Section A -Research paper

A review on different synthetic approaches for potential Thiazolidine-4-One nucleus derivatives as anticancer agents

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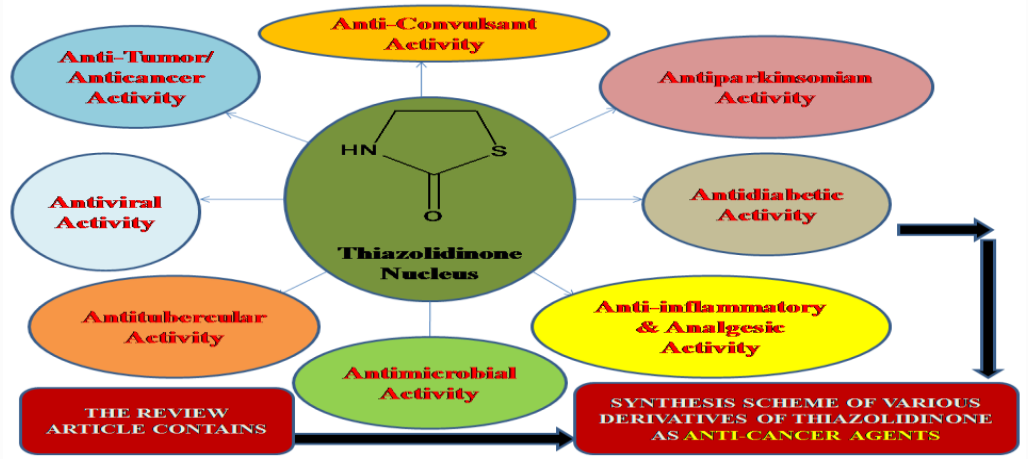
Abstract

The review covers different synthetic approaches for thiazolidinone-4-one derivatives with their anticancer activity was also discussed in this paper. Thus, this study may assist to produce more potent and efficient thiazolidinone-4-one derivatives compounds as anticancer agents. Accessible information can be utilized as a practical clue for the rational design of novel small molecules with potent biological activity among thiazolidin-4-ones nucleus. The Research & Development in the area of anticancer is occurring towards the path where the new elements are created which are low in toxicity and are with further developed action. Thiazolidinone-4-one and its derivatives signify a very imperative class of heterocyclic compounds, which have miscellaneous therapeutic actions. As of late, numerous dynamic mixtures incorporated are extremely compelling; with thiazolidinone-4-one moiety have likewise demonstrated to be powerful towards malignant growth.



Keywords:

Thiazolidin-4-ones; Structure activity relationship; Biological Activities; Heterocyclic compounds; Cytotoxicity; Anticancer drug.

1. Introduction

Thiazolidinones (TZDs) falls in the class of heterocyclic compounds and known as the activators of peroxisome proliferator activated receptors (PPARs) specifically PPARγ (PPAR-gamma) gathering of atomic receptors broadly utilized for the cure of type 2 diabetes. Lately, Thiazolidinediones, PPAR gamma ligands also investigated to exhibit anticancer action in a boundless malignant growth models by upsetting various cell cycle, its multiplication, separation and apoptosis as well as halting cancer angiogenesis.[1]

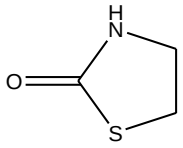
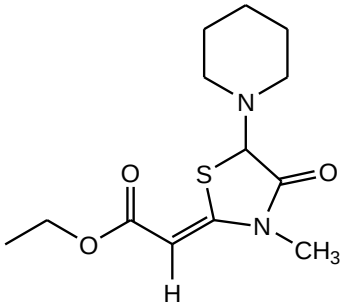
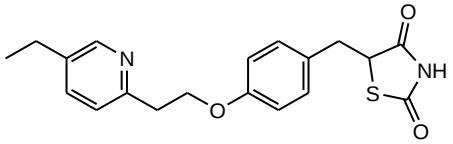


Figure 1. Structure of Thiazolidinone ring [1].

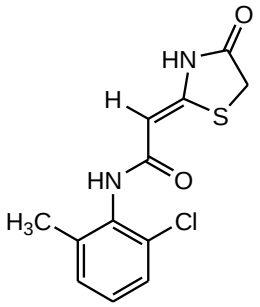
The class of heterocyclic compounds containing nitrogen, sulfur, and thiazole nucleus comprises center design of various organically intriguing mixtures. Writing overview shows that thiazole subordinates assume a vital part in organic fields such as antimicrobial, antidiabetic, antiviral, anti-inflammatory, anti-tuberculosis, and anticancer exercises. 1, 2, 4-Triazole is among the different heterocyclic that stands during last previous decades for a long time as dormant antimicrobial specialists. Schiff base have diverse antimicrobial as well as antifungal movements, and it tends to be ready by the corrosive catalyzed response of different carbonyl compounds and amines. Thiazolidin-4-one subordinates are familiar to gives different pharmacological activities for example, antidiarrheal, anticonvulsant, antimicrobial, antidiabetic, antihistaminic, anticancer, against HIV, cyclooxygenase inhibitory, antiplatelet initiating factor.[2] Thiourea on reaction with acetylenic esters differently answered to exhibited thiazoline-4-one nucleus, known as imidazolinthion or 1, 3-thiazin-4-one. Lateral research shown that as a matter of fact the principal nucleus is thiazoline-4-one. Thiazolidinones with their subordinates have drawn in proceeding interest in light of their possible jobs as antitumor and anticancer specialists in chemotherapy.[3-9] The 1, 3-thiazolidine-4-one framework act as a center for numerous engineered accumulates of extraordinary interest in therapeutic science. This platform is an underlying part of different natural products, like thiamine (vitamin B1), acidomycin (confined from different species of Streptomycin) and numerous metabolic products (cytotoxic cyclopeptides) of growths and crude marine creatures. A few thiazolidine-4-one based medications, for example, ralitoline (anticonvulsant), etozoline (circle diuretic) and pioglitazone (oral enemy of diabetic medication) have previously been endorsed for remedial use (Fig. 2). Writing evidences for thiazolidine-4-one framework shows significant organic impacts, for example, calming, cancer prevention agent, platelet-actuating factor (PAF) adversary, cyclooxygenase (COX) restraint, growth putrefaction factor along with anticancer, anticonvulsant, antimicrobial, antiviral and hostile to HIV impacts.[10-19] Thiazolidinones compounds falls in the category of heterocyclic bearing 5 member saturated ring containing thio ether, amino at 1 and 3 position with carbonyl group. Thiazolidinones also known to be sulfur analogue of oxazolidine. The condensation reversible reaction between thiol and aldehyde or ketone gives thiazolidinone. Thiazolidinone are prone to hydrolysis in aqueous solution. On hydrolysis thiazolidinone again gives back thiol and aldehyde from where it was synthesized.[20]



Etozoline



Pioglitazone



Ralitoline

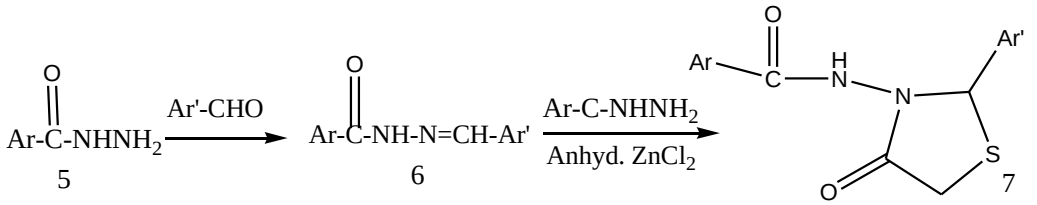
Figure 2. Illustrative drug containing Thiazolidinone nucleus.[10-19]

The study of five-membered heterocyclic rings bearing two heteroatoms has been an intriguing field of read up for a really long time. Among which 4-thiazolidinone ring framework has been concentrated widely as it contains basic structure in different synthesized analogous with a significant framework familiar to be related with a few organic schemes. The writing overview uncovered this 4-thiazolidinone nucleus subbed at positions 2, 3 and 5, yet replacement at 2-position explicitly gives primarily different with strong subordinates.[21]

2. Synthesis of 4-thiazolidinone derivatives

2.1. Synthesis of 2-substituted-4-thiazolidinones derivatives

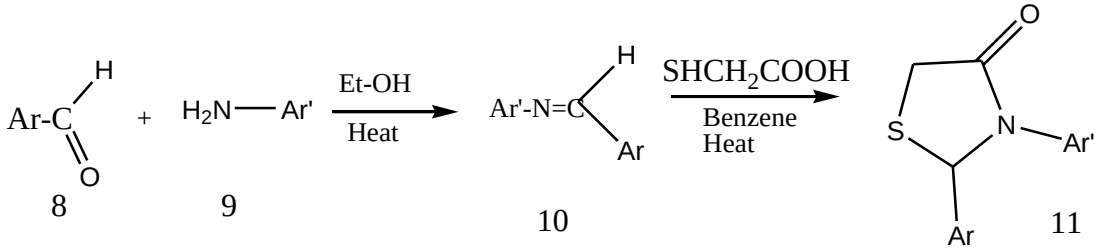
Corresponding hydrazones **6** formed from the reaction between acid hydrazide **5** with aromatic aldehyde, and on further proceedings hydrazones **6** gives 2-substituted-4-thiazolidinones **7** on reaction with thioglycolic acid in presence of methanol.[22]



5 6 7

2.2. Synthesis of N-substituted-4-thiazolidinones derivatives

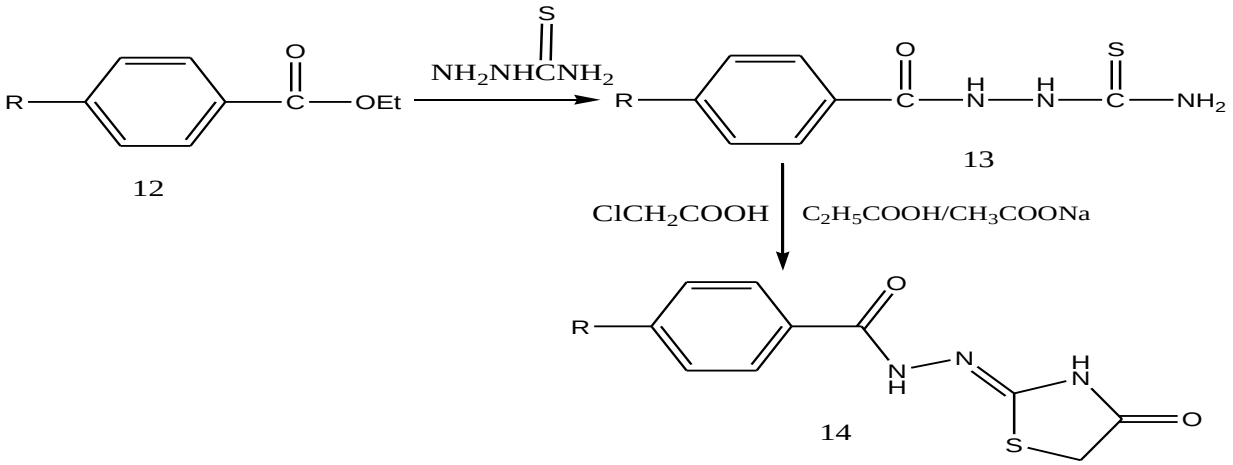
Thiazolidinones **11** synthesized by reacting an amine, a carbonyl compound with mercapto corrosive divided between two stages. Responses of first stage further carried out with introductory development of imine (Nitrogen desubstituted from amine and substitute with carbonyl group), Second stage involves sulfur nucleophile assault followed by intramolecular cyclization with removal of water.[23]



8 9 10 11

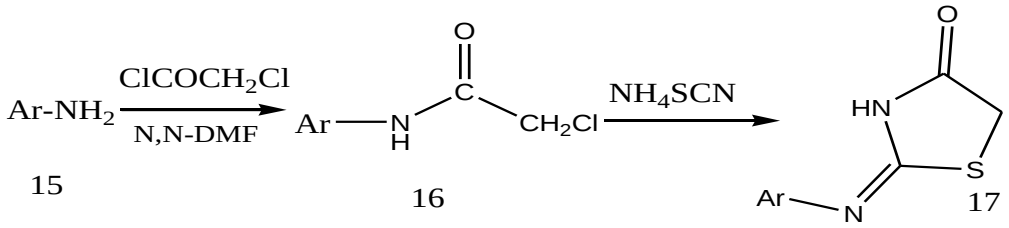
2.3. Synthesis of 2-hydrazine substituted-4-thiazolidinones derivatives

Aromatic ester **12** on reaction with thiosemicarbazide gives the intermediate Hydrazine carbothioamide **13** which on further reaction with chloroacetic acid and sodium acetate gives thiazolidin-4-one derivative **14**.[24]



2.4. Synthesis of 2-phenylamine substituted-4-thiazolidinones derivatives

Chloroacetyl chloride in presence of DMF reacts with desirable amine resulting in formation of intermediate acetamide which on further undergoes cyclisation to give finally thiazolidin-4-ones **17** in presence of ammonium thiocyanate.[25]



3. SAR (Structural Activity Relationship) of thiazolidinone nucleus

The SAR of 4-Thiazolidinone shows various different biological activities by different substitutions at position R_1, R_2 and R_3 on 4-Thiazolidinone nucleus given in **Figure 3**.[21]

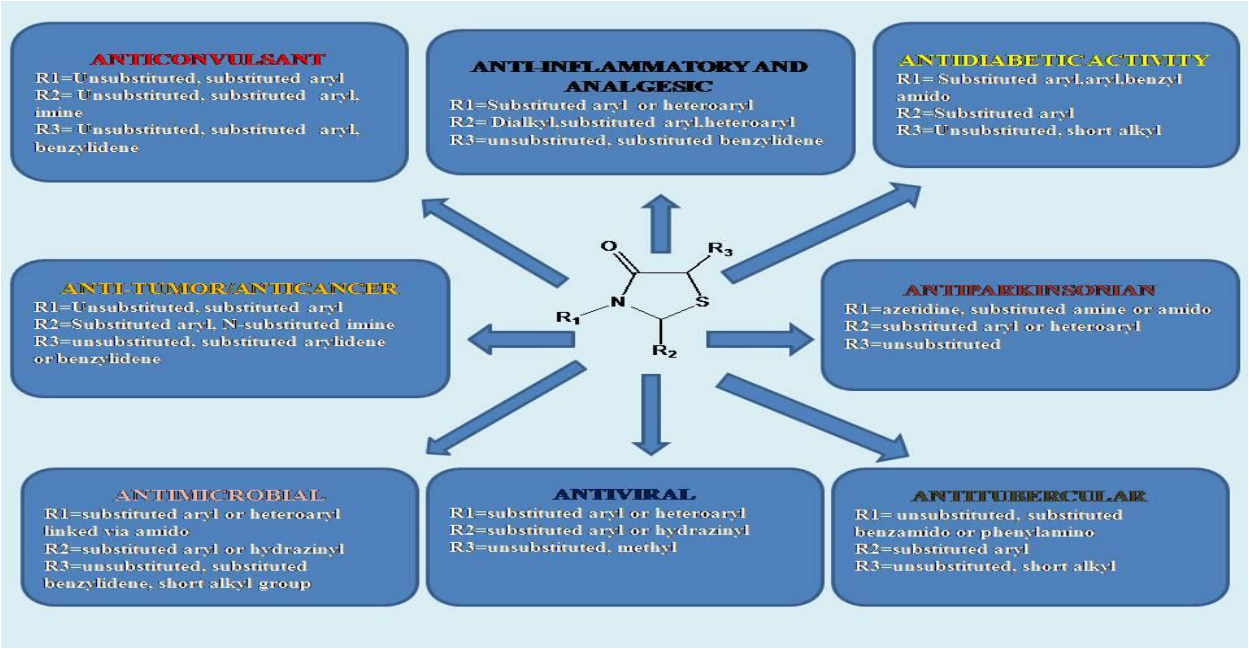
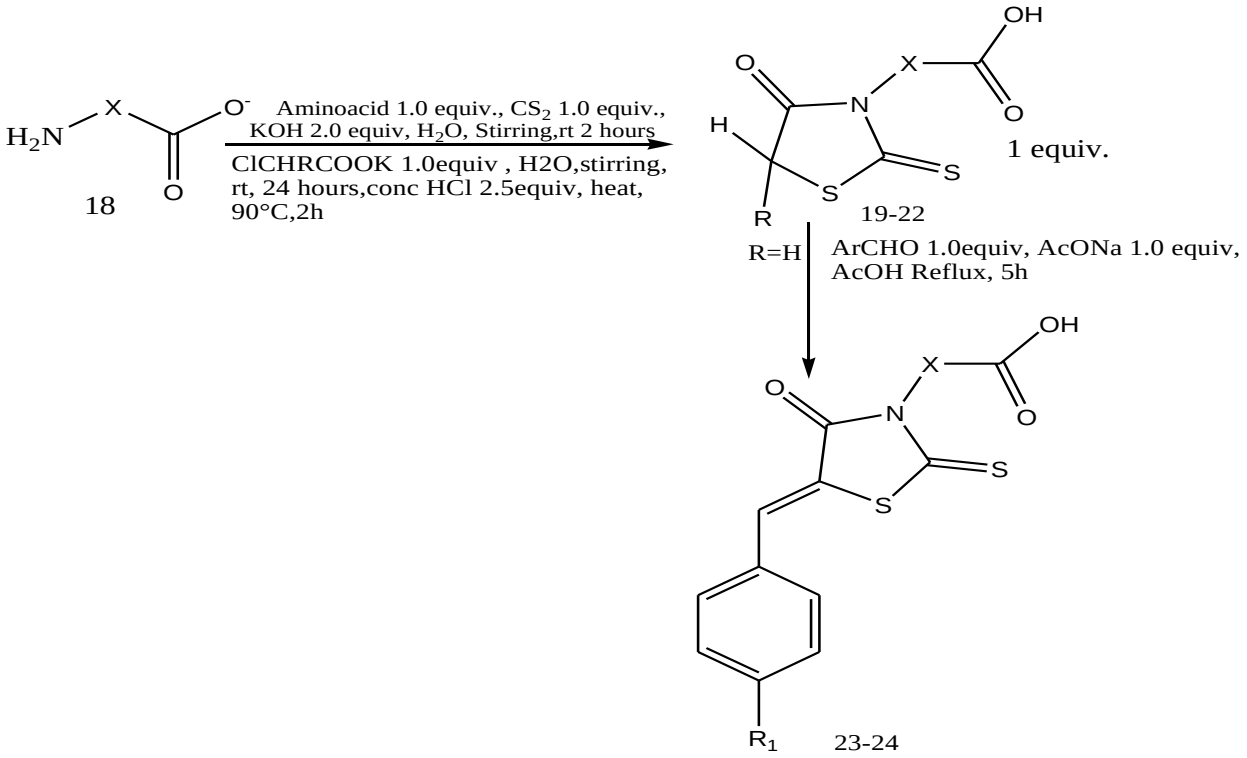


Figure 3. SAR of Thiazolidinone nucleus [21].

4. Synthesis of different thiazolidinone compounds as anticancer agents

4.1. Synthesis of Phenyl substituted thiazolidinone compounds:

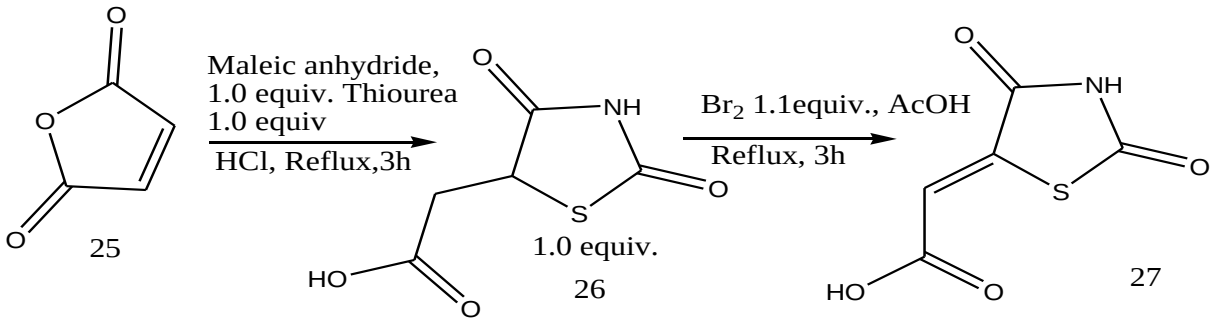
The scheme involves [2+3]-cyclocondensation of the compound dithiocarbaminates **18** (in situ preparation) and α-chlorocarboxylic acid results in 5-unsubstituted and 5-ethylrhodanine-3-carboxylic acids **19-22**. The intermediate undergoes Knoevenagel condensation with aromatic aldehydes results in the modification at C-5 position of core ring **23-24**.[26]



	R	R_1	X
19	H	-	CH_2
20	H	-	$(CH_2)_2$
21	H	-	$(CH_2)_5$
22	Et	-	CH_2
23	-	MeO	CH_2
24	-	Me_2N	$(CH_2)_2$

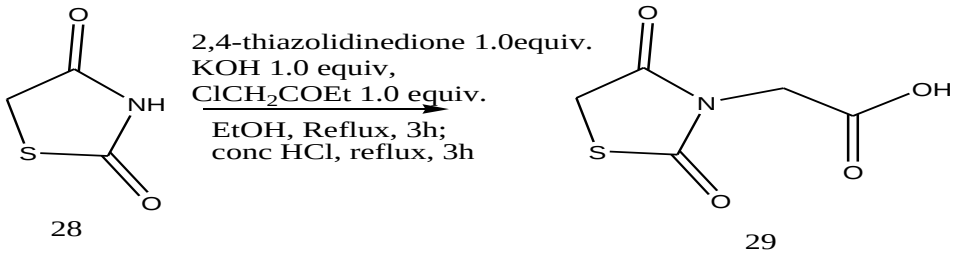
4.2. Synthesis of compound 2, 4-dioxo-thiazolidin-5-ylidene-acetic acid:

It involves one phase maleic anhydride method for the synthesis of analogue 2, 4-Thiazoliodinedione-5-carboxylic acids **26-27** by condensation reaction. Further the reaction involves acid hydrolysis and bromination for synthesis of 2, 4-dioxo-thiazolidin-5-ylidene-acetic acid **27**.[27-28]



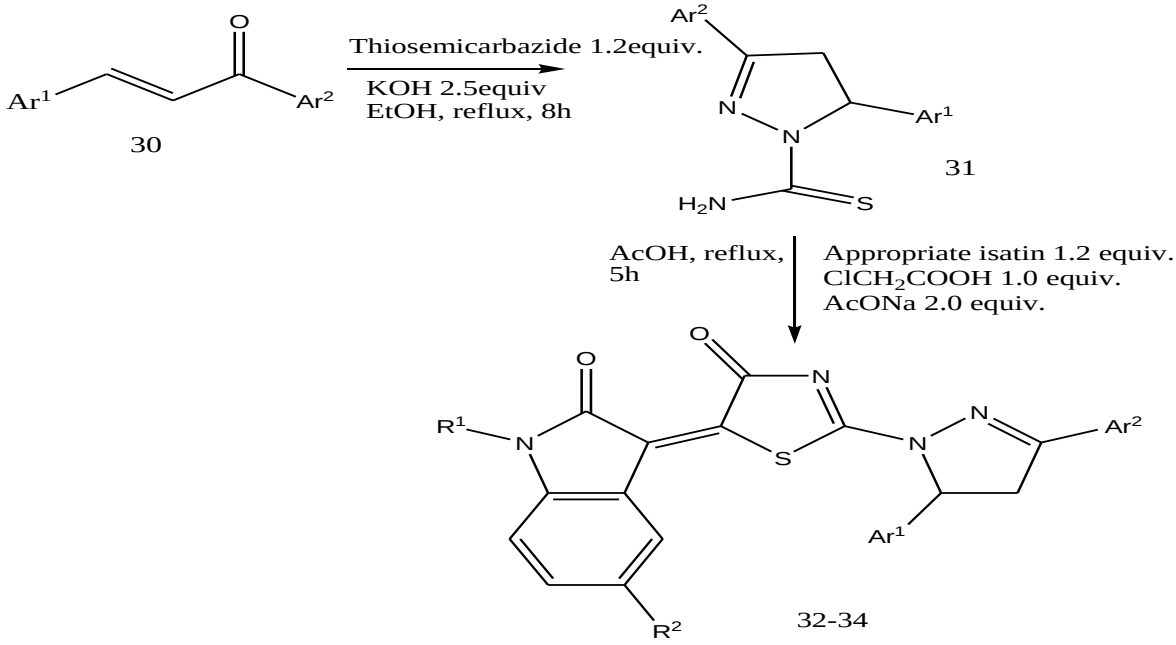
4.3. Synthesis of compound 2, 4-Thiazolidinedione-3-acetic acid:

2, 4-thiazolidinedione **28** undergoes alkylation to form 2, 4-Thiazolidinedione-3-acetic acid **29**.[29]



4.4. Synthesis of different analogues of 3-[2-(3,5-Diaryl-4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-ylidene]-2,3-dihydro-1H-indol-2-ones:

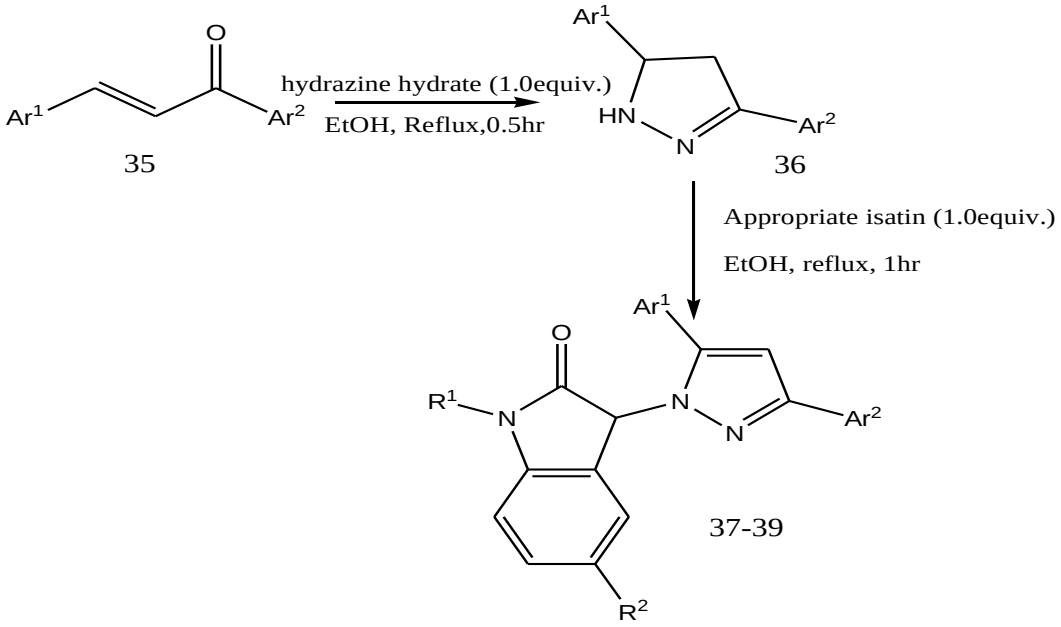
Diarylketone **30** on reflux reaction with thiosemicarbazide, potassium hydroxide and ethanol as solvent gives 3,5-diaryl-1-thiocarbamoyl-2-pyrazolines intermediate **31** which on further reaction with chloroacetic acid and isatins in appropriate manner with sodium acetate and refluxing solvent as acetic acid gives 3-[2-(3,5-Diaryl-4,5-dihydropyrazol-1-yl)-4-oxo-4,5-dihydro-1,3-thiazol-5-ylidene]-2,3-dihydro-1H-indol-2-ones **32-34**.[30]



Thiazolidinone Analogues	Ar^1	Ar^2	R^1	R^2
32	2-OH-C_6H_4	Ph	H	Br
33	4-OMe-C_6H_4	4-OMe-C_6H_4	H	Cl
34	4-Cl-C_6H_4	naphthalen-2-yl	H	H

4.5. Synthesis of different analogues of 3-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-3-hydroxy-2,3-dihydro-1H-indol-2-ones by dehydrogenation of pyrazoline cycle:

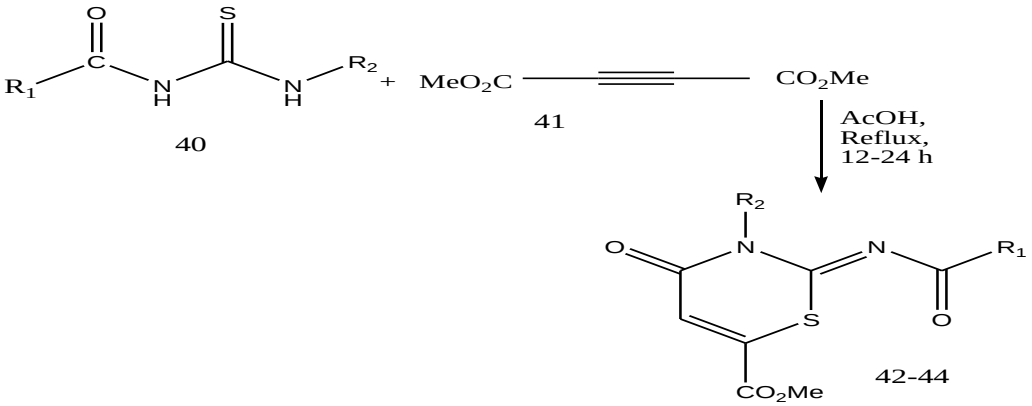
Diarylketone **35** on reaction with hydrazine hydrate gives intermediate compound **36** which further involves its secondary amine nucleophilic attack on isatin to give 3-(3,5-diaryl-4,5-dihydropyrazol-1-yl)-3-hydroxy-2,3-dihydro-1H-indol-2-ones by dehydrogenation of pyrazoline cycle **37-39**.[31]



Thiazolidinone Analogues	Ar^1	Ar^2	R^1	R^2
37	2-OH-C_6H_4	Ph	CH_2COOH	H
38	4-OMe-C_6H_4	4-OMe-C_6H_4	H	Br
39	4-Cl-C_6H_4	naphthalen-2-yl	H	Br

4.6. Synthesis of different analogues of 1, 3-thiazinones :

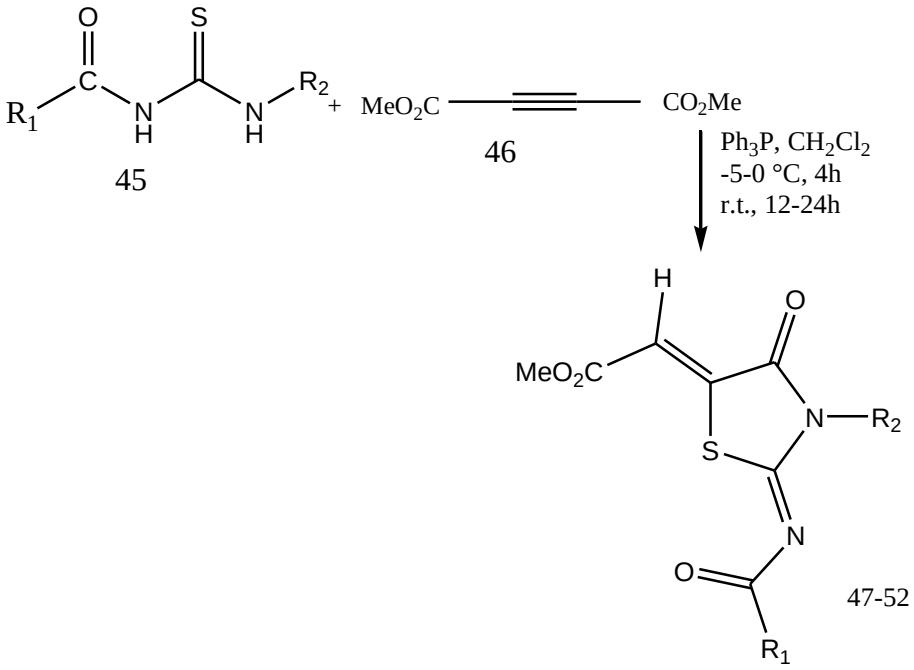
3-aroyl-1-arylcarbonylthioureas **40** on reflux reaction with dimethylbut-2-ynedioate **41** in presence of acetic acid to yield 1, 3-thiazinones **42-44**.[32]



Thiazolidinone Analogues	R_1	R_2
42	C_6H_5	C_6H_5
43	4-CH_3-C_6H_4	C_6H_5
44	4-CH_3O-C_6H_4	C_6H_5

4.7. Synthesis of different analogues of N-substituted thiazolidinone derivatives:

This also involves reflux synthesis between 3-aroyl-1-arylcarbonylthioureas **45** with dimethyl but-2-ynedioate **46** in presence of Triphenylphosphin and Dichloromethane to give thiazolidinone derivatives **47-52**.[33]

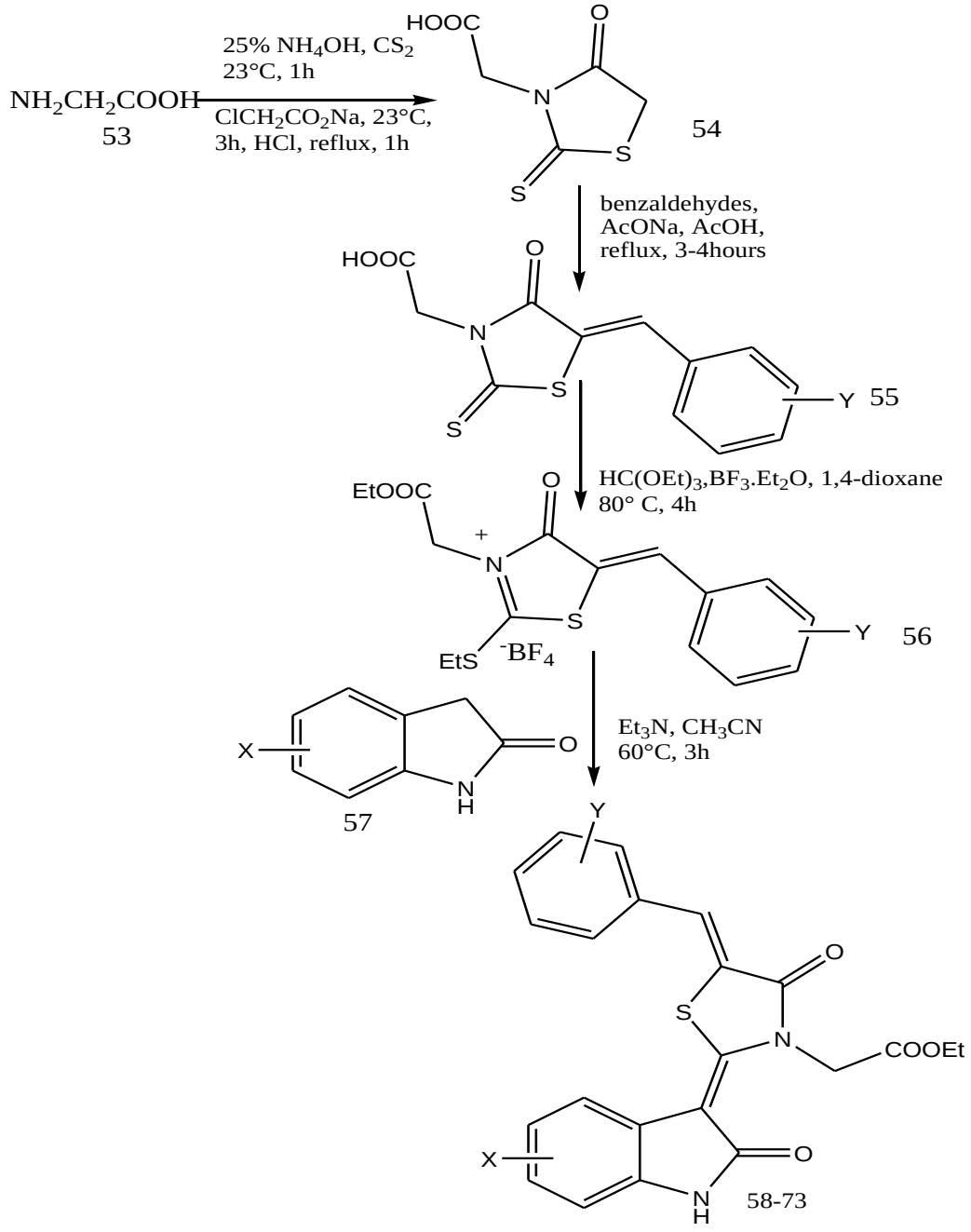


Thiazolidinone Analogues	R_1	R_2
47	C_6H_5	C_6H_5
48	4-CH_3-C_6H_4	C_6H_5
49	4-CH_3O-C_6H_4	C_6H_5
50	4-CH_3-C_6H_4	4-I-C_6H_4

51	4-CH_3-C_6H_4	4-CH_3-C_6H_4
52	1-naphthyl	4-CH_3O-C_6H_4

4.8. Synthesis of different analogues of indoline-2-one substituted thiazolidinone derivatives:

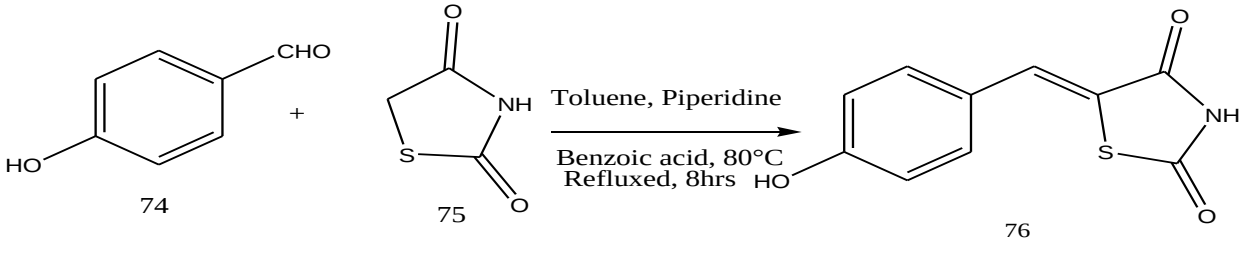
Synthesis starts with the reaction between glycine **53** and carbon disulfide to form Rhodanine-3-acetic acid **54**. The first step involves closure of ring by chloroacetic acid. Second step is reflux Knoevenagel condensation of the intermediate with significant benzaldehyde in solvent acetic acid to gives 2-(5-benzylidene-2-thioxo-4-thiazolidin-3-yl) acetic acids **55**. Third step involves S-ethylation of second intermediate with boron trifluoride diethyl etherate and triethyl orthoformate to gives thiazolinium salts intermediate **56**.[34-35] Final step is the reaction between intermediate salt and indolin-2-ones with triethylamine to give final thiazolidine-4-one derivatives **58-73**.[36]

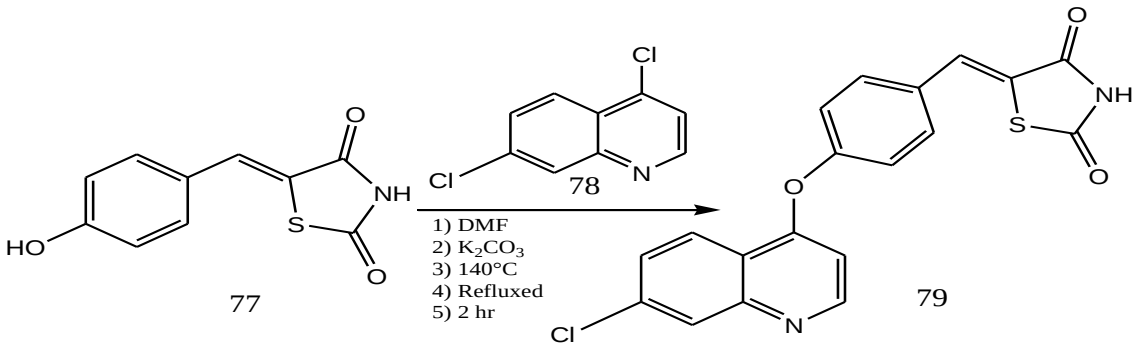


Thiazolidinone Analogues	X	Y
58	H	H
59	H	4-F
60	H	4-CF_3
61	H	3,4,5-trimethoxy
62	5-F	2-F
63	5-F	4-CF_3
64	5-F	2,4-dichloro
65	5-F	3,4,5-trimethoxy
66	5-CH_3	H
67	5-CH_3	2-F
68	5-CH_3	4-F
69	5-CH_3	3,4,5-trimethoxy
70	6-F	H
71	6-F	2-F
72	6-F	4-F
73	5-Br	4-F

4.9. Synthesis of p-hydroxyphenyl substituted thiazolidinone derivative:

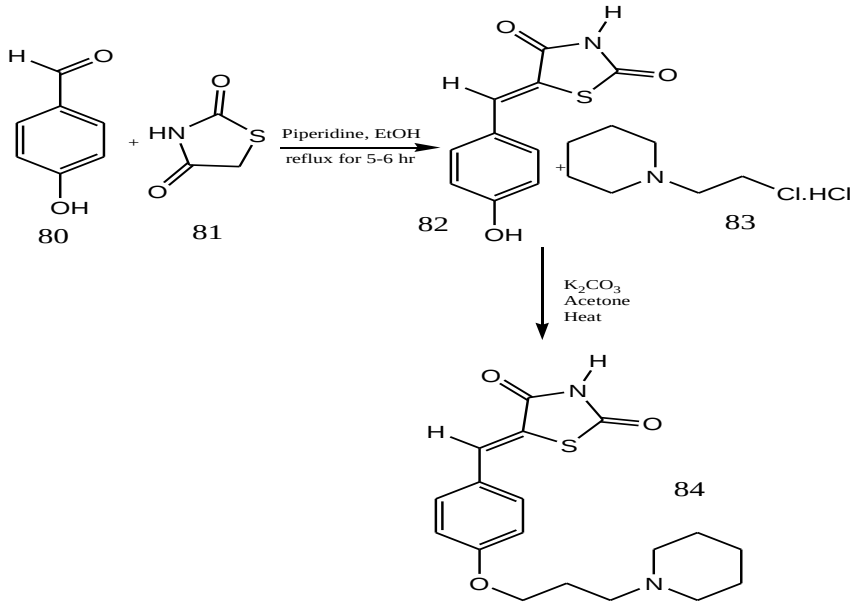
It occurs in two step reaction. Step I is synthesis of derivatives of thiazolidinedione **76** by cross aldol reflux condensation reaction between 4-hydroxybenzaldehyde **74** and Thiazolidine-2, 4-dione **75** with solvent toluene, base piperidine to gives basic nucleus **76**. Step II is derivatization of basic pharmacophore **76** on reflux reaction with 4, 7-dichloroimidazole **78** to produce final analogue **79**.[37]





4.10. Synthesis of 5-(4-alkylbenzyledene)thiazolidine-2,4-dione derivative:

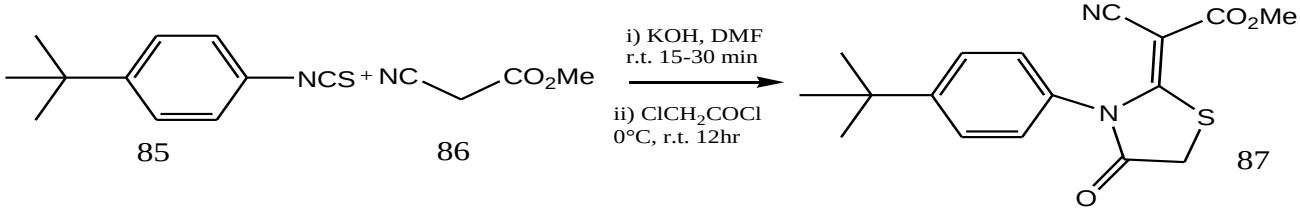
It involves formation of 5-(4-alkylbenzyledene) thiazolidine-2, 4-dione derivative **84**. Synthesis starts from knoevenagel condensation reaction of 4-hydroxybenzaldehyde **80** with 2,4-thiazolidinedione **81** in the presence of piperidine and solvent ethanol, the reaction kept reflux for 5-6 hour.[38-41] Further reaction carried out by treatment of intermediate compound **82** with tertiary alkyl amino chlorohydrochlorides **83** in the solvent acetone and catalyst K_2CO_3 under reflux conditions to give final 5-(4-alkylbenzyledene)thiazolidine-2,4-dione derivatives **84** in adequate practical yields.[42]



80 81 82 83 84

4.11. Synthesis of 1-*tert*-butylbenzene substituted and naphthalene substituted different derivatives of thiazolidinone:

The given scheme involves reaction between Aryl isothiocyanates **85, 88** with compounds of active methylene **86** in the presence of potassium hydroxide and solvent DMF gives ketene-N, S-acetal salts. The intermediate salts again treated with 2-chloroacetyl chloride to produce different analogues of thiazolidinone nucleus. Among studies compound **87** and **89** found to be most active with IC_{50} values of 1.75 and 1.12 µM respectively.[43]



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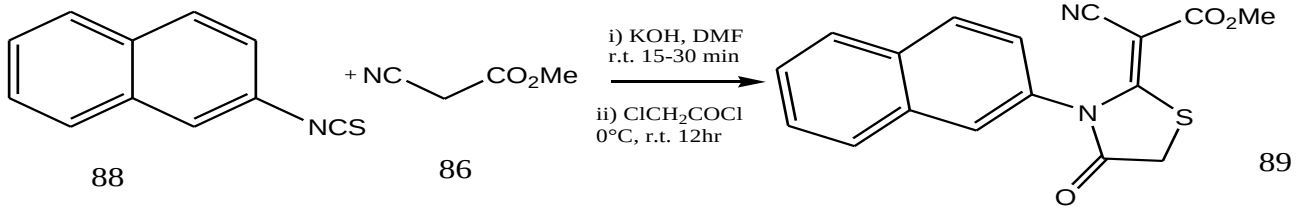
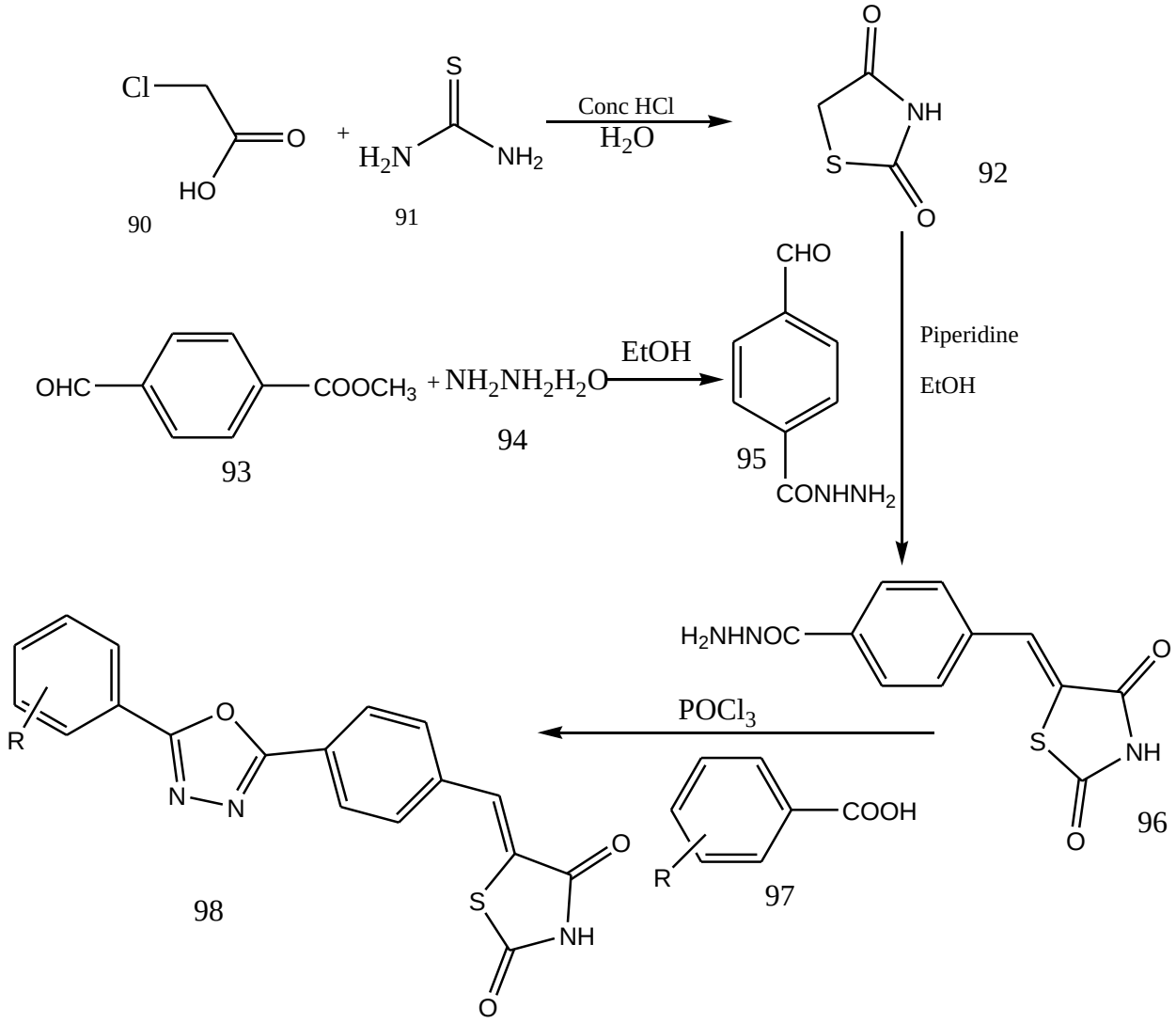


88 86 89

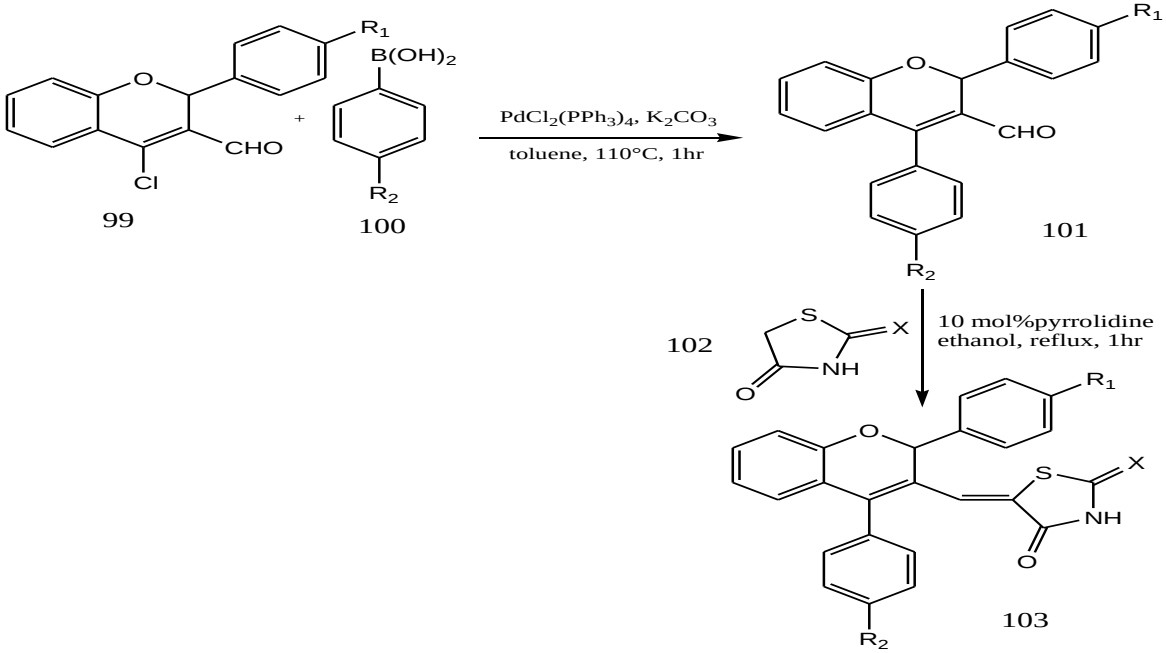
4.12. Synthesis of compound 5-(4-(5-phenyl-1,3,4-oxadiazol-2- yl) benzylidene) thiazolidine-2,4-diones:

Vivek *et al.* designed synthesized and done docking studies of 24 new thiazolidine-2, 4-dione analogues. Thiazolidine-2, 4-dione **92** was taken as precursor for the synthesis of final analogues which was itself synthesized by the reaction between chloroacetic acid **90** and thiourea **91**. Second step occurs with 4-formylbenzohydrazide **95** which is produced by fusion of methyl 4-formylbenzoate **93** with hydrazine hydrate **94** in the presence of solvent ethanol. Second step is the reflux condensation reaction between thaizolidine-2, 4-dione **92** with 4-formylbenzohydrazide **95** in the presence of base piperidine and solvent ethanol, reaction kept for 24 hours to produce 4-((2, 4-dioxothiazolidin-5- ylidene) methyl) benzohydrazide **96**. Last step involves reflux condensation reaction of 4-((2,4-dioxothiazolidin-5- ylidene)methyl)benzohydrazide **96** with different benzoic acid derivatives **97** at the temperature 60-70°C for the time 14 hours in the presence of cyclizing agent $POCl_3$, reaction further forwarded by the addition of crushed ice followed by sodium bicarbonate as neutralizing agent which results in final synthesis of 5-(4-(5-phenyl-1,3,4-oxadiazol-2- yl) benzylidene) thiazolidine-2,4-diones **98**. Compound **98** showed best potent activity with GI_{50} = 0.004 µM and best binding interactions with different amino acid residues like LYS67, ASP186, ASP131 and GLU124 of PIM-1 kinase.[44]



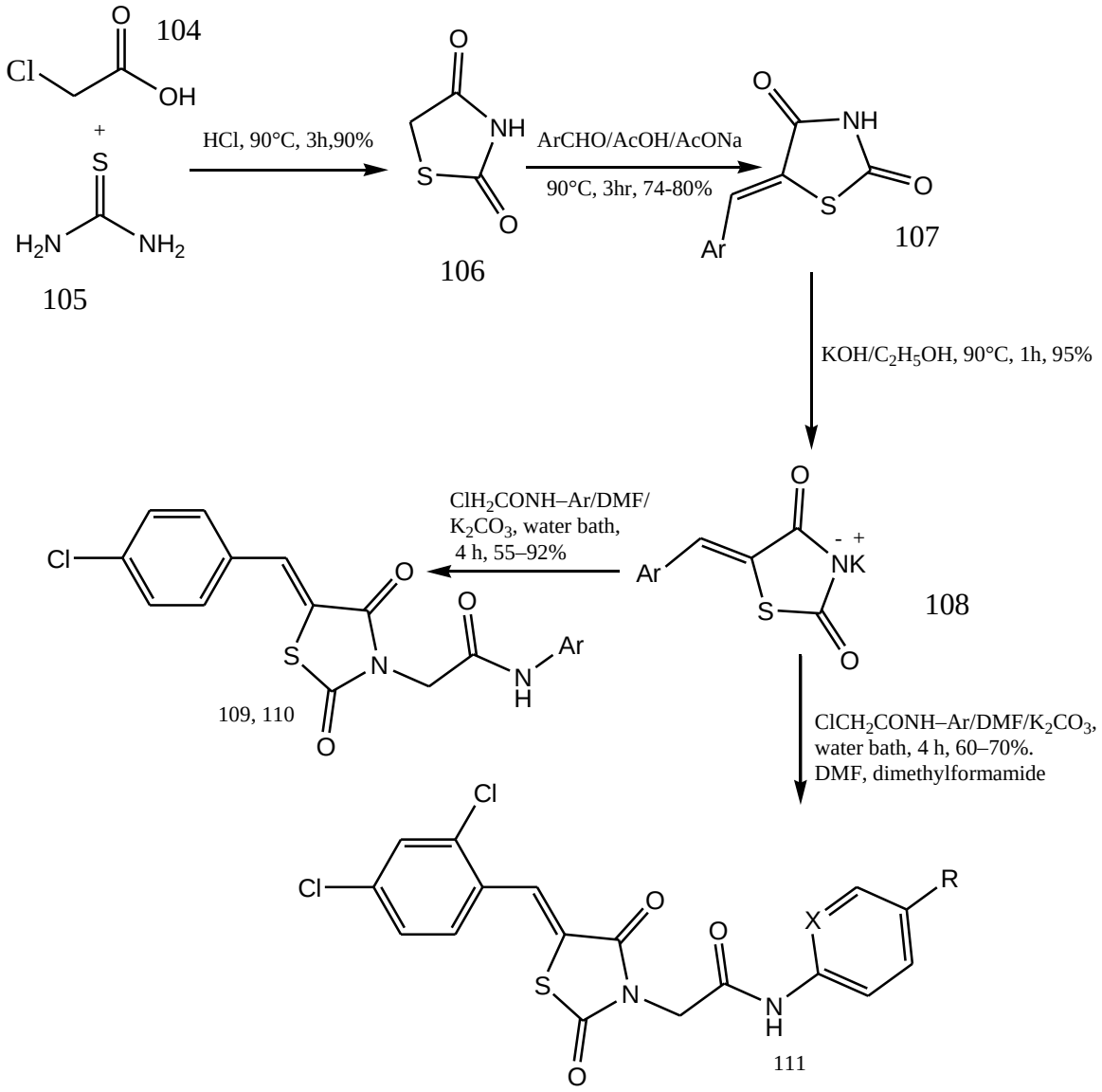
4.13. Synthesis of (Z)-5-{(2, 4-diphenyl-2H-chromen-3-yl) methylene}-2-thioxothiazolidin-4-ones derivative:

The following scheme involves synthesis of (Z)-5-{(2, 4-diaryl-2H-chromen-3-yl) methylene}-2-thioxothiazolidin-4-ones analogues which were prepared in two step reactions. First step involves reaction between 4-chloro-2-aryl-2H-chromene-3-carbaldehyde **99** with aryl boronic acid **100** analogues in the presence of triphenylphosphine palladium chloride and potassium carbonate with solvent toluene at 110°C for 1 hour gave novel 2,4-diphenyl-2Hchromene-3-carbaldehydes **101** intermediates which on further reacts with 2-Thioxothiazolidin-4-one **102** in presence of pyrrolidine and ethanol to gives final (Z)-5-{(2, 4-diphenyl-2H-chromen-3-yl) methylene}-2-thioxothiazolidin-4-ones derivatives.[45-47] Compound **103** showed strongest cytotoxicity against B-16 and A549 cell lines with IC_{50} value of 2.0 µg/mL and 4.0 µg/mL respectively.[48]



4.14. Synthesis of N-substituted thiazolidinediones derivatives:

The first step of synthesis starts with cyclocondensation reaction between chloroacetic acid **104** and thiourea **105** in the presence of hydrochloric acid to gives respective thiazolidinediones intermediate **106**. Next step of synthesis involves condensation reaction between first intermediate with 4-chlorobenzaldehyde in the presence of sodium acetate to gives second 5- (4-chlorobenzylidene) thiazolidine-2,4-dione intermediate **107**. Further reaction proceeded with the heating of second intermediate with potassium hydroxide and ethanol as a solvent to gives appropriate potassium salts **108**. Last step of synthesis involves reaction between potassium salts and α-chloro-N-arylamides derivatives to gives final amide derivatives as novel thiazolidine-2, 4-diones analogues.[49-53] Among all analogues **109, 110 and 111** compounds were most potent against different cancer cell lines HepG2, HCT-116, and MCF-7 with their IC_{50} values ranging between 38.76 to 53.99 µM.[540]

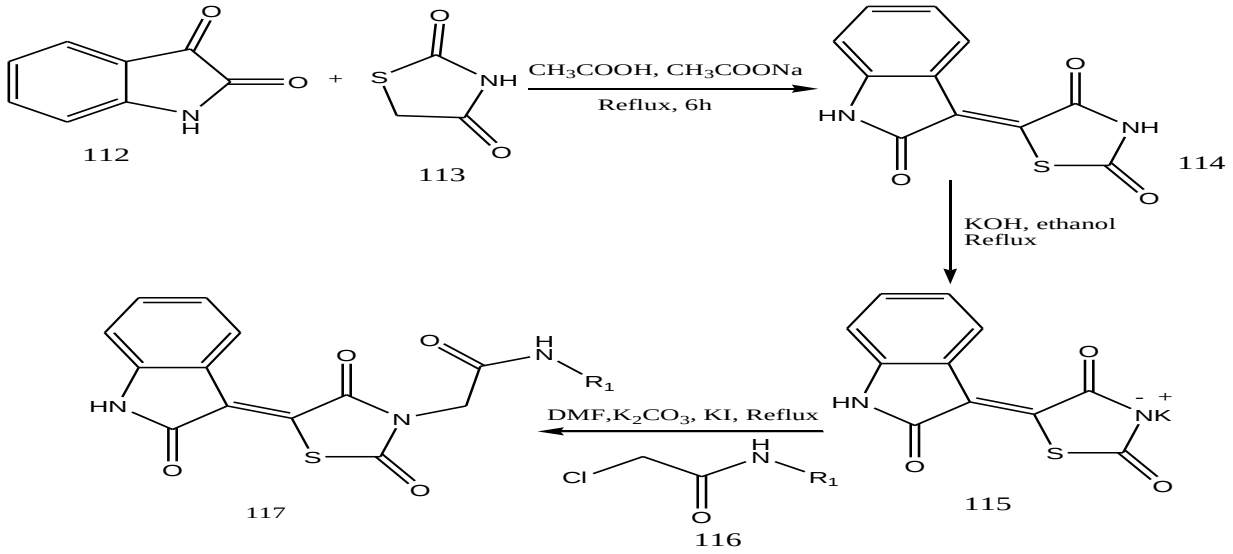


Thiazolidine Analogues	Ar	X, R
109	4-$COOHC_6H_4$	-
110	4-$NH_2COC_6H_4$	-
111	-	X=C, R=COOH

4.15. Synthesis of N-paratolylalkylamide-indoline-2-one derivatives of thiazolidinediones:

Synthesis involves condensation reaction of isatin **112** with thiazolidine- 2, 4-dione **113** takes place in first step of synthesis which occurs in the presence of sodium acetate in the solvent acetic acid to gives different isatin derivatives as intermediate **114** with good yield. Further, isatin intermediate reacts with alcoholic potassium hydroxide solution to gives potassium salt **115**. On further reaction heating of salt takes place with 2-chloro-N-substituted acetamide **116** derivatives and KI in the solvent DMF gives respective thiazolidine analogoues.[55]

Compound **117** was the most potent analogue against the investigated cell lines having IC_{50} values of 2, 10, and 40 µM, respectively.[56]



Conclusion: Cancer is the subsequent driving reason for mortality around the world. Many drugs used alone or in combination to treat different types of cancer but still there is unmet need of drugs to treat disease. Keeping of this point of view the given article contains many synthesis of different thiazolidinone derivatives used as anticancer agents designed in previous some decades. The scaffold used as it have so many pharmacological activities also shown by its structure activity relationship (SAR). Anticancer is also one of the potent activity given by thiazolidinone nucleus. Many work had been done for the synthesis of different compounds with thiazolidinone nucleus having anticancer activity which were concluded in the article. The work may help researchers for the development of more potent and effective anticancer compounds in future aspects.

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