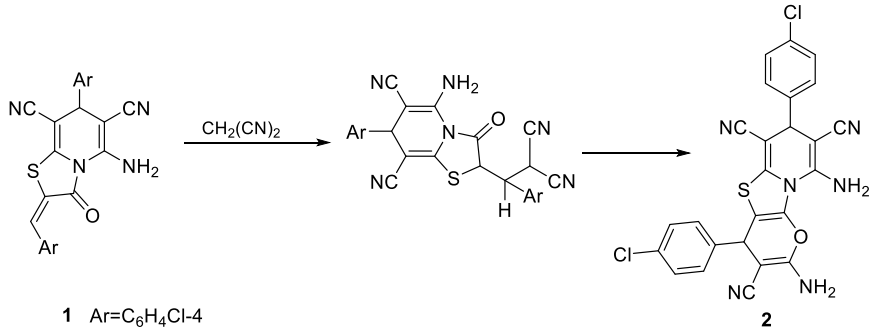
The original work of this thesis can be classified into two parts:

The first part deals with synthesis of 5-amino-2-(4-chlorobenzylidene)-7-(4-chlorophenyl)-3-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-6,8-dicarbo nitrile **1** by the one-pot multicomponent reactions (MCRs) of *p*-chloro benzaldehyde, malononitrile and thioglycolicacid (2:2:1 molar ratio) in absolute ethanol in the presence of a catalytic amount of piperidine in good yields **(Scheme 1)**.



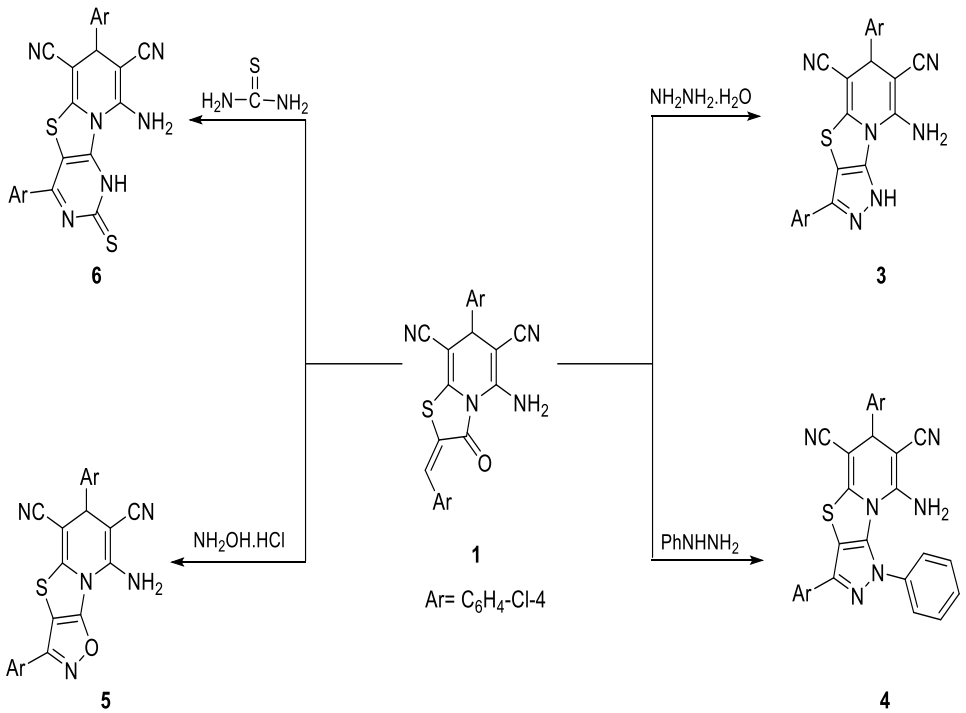
(Scheme 1)

Treatment of **1** with malononitrile afforded 4H,7H-pyrano [2',3':4,5] thiazolo[3,2-a] pyridine-3,6,8-tricarbonitrile derivative **2 (Scheme 2)**.



(Scheme 2)

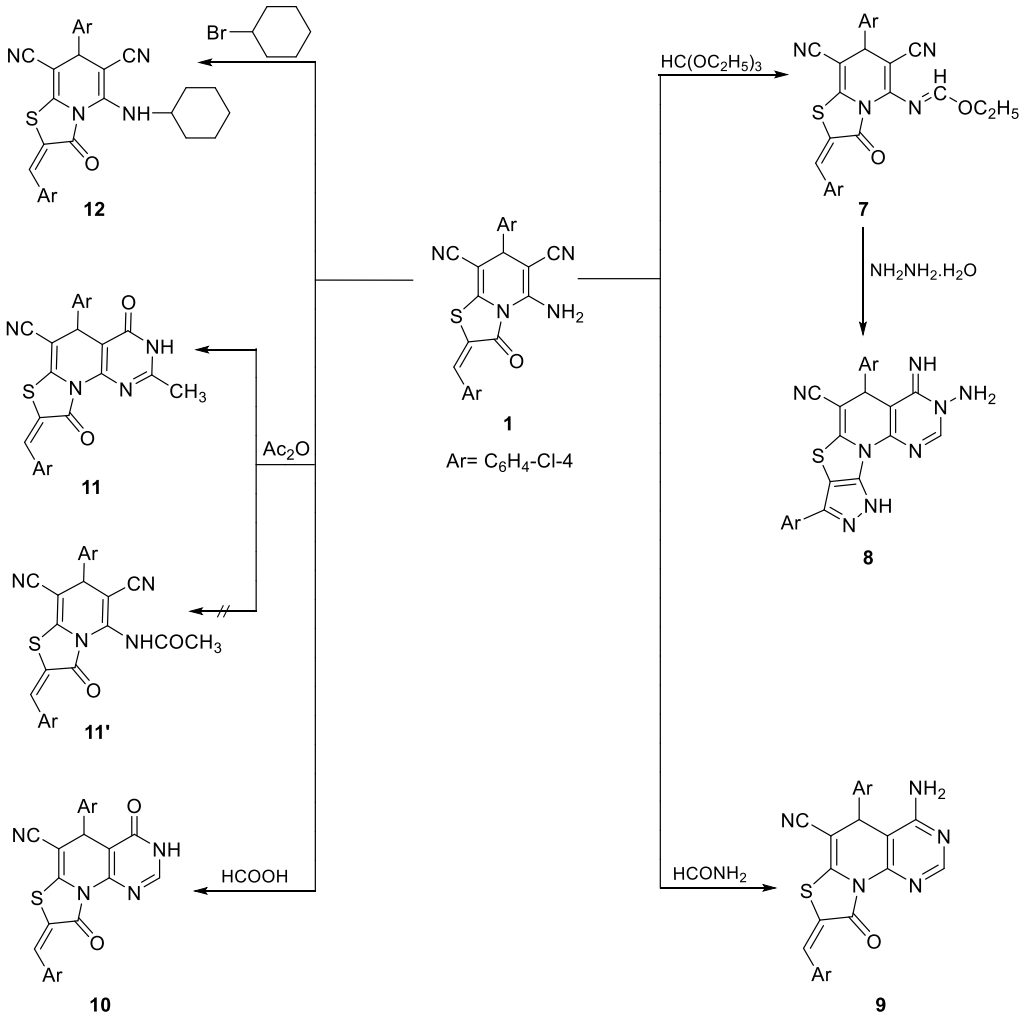
Compound **1** proved to be a useful key intermediate for synthesis of new fused heterocyclic derivatives. Thus, treatment of **1** with hydrazine derivatives (binucleophile) afford the corresponding pyrazolo [3',4':4,5]thiazolo[3,2-a]pyridine derivatives **3, 4**. On the other hand, reaction of **1** with hydroxylamine hydrochloride afforded isoxazolo[5',4':4,5]thiazolo[3,2-a] pyridine derivative **5**. When compound **1** allowed to react with thiourea, 9-amino-4,7-bis(4-chlorophenyl)-2-thioxo-1,2-dihydro-7H-pyrido[2',1':2,3]thiazolo[4,5-d]pyrimidine-6,8-dicarbonitrile **6** was obtained **(Scheme 3)**.



(Scheme 3)

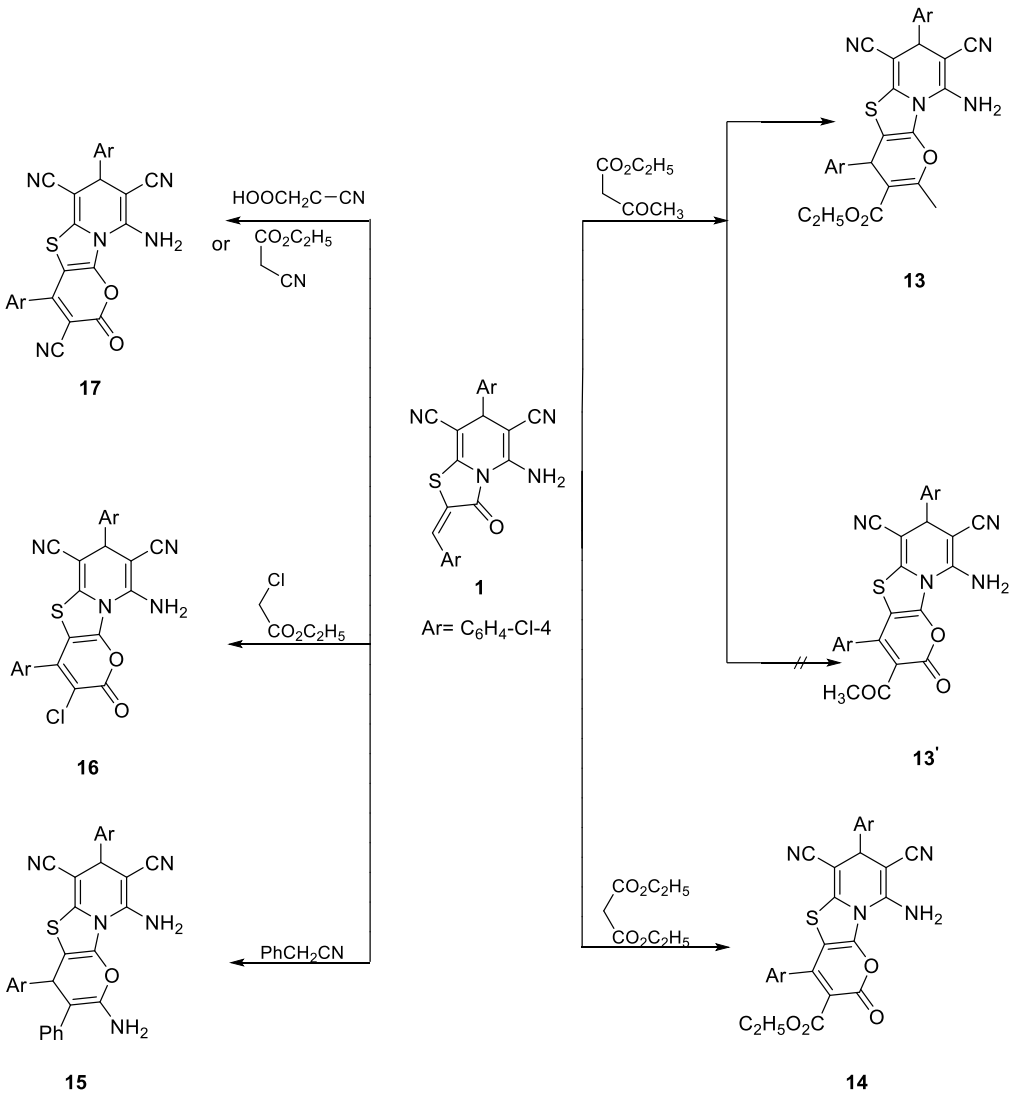
Thiazolo[3,2-a]pyridine derivative **1** when treated with triethylorthoformate gave the corresponding ethyoxymethylene derivative **7**, which underwent hydrazonolysis and cyclization to give pyrazolo [3",4":4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine-6-carbonitrile **8**.

Furthermore, treatment of **1** with formamide and formic acid gave the corresponding thiazolopyridopyrimidine derivatives **9** and **10** respectively. On the other hand, the reaction of **1** with acetic anhydride afforded 2-methyl-4,9-dioxo-3,5,8,9-tetrahydro-4H-thiazolo[3',2':1,6]pyrido [2,3-d]pyrimidine-6-carbonitrile derivative **11**. Alkylation of Thiazolo[3,2-a] pyridine derivative **1** with alkylating reagent such as bromo cycloalkane gave 5-(cyclohexylamino)-3-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile derivative **12 (Scheme 4).**



(Scheme 4)

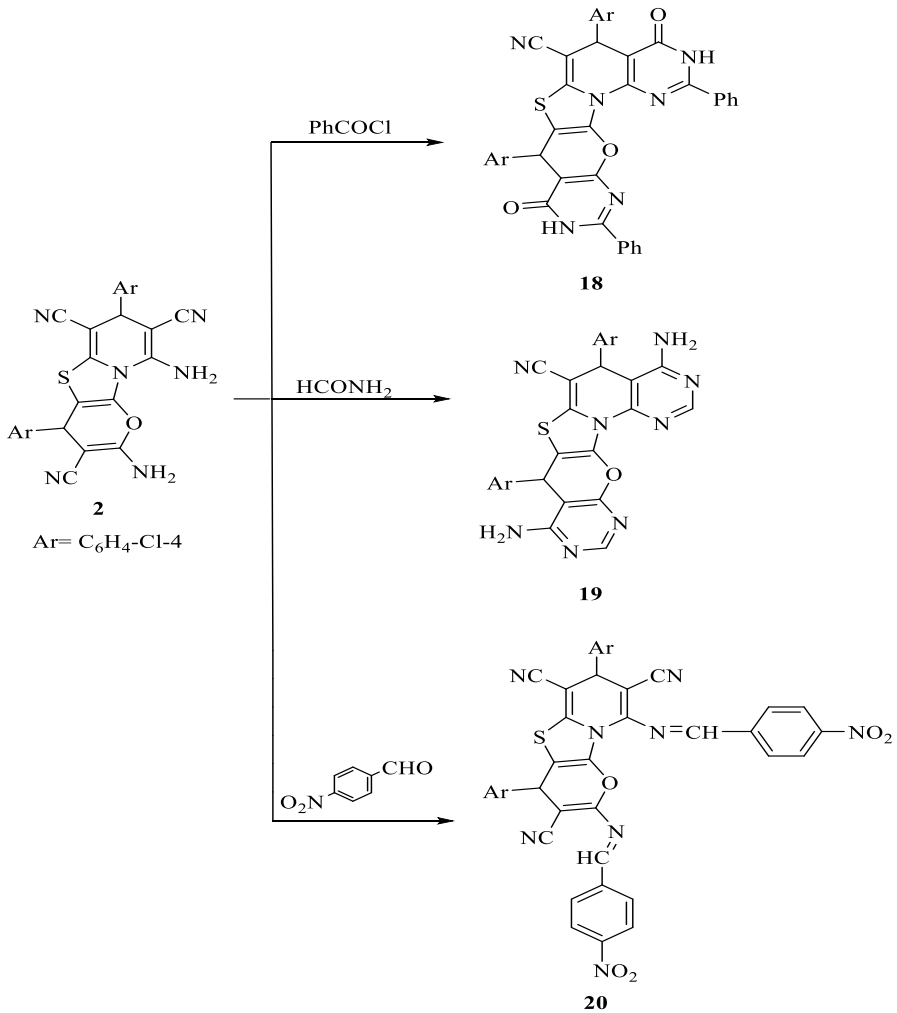
Pyrano [2',3':4,5] thiazolo [3,2-a]pyridine derevatives **13**, **14**, **15**, **16, 17** were obtaineded when compound **1** was reacted with different active methylene compounds such as ethylacetoacetate, diethylmalonate, benzylcyanide, ethylchloroacetate, cyanoaceticacid and/ or ethylcyanoacetate respectively **(Scheme 5)**.



(Scheme 5)

Reaction of pyrano[2',3':4,5]thiazolo[3,2-a]pyridine- derivative **2** with benzoylchloride and formamide gave in a 'one step reaction' pyrimidino[3'",4'":5",6"]pyrano[2",3":4',5']thiazolo[3',2':1,6]pyrido[2,3-d]pyrimidine derivatives **18** and **19** respectively.

Furthermore, 4,7-bis(4-chlorophenyl)-2-((-4-nitrobenzylidene) amino)-9-((4-nitrobenzylidene)amino)-4H, 7H- pyrano [2',3':4,5] thiazolo[3,2-a]pyridine-3,6,8-tricarbonitrile **20** was obtained by reaction of **2** with *p*-nitrobenzaldehyde **(Scheme 6)**.



(Scheme 6)

Anti-cancer activity:

Most of the synthesized compounds were tested for their anti-cancer activity against two human anticancer cell lines (HePG2, MCF-7).

The results showed that compounds **3** and **8** have a very strong cytotoxicity, while compounds **2**, **15** and **19** possess a strong cytotoxicity; however compounds **4**, **5**, **6**, **9**, **12** and **17** exerted a moderate cytotoxicity, furthermore compounds **1**, **11**, **13**, **16** and **20** showed a weak cytotoxicity against HePG2.

In continuation, compounds **3** and **8** have a very strong cytotoxicity, while compounds **2**, **6**, **15** and **19** possess a strong cytotoxicity; however compounds **4**, **5**, **9**, **12**, **13** and **17** exerted a moderate cytotoxicity, furthermore compounds **1**, **11**, **16**, **18** and **20** showed a weak cytotoxicity against MCF-7.

I-Chemistry of 4-thiazolidinones

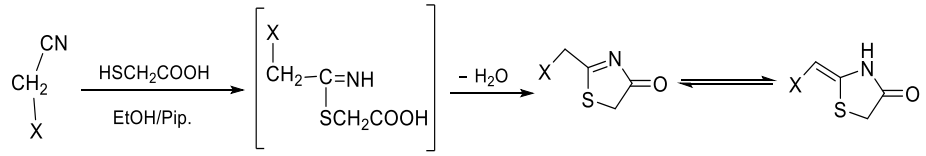
A comprehensive review [1] has been written on 4-thiazolidinones in 1961. Later on, a review article [2] appeared which deals with the use of thiazolidinones derivatives as stabilizers for polymeric materials. Recently two reviews [3, 4] the main objective of the present survey is to provide a comprehensive account of the synthetic utility of 4-thiazolidinones in building various organic compounds. Thiazolidine derivatives such as thiazolidinones belong to an important category of heterocyclic compounds containing S and N elements in a five membered ring. A many research works on thiazolidinones have been reported in the past. Also, the nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities [5] .various substituted 4-thiazolidinone derivatives are associated with diverse pharmacological activities such as antitumor [6, 7], anti-diabetic [8], anti-Parkinson [9], antivirals [10], anthelmintic [11], anti-inflammatory, anti- proliferative, antihistaminic, anti-HIV [12-14] and antibacterial activities [15] .

1-Synthesis of 4-thiazolidinone derivatives:

Several methods for synthesis are available in literatures which involve conventional one pot, two pot synthesis as well as combinatorial synthesis methods [5].

1. From activated nitriles:

Cyclization of nitriles **1 a-c** with thioglycolic acid at room temperature (R.T.) in ethanolic solution with drops of piperidine afforded 4-thiazolidinone derivatives **2 a-c** [16].

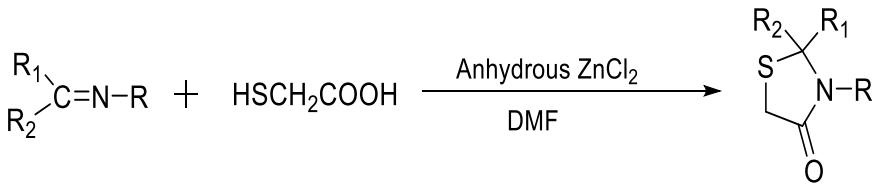


1 a-c **2 a-c**

X= a; CN
b; $CO_2C_2H_5$
c; $CONH_2$

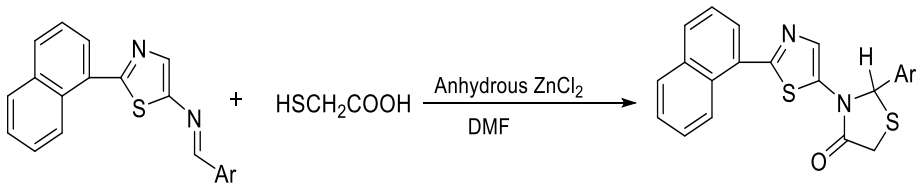
2. From imines:

Imines **3** obtained by condensation of ketones and amines which treated with thioglycolic acid in N,N-dimethyl formamide (DMF) and anhydrous zinc chloride gave 4-thiazolidinone derivatives **4** [17].



3 **4**

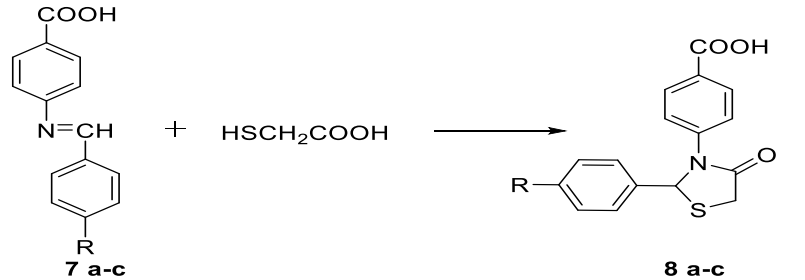
Also, derivatives **6 a-e** were obtained by reaction of 4-(naphthalene-1-yl) thiazol-2-amine derivatives **5 a-e** with thioglycolic acid [18].



5 a-e **6 a-e**

Ar= a; C_6H_5
b; C_6H_4-OCH_3-4
c; C_6H_4-OH-4
d; C_6H_4-OH-2
e; C_6H_4-CH_3-4

4-(4-Oxo-2-*p*-alkylphenylthiazolidin-3-yl)benzoic acid derivatives **8 a-c** have been synthesized through the reaction of compound **7 a-c** with thioglycolic acid under reflux conditions [19].

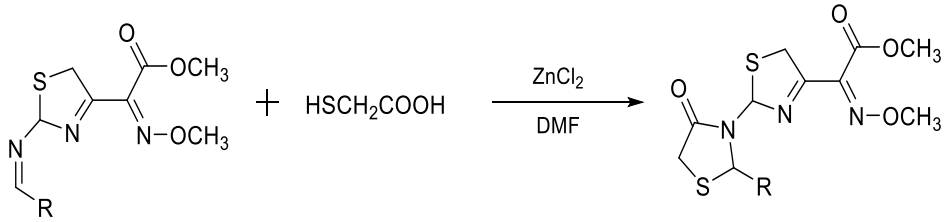


7 a-c

8 a-c

R= a; $N(CH_3)_2$
b; OH
c; NO_2

The hetero cyclization of alkyl or aryl 2-(2-ethylidene amino-2,5-dihydrothiazol-4-yl)-2-(methoxyimino) acetate **9 a,b** with thioglycolic acid afforded 4-thiazolidinone derivatives **10 a, b** [20-21].

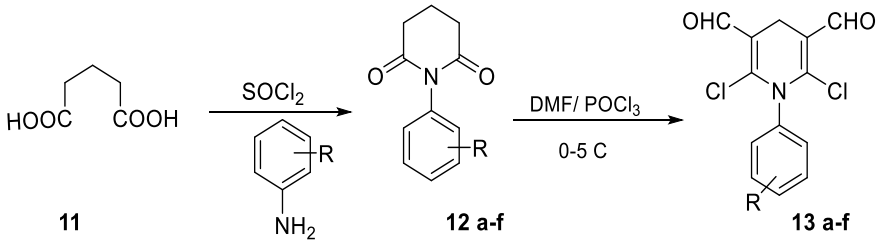


9 a, b

10 a, b

R= a; C_6H_5
b; C_6H_5-Cl-4

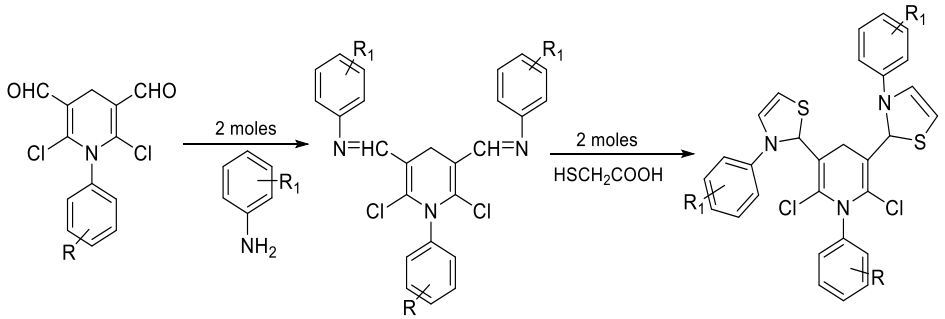
Treatment of Glutaric acid **11** with aromatic amines gave N- substituted phenyl glutarimides **12 a-f** which were then diformylated using Vilsmeier-Haack reaction to form **13 a-f** [22].



11 **12 a-f** **13 a-f**

R =a; -H
b; -4-CH_3
c; -2-Cl
d; -4-Cl
e; -3-Cl
f; -4-OCH_3

Refluxing of 2,6-dichloro-1-(N-substituted phenyl)-1,4-dihydro pyridine-3,5-dicarbaldehyde **13 a-f** with two different aromatic primary amines (1:2 molar ratio) in water bath for 4-5 hours using ethanol as solvent and few drops of glacial acetic acid afforded **14 a-f** [34]. General procedure for synthesis of 4-thiazolidinone derivatives **15 a-f**, the Schiff bases **14 a-f** allowe to react with thioglycolic acid (1:2 molar ratio) in the presence of anhydrous $ZnCl_2$ for 7 hours to give **15 a-f** [22].



13 a-f

14 a-f
R = a; -H
b; -4-CH_3
c; -2-Cl
d; -4-Cl
e; -3-Cl
f; -4-OCH_3

15 a-f
R_1= a; -4-Me
b; -4-Cl