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Review

Synthetic Approaches of Benzimidazole Derivatives on Anti-Diabetic Activity: A Review

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Abstract:

Background: Thiazolidine-2,4-dione (2,4-TZD) is a versatile and valuable chemical structure that features a five-membered ring with an oxygen atom at the 2-position, a double bond at the 4-position, and contains both a nitrogen and a sulphur atom within the ring. This structure serves as an effective pharmacophore, which is a key component in drug design. The electron-rich nitrogen atom in the compound enhances its electronic properties, making it useful in various applications. Thiazolidine-2,4-dione analogues have been synthesized through different methods, all of which have demonstrated significant biological activity. **Objective:** The exploration of the biological activity of Thiazolidine-2,4-dione derivatives has been an interesting area in pharmaceutical chemistry, serving a variety of purposes. This study focuses on the derivatives described in the literature from 1995 to 2023. The review delves into Thiazolidine-2,4-diones, covering their introduction, general synthesis methods, synthetic pathways, and their significance in the treatment of diabetes. **Conclusion:** Thiazolidine-2,4-diones are prominent heterocyclic compounds with significant scientific interest. Various methods have been developed for their synthesis. In several derivatives of thiazolidine-2,4-diones exhibit antidiabetic activity, encouraging further research. Their potential application in antidiabetic treatment has captured researcher attention, detailed exploration of these versatile compounds.

Keywords: Benzimidazole, Receptor, Synthetic Scheme, Reaction, Pharmacological Activity.

Introduction

Thiazolidinediones (TZDs), commonly referred to as glitazones, are a class of medications used in the management of type 2 diabetes mellitus.[1] Diabetes is a chronic metabolic disorder characterized primarily by high blood glucose levels due to issues with insulin secretion, insulin action, or both.[2] In latest year, the chemistry of 2,4-thiazolidinediones (TZDs) shows many properties such as antihyperglycemic, anti-inflammatory, anti-malarial, antioxidant, antitumor, cytotoxic, antimicrobial activity shows.[3]The utilize of an insulin-sensitizing agent, 2,4-thiazolidine (TZD) , in transition dairy cattle develop in augment DMI and reduce plasma NEFA concentration during the transition period (smith et al.. 2007. 2009).[4] The potential of TZD-based small molecules as AR inhibitor. [5] The medicinal chemistry of thiazolidinediones as PPARγ ligands has been latest reviewed. [6][7] PPAR activity was think to be limited to lipid metabolism and glucose homeostasis. [8] TZDs target vascular cells13 and monocytes/macrophages. [9] The docking outcome suggested that these 2,4-thiazolidinediones derivatives are active COX inhibitors with a obvious preference for COX2. [10] Thus, the dose need for

anticancer activity of thiazolidinediones would be notably lower than that need to bring about hypoglycemic activity. [11] Activation of PPARg by TZDs contribute to adipose-cell distinctness and augment insulin sensitivity in obese rats. [12] The PPARcs are a group of nuclear receptors that act as transcription factors which act a major part in the regulation of lipid metabolism storage. [13] The combination of a thiazolidinone moiety and a structural fragment of the Ciminalum in one hybrid molecule is an active approach for the design of possible anticancer agents. [14] 1,3-Thiazolidines are the recent class of antimicrobial agents with activity against broad spectrum of Gram-positive pathogens along with Staphylococci, Streptococci, and Enterococci. [15] Although TZDs spectacle durability in action higher than seen with either metformin or sulfonylureas, weight gain caused by TZDs has restrained his clinical utility. [16] However, there is limited information on the combination therapy of SGLT2 inhibitor and TZD in diabetic nephropathy.[17] Obviously, hybridization of thiazolidine-2,4-dione with isoxazoline may provide new candidates with excellent potency pharmacological.[18] Most of the published literature on TZDs and fractures in humans consists of adverse event reporting from large randomized controlled trials, small observational studies, a case-control study, and a meta-analysis.[19] TZD nucleus and aryl/alkyl sulfonate moiety using fragment-based synthetic approach and evaluated them for in vitro PTP1B inhibitory and in vivo anti-hyperglycemic activity.[20] The photophysical properties of TZD derivatives are mainly governed by the polarity of the medium, hydrogen bonding and electronic substituent effects at arylidene moiety (Rančić et al., 2013; Sarkar et al., 2009).[21] The compounds that contain a thiazolidinic nucleus, 2,4-thiazolidinedione and rhodanine were studied by Lima (1999) with respect to the antiedematogenic properties of their isosters.[22] The use of the putative PPARγ agonist 2,4-thiazolidinedione (2,4-TZD) in dairy goats with induced sub-clinical intramammary infection improved overall liver function and increased the level of myeloperoxidase in blood, i.e., the killing capacity of neutrophils.[23] A study reported by Divya et al., showed that TZD derivative ciglitazone significantly decrease the VEGF production in human granulosa cells in an in vitro model.[24] It has also been found that TZDs are high-affinity ligands for PPAR-γ and inhibit the production of MCP-1 in some human tissues.[25] Combination therapy includes treatment with two or more agents with different, complementary mechanisms of action, for example, the combination of a thiazolidinedione and a biguanide improves insulin sensitivity and lowers blood glucose through complementary pathways, and therefore produces an additive effect.[26] Various new classes of PPARy ligands not sharing the TZDs ring has more recently been designed and evaluated for PPARy agonistic activity.[27] The thiazolidinethione and thiazolidinedione would likely form stronger chelate complexes with Sn(IV) and Ti(IV) due to their ability to coordinate through multiple donor atom.[28] Some thiazolidinedione derivatives also showed Cu2+ mediated lipid-peroxidation inhibitory activity9 and were found to inhibit serum ALT, AST as well as c-GTP levels significantly during treatment in patients with type 2 diabetes.[29] The thiazolidinediones are rapidly absorbed and reach peak concentrations within a few hours. . Thiazolidinediones are metabolised by cytochrome P450 2C8 (and by CYP3A4 for pioglitazone), but at conventional doses apparently do not affect the activity of those enzymes. When activated by a ligand, such as a thiazolidinedione, PPARγ binds to the 9-cis retinoic acid receptor (RXR [retinoid X receptor]) to form a heterodimer. [30] Rosiglitazone (RSG) is a member of the thiazolidinedione (TZD) class of antidiabetic agents, a group of pharmaceuticals that has proven successful in the treatment of Type 2 diabetes mellitus (T2DM) in humans, improving glycaemic control by enhancing insulin sensitivity.[31] Most importantly, two recent reports demonstrated anti-breast cancer activity of TZDs, but the molecular mechanisms underlying the treatment of breast cancer cells with these compounds were not clarified. Thus, in our present study three synthesized TZDs (5, 7 and 9) were evaluated against human breast cancer cell lines (MCF-7 and MDA-MB-231) and human breast cancer cells. We also monitored the molecular mechanisms underlying treatment of breast cancer cells with the three thiazolidinediones 5, 7 and 9. [32] we therefore tested the ability of BRL 49653 and a natural ligand for PPAR-y2 - 2, 15-d-delta -[12,14] -prostaglandin J2 (1 5 - d PGJ2), to antagonize TNF- –induced lipolysis. Because of the known interactions between TZDs and TNF-alpha on protein expression, the expression of two proteins

involved in lipolysis, hormone-sensitive lipase (HSL) and perilipin A, were examined as a fir s t step in understanding the mechanism of action of TZDs on T N F -alpha –induced lipolysis.[33] The current study was an attempt to evaluate these benzylidene thiazolidinediones (BTZDs) derivatives for their effect on blood lipid profile, blood glucose levels, and insulin resistance in mice fed a high-fat diet.[34] the synthesis and insulinotropic activity in INS-1 cells of thiazolo-benzylsubstituted-thiazolidinedione derivatives Ia-f and IIa- (Bozdag˘-Du¨ndar et al., 2006). As part of this ongoing research, herein, in view of the preventive antioxidant action of thiazolidinediones (Da Ros et al., 2004), Ia-f and IIa-f derivatives that have already been shown to have antidiabetic activities have been screened for their antioxidant activities by comparing with butylated hydroxytoluene (BHT) and superoxide dismutase (SOD), a well-known antioxidant and antioxidant enzyme, respectively.[35][36] On the other hand, flavonoids possess spasmolytic, capillary resistance activity, antidiabetic, coronary dilatory and antibacterial effects so we synthesised a series of compounds containing the thiazolidinedione moiety and flavone nucleus in one frame in order to study their antimicrobial activity.[37] These unique characteristics may account for variation in the TZDs' individual tolerability and safety profiles that have been observed during clinical trial programs and in clinical practice.[38] Slightly better antitubercular activity against M. tuberculosis H37Rv demonstrated 2-(2-chloroquinolin-3-yl)-3-(4- fluorophenyl)-1,3-thiazolidin-4-one [39] The treatment of dairy cows with 2,4-thiazolidinedione (2,4-TZD), a putative PPARγ agonist, during the prepartum period did not affect milk fat percentage and either did not affect or numerically decreased milk fat yield in early postpartum cows.[40] Phenyl substituents were investigated that could exert electron- releasing or electron-withdrawing effects on the TZD ring, which could potentially alter its metabolism and hence toxicity.[41][42] Treatment with all thiazolidinediones is associated with weight gain. The causes for this weight gain could be fluid retention, increased fat mass or improvement in hyperglycaemia. As stated earlier, thiazolidinediones promote body fat redistribution with accumulation occurring in the subcutaneous, rather than the visceral fat depots.[43] 3T3-L1 and 3T3-F442A adipocytes have been treated with a variety of thiazolidinediones, resulting in increases in transport activity and transporter expression.[44] TZDs are effective in reducing glycosylated hemoglobin (HbA1c). It is generally recommended that thiazolidinediones should be used in combination with metformin only in obese patients.[45] we used a fragment of 4-(chlorophenyl)thiosemicarbazone as a structural motif containing N-N-C(=S)-N. This fragment was connected with TZD derivatives in five positions of a heterocyclic ring, leading to new TZD-chlorophenylthiosemicarbazone hybrids.[46] Similar to the glitazones, DCPT contains a TZD ring; however, DCPT produces liver damage in a common laboratory rodent species.[47] First, the chemical reactivity of the RD and TZD has been estimated using the standard global (point) DFT descriptors as electronegativity, electrophilicity/nucleophilicity, chemical hardness/softness of molecules, as well as the ΔE=EHOMO–ELUMO energy gap.[48] In continuation of our earlier interest to synthesize new analogues of bioactive 2,4-thiazolidinediones, here an attempt is made to synthesize the titled products by overcoming the limitations of the condensations and developed one-pot multicomponent synthetic route. The multicomponent reactions approach was considered because of its wide range of advantages and exceptional synthetic efficiency.[49] Knoevenagel condensation of 2,4-thiazolidinediones with aldehydes is a key step in the synthesis of some clinically used antidiabetic agents like rosiglitazone, englitazone and netoglitazone.[50] A series of new chromone derivatives with a C-3 imidazolidine-2,4-dione or thiazolidine-2,4-dione substitution connected with phenyl ring bearing various electrophilic substitutions were evaluated for their free radical and antioxidant activities.[51] The bovine PPARG receptor appears TZD-responsive, with its activation potentially leading to greater adipogenesis and lipogenesis in SAT, while differentially regulating glucose homeostasis and fatty acid oxidation in skeletal muscle.[52] In the light of the drawbacks of the hydroxamate ZBG regarding potential mutagenicity, poor pharmacokinetics and bioavailability, a broad variety of alternative ZBGs were explored and the structure-activity relationship of corresponding classes of inhibitors analyzed.[53] Molecular docking and molecular dynamic simulations of the most potent inhibitor 5i into the

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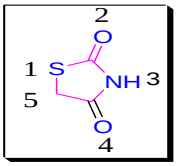
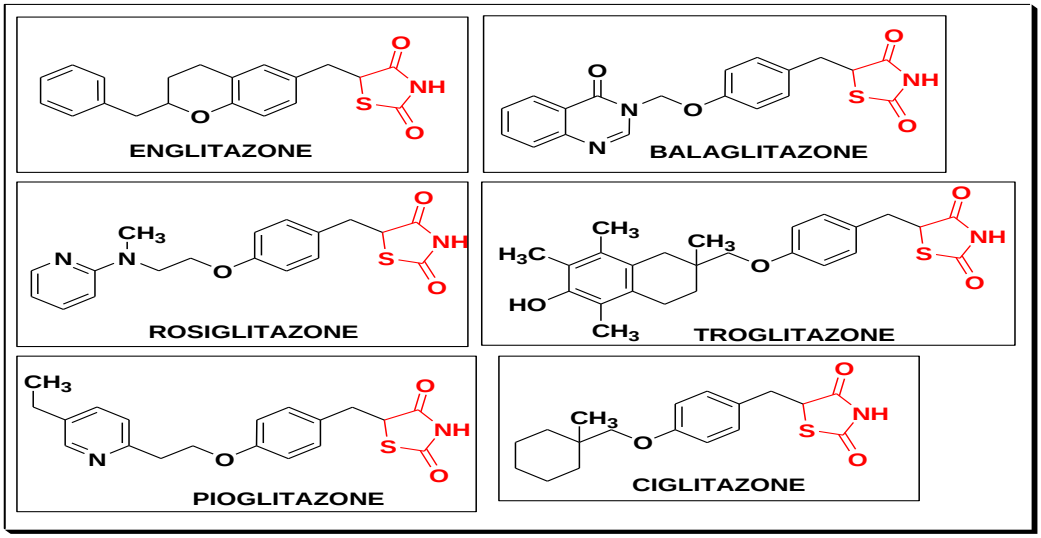
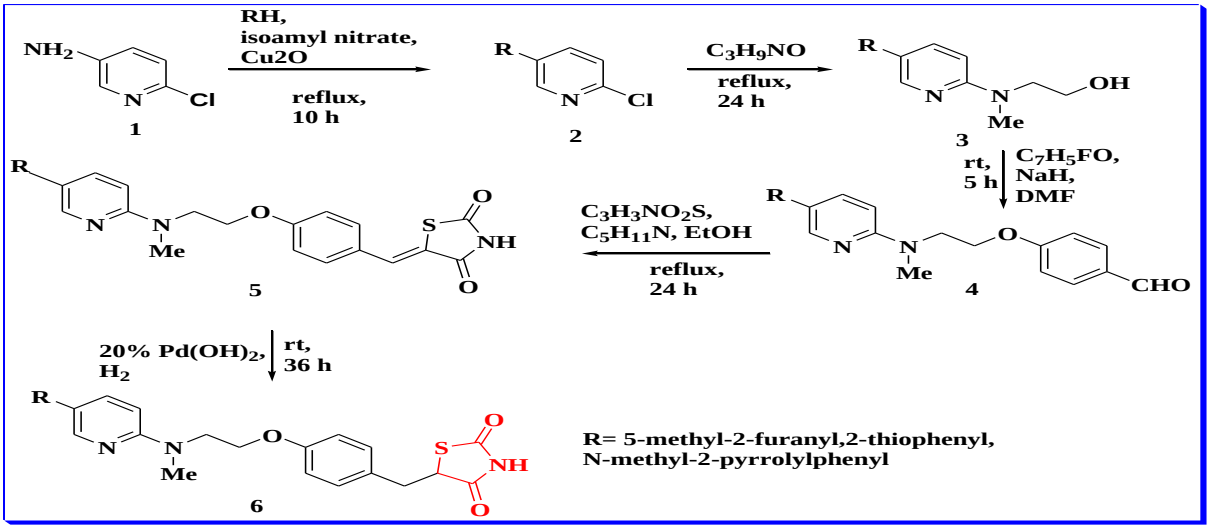
human ALR2 binding site was carried out, in order to propose the mode of binding of the novel acids.[54] Chemically, TZD nucleus has two carbonyl moieties at 2nd and 4th position sparing behind -NH and methylene (-CH2) of thiazole ring for structural modifications to develop various analogues.[55] The antibacterial activity of the thiazolidinedione and rhodanines containing synthetic intermediates 3a,b and also the aryl analogues 8a,b and f, and the heterocyclic analogues 8c–e in order to gain further SAR data on this series.[56] Marbling or IM fat has been positively correlated with meat quality because of the improvement in beef tenderness and palatability. The development of IM fat primarily depends on the animal's breed, gender, age, and nutrition.[57] Our own interest in ionic liquids (ILs) and in green synthetic transformations prompted us to explore the catalytic activities of TMG-based ILs in the synthesis of 2-TZD and rhodanine derivatives. On top of all these factors, sonication is finding extensive use as it saves time and is environmentally friendly.[58] There is some evidence regarding the effects of TZD discontinuation on bone mineral density (BMD).[59] The structural characteristic common to all TZDs is a thiazolidinedione ring, to which divergent molecular moieties are attached.[60]



Structure of 2,4-thiazolidine





Scheme 1: Synthesis of 2,4-thiazolidediones

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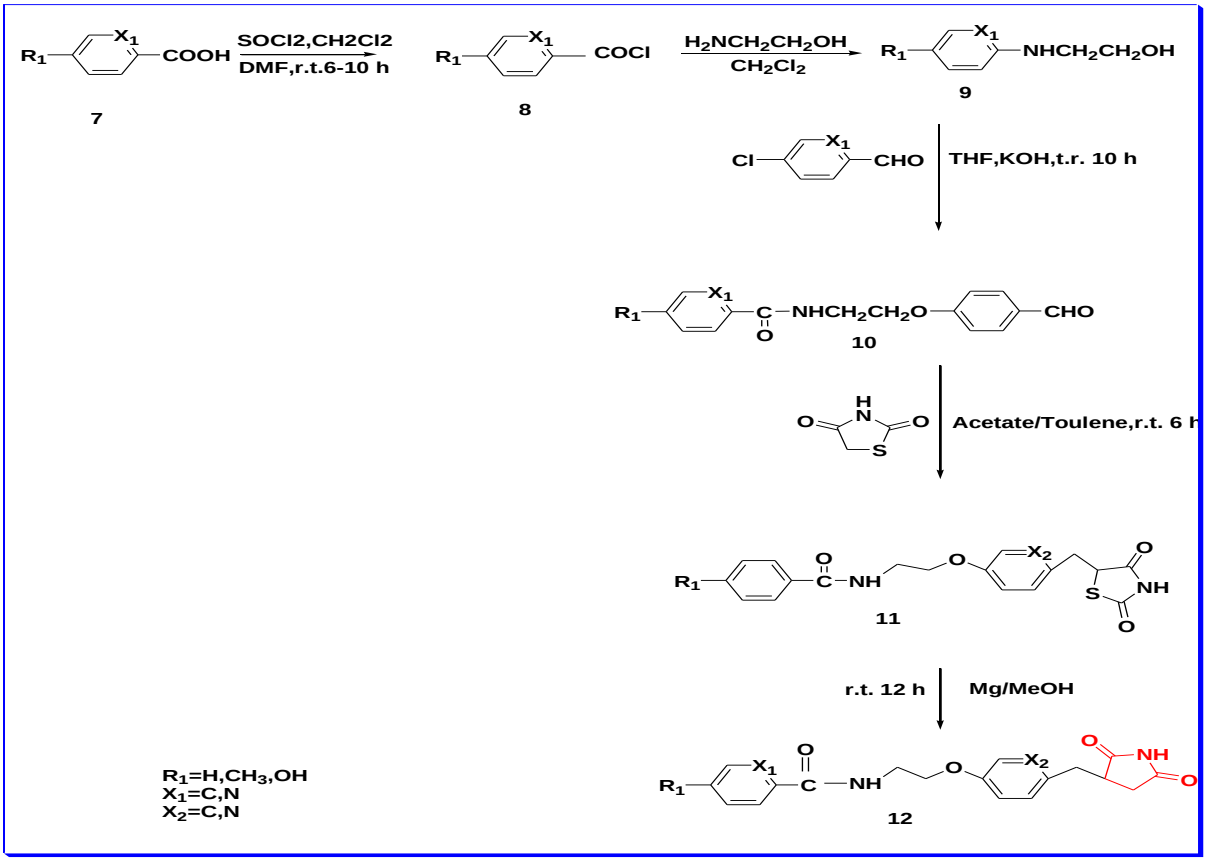
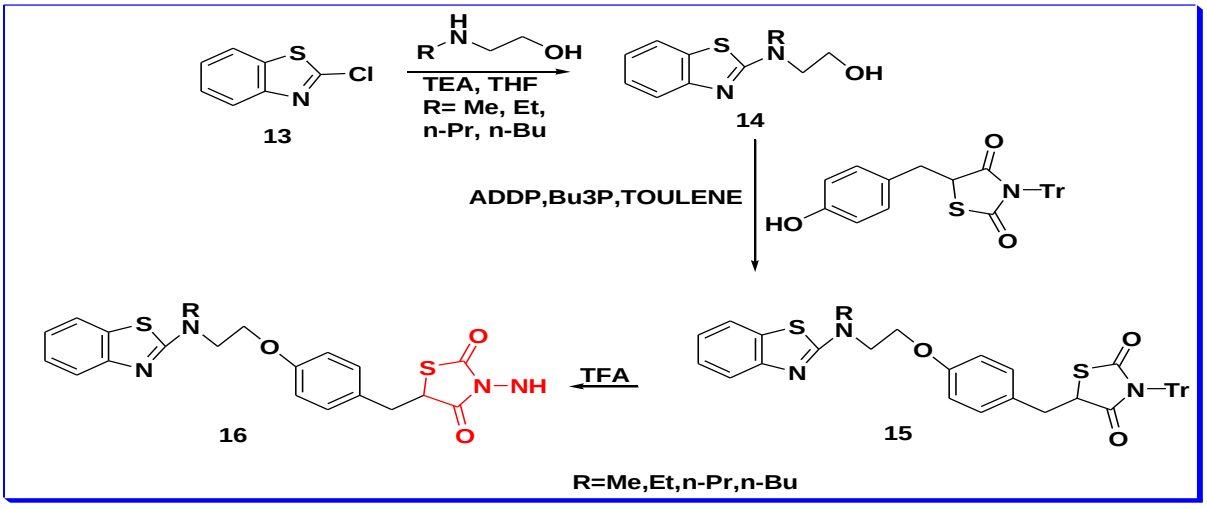
Kim *et al.*, described that 2,4-thiazolidinediones derivatives were developed from 6-Chloro-pyridin-3-ylamine **(1)** reacted with isoamylnitrate in the presence of copper oxide an initiating material **(scheme 1)**. Among the synthesized compounds checked for their antidiabetic activity against 3T3-L1 cells. Potential compound 5-[4-(2-{methyl-[5-(1-phenyl) pyridin-2-yl]amino}ethoxy)benzyl]thiazolidine-2,4-dione showed significant activity against 3T3-L1 cells. [61]



Scheme 2: Synthesis of 2,4-thiazolidinediones

Zou Huiying, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from substituted benzoic acid **(7)** reacted with thionyl chloride in the presence of dichloromethane as an starting material **(Scheme 2).** All the synthesized compounds evaluated for their antidiabetic activity against PPARy. Potential compound N-(2-(4-((2,4-dioxothiazolidin-5-yl) methyl) phenoxy) ethyl)-4-methylbenzamide showed significant activity against PPARy.[62]



Scheme 3: Synthesis of 2,4-thiazolidinediones

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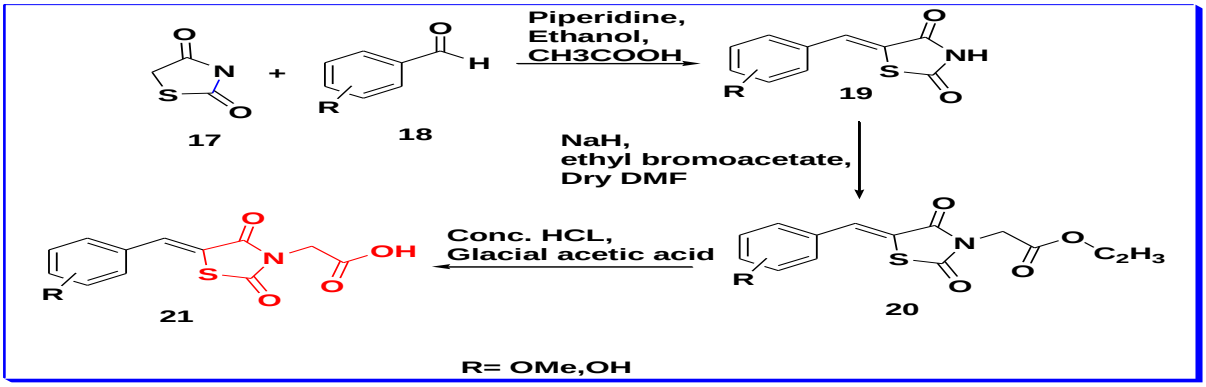
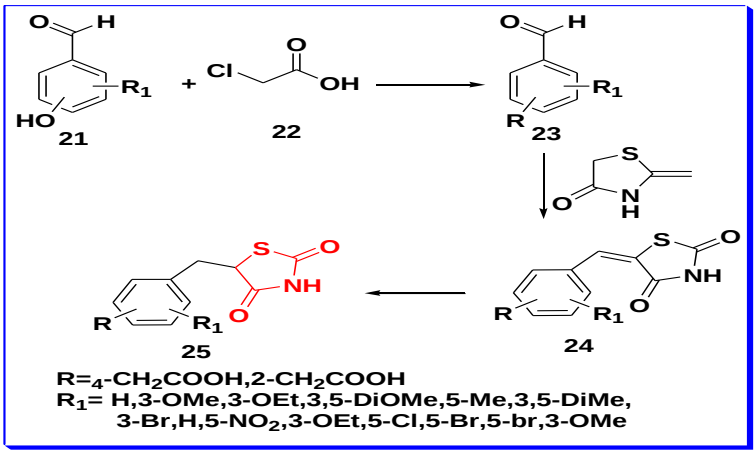
Roak Jeon, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from 2-chlorobenzothiazole **(13)** reacted with substituted 2-methylamino-ethanol in the presence of tetrahydrofuran and triethanolamine as an starting material **(Scheme 3).** All the synthesized compounds evaluated for their antidiabetic activity against PPARy. Potential compound 5-[4-[2-(Benzothiazol-2-ylmethylamino)ethoxy]benzyl] thiazolidine-2,4-dione showed significant activity against PPARy.[63]



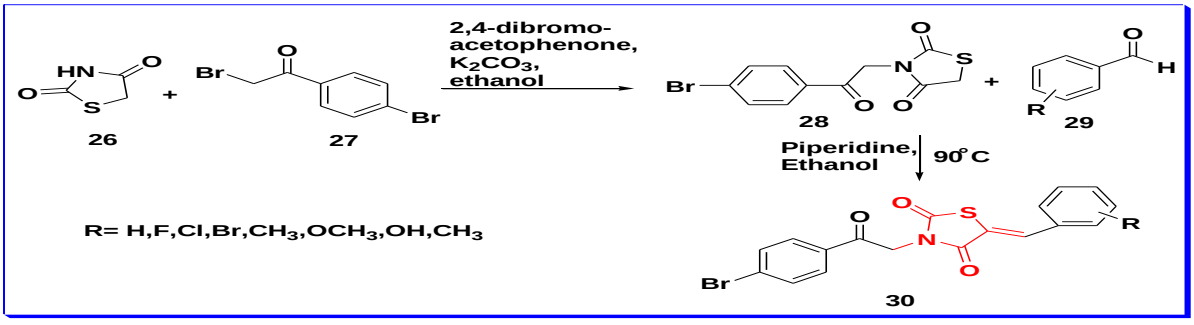
Scheme 4: Synthesis of 2,4-thiazolidinediones

Prasanna A. Datar, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from thiazolidine-2,4-diones **(17)** reacted with substituted benzaldehyde in the presence of piperidine, ethanol and acetic acid as an starting material **(Scheme 4).** All the synthesized compounds evaluated for their antidiabetic activity against PPARy protein. Potential compound 5-(3,4-dimethoxy)benzylidine-2,4-thiazolidinediones showed significant activity against PPARy protein.[64]



Scheme 5: Synthesis of 2,4-thiazolidinediones

Syed Nazreen, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from substituted benzaldehyde with methanol **(21)** reacted with chloro-acetic acid as an starting material **(Scheme 5).** All the synthesized compounds evaluated for their antidiabetic activity against PPAR-y. Potential compound 5-(2-Carboxymethoxy-5-bromo-3-methoxybenzyl)-2,4-thiazolidinedione showed significant activity against PPAR-y. [65]



Scheme 6: synthesis of 2,4-thiazolidinediones

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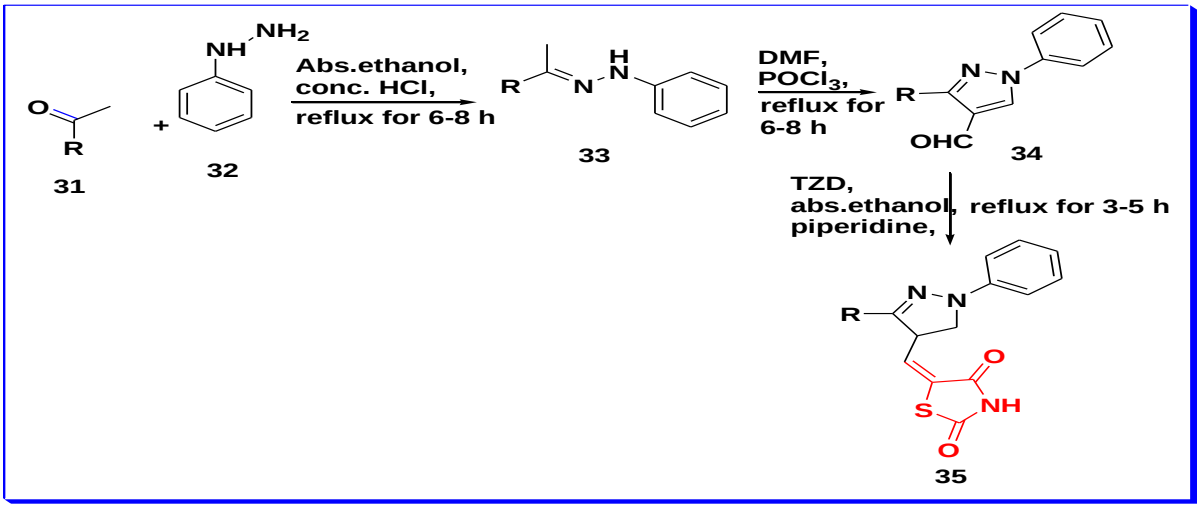
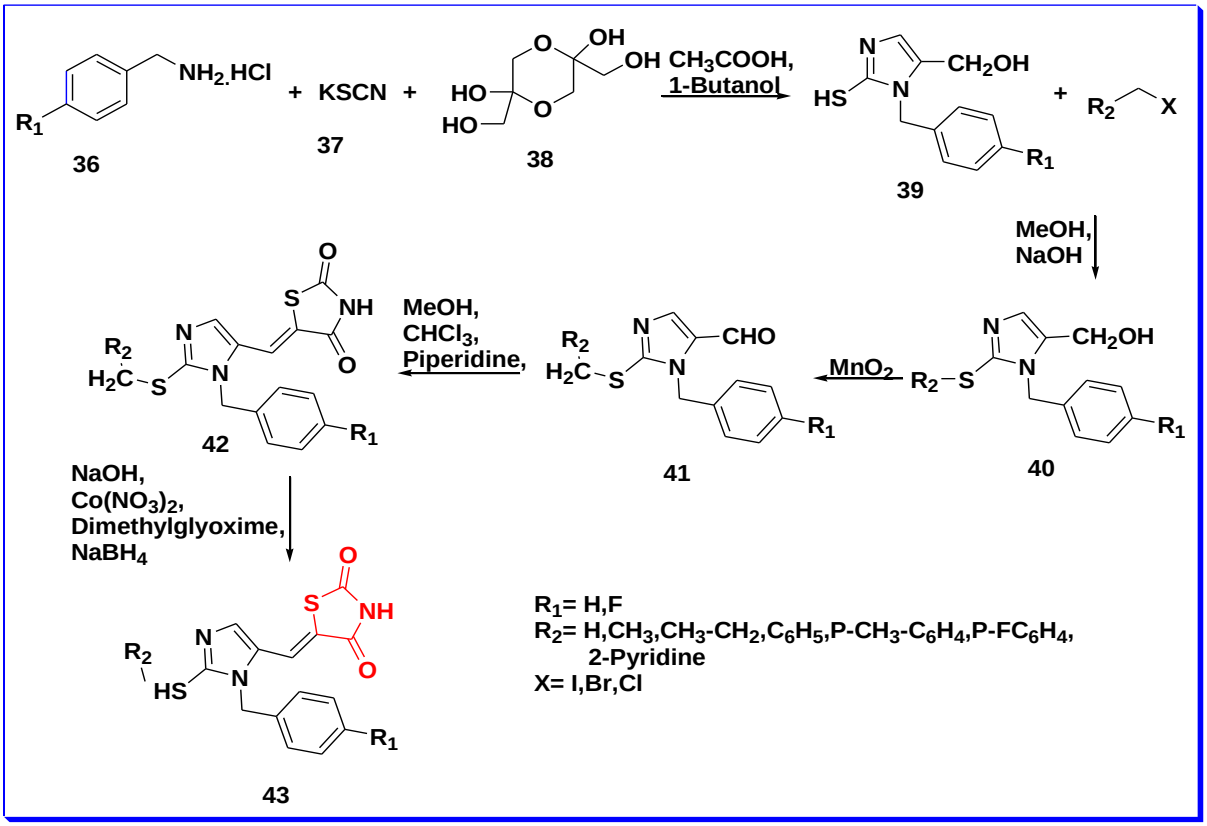
Juan sun, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from thiazolidine-2,4-diones **(26)** reacted with 2-Bromo-1-(4-bromo-phenyl)-ethanone in the presence of 2,4-dibromoacetophenone, K_2CO_3 and ethanol as an starting material **(Scheme 6).** All the synthesized compounds evaluated for their antidiabetic activity against PPARy agonist. Potential compound 3-(2-(4-Bromophenyl)-2-oxoethyl)-5-(2-methoxybenzylidene) thiazolidine-2,4-dione showed significant activity against PPAR-y agonist. [66]



Scheme 7: synthesis of 2,4-thiazolidinediones

Mohd. Javed Naim, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from phenyl-hydrazine **(32)** reacted with substituted acetaldehyde in the presence of Abs. ethanol and conc. HCl as an starting material **(Scheme 7).** All the synthesized compounds evaluated for their antidiabetic activity against PPAR-y gene. Potential compound 5-((3-(Naphthalen-2-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)- thiazolidine-2,4-dioneS showed significant activity against PPAR-y gene. [67]



Scheme 8: synthesis of 2,4-thiazolidinediones

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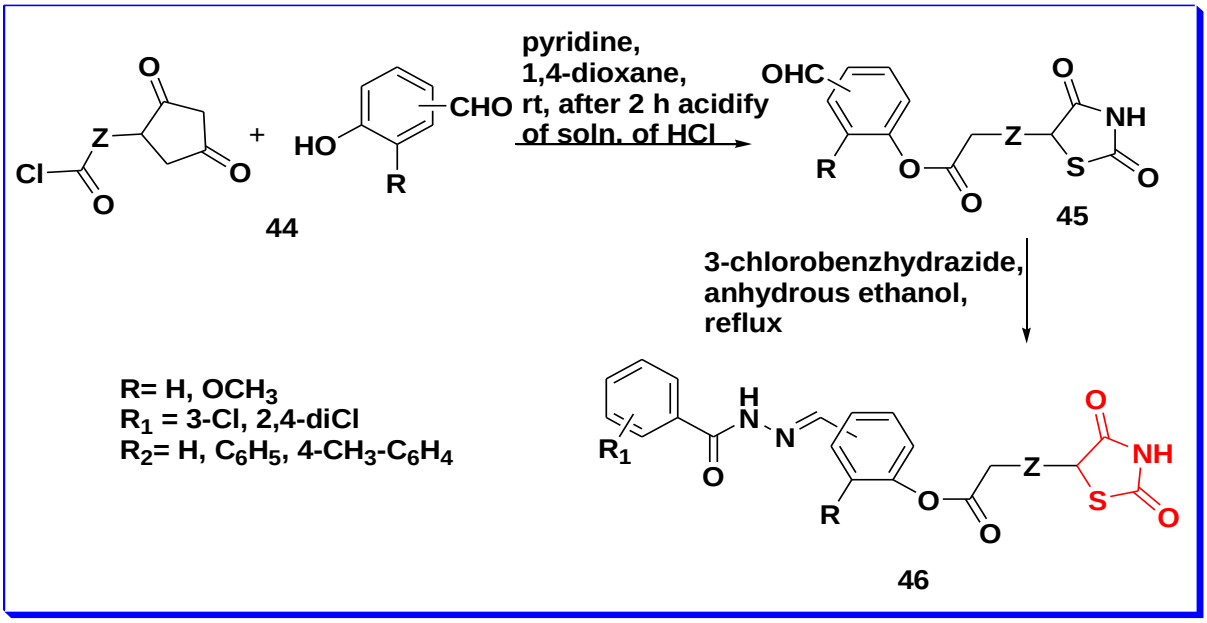
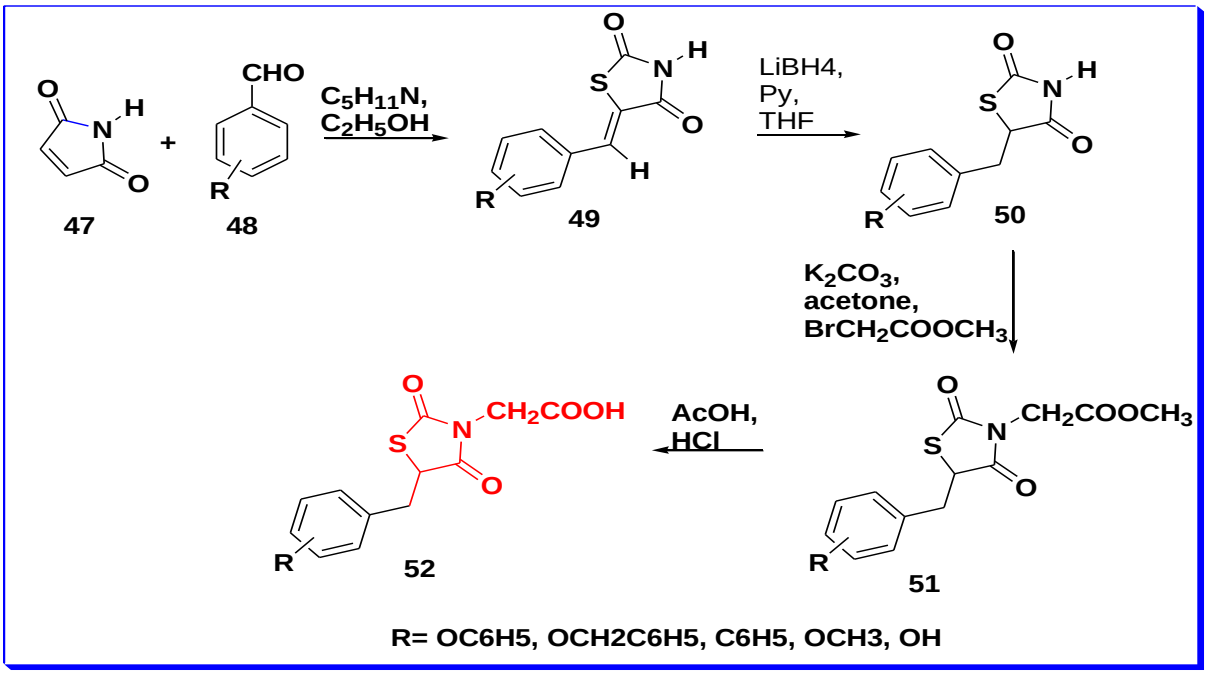
Neda Shakour, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from substituted benzylamine **(36)** reacted with 2,5-Bis-hydroxymethyl-[1,4]diox-2,5-diol and potassium thiocyanate in the presence of acetic acid and 1-butanol as an starting material **(Scheme 8).** All the synthesized compounds evaluated for their antidiabetic activity against PPAR-y gene. Potential compound 5-((1-benzyl-2-((4-methylbenzyl) thio)-1H-imidazol-5-yl) methyl) thiazolidine-2,4-diones showed significant activity against PPAR-y gene. [68]



Scheme 9: synthesis of 2,4-thiazolidinediones

Nazar Trotsko, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from (2,4-Dioxo-cyclopentyl)-acetylchloride **(44)** reacted with substituted phenylacetaldehyde in the presence of pyridine and 1,4dioxane as an starting material **(Scheme 9).** All the synthesized compounds evaluated for their antidiabetic activity against A549, HepG2, and MCF-7 cell line. Potential compound 2-{[2-(3- Chlorobenzoyl) hydrazinylidene] methyl}phenyl (2,4-dioxo-1,3-thiazolidin-5-ylidene)acetate showed significant activity against A549, HepG2, and MCF-7 cell line. [69]



Scheme 10: synthesis of 2,4-thiazolidinediones

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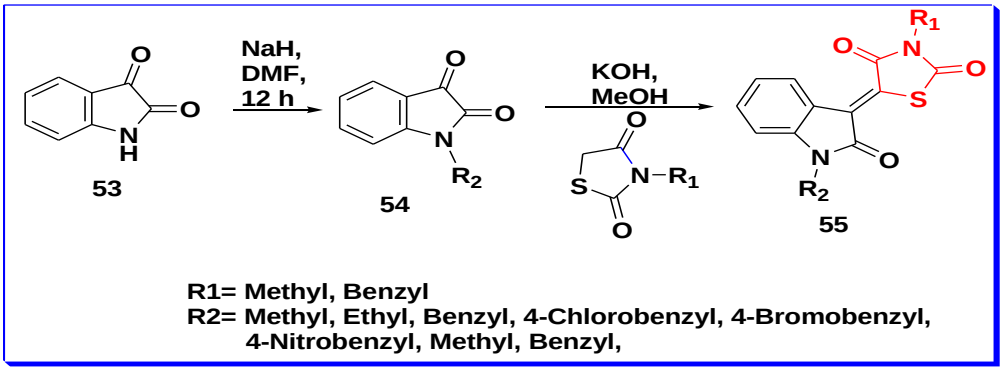
Dietmar Rakowitz, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from pyrazole-2,4-dione (**44**) reacted with substituted benzaldehyde in the presence of piperidine and ethanol as an starting material **(Scheme 10).** All the synthesized compounds evaluated for their antidiabetic activity against that they enhanced ALR2 inhibitory potency. Potential compound 5-(4-Benzyloxybenzyl)-2,4-thiazolidinedione showed significant activity against that they enhanced ALR2 inhibitory potency. [70]

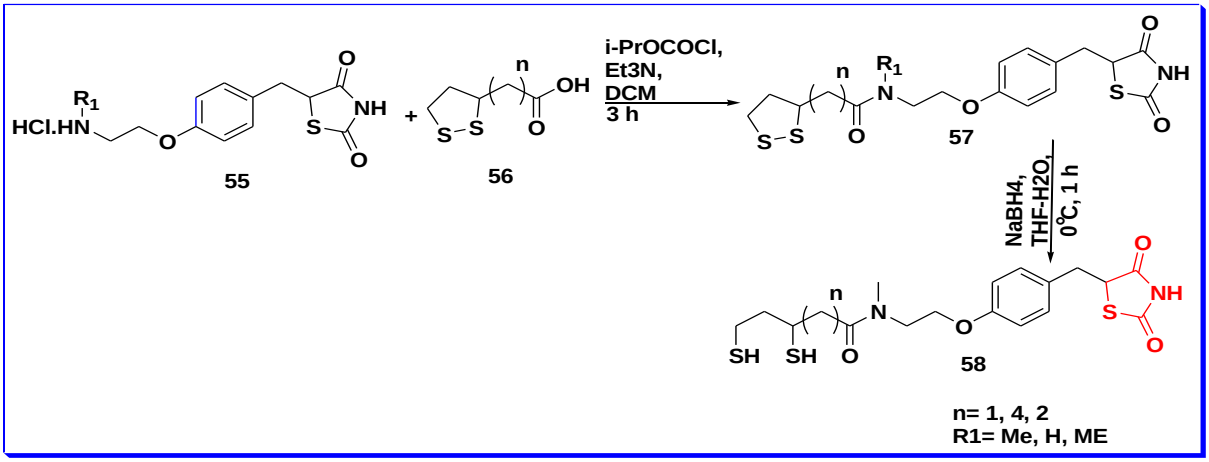


Scheme 11: synthesis of 2,4-thiazolidinediones

Ginson George, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from isatin (**53**) reacted with sodium hydride in the presence of dimethylformamide and ethanol as an starting material **(Scheme 11).** All the synthesized compounds evaluated for their antidiabetic activity against that they enhanced PL inhibitory activity. Potential compound (Z)-3-Benzyl-5-(1-benzyl-2-oxoindolin-3-ylidene)thiazolidine-2,4-dione showed significant activity against that they enhanced PL inhibitory activity. [71]

Scheme 12: synthesis of 2,4-thiazolidinediones

Zafar Iqbal, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from bicyclo[2.2.1]heptan-2-one (**54**) in the presence of potassium cyanide, ammonium carbonate and HCl as an starting material **(Scheme 12).** All the synthesized compounds evaluated for their antidiabetic activity against that they enhanced PL inhibitory activity. Potential compound 3-arylsulfonylspiroimidazolidine-2,4-diones showed significant activity against that they enhanced PL inhibitory activity. [72]



Scheme 13: synthesis of 2,4-thiazolidinediones

Amar G. Chittiboyina, ***et al.,*** described that 2,4-thiazolidinediones derivatives were developed from substituted hydroxylammonium chloride 5-(4-Propoxy-benzyl)-thiazolidine-2,4-dione (**55**) reacted with [1,2]Ditholan-3-yl-acetic acid in the presence of triethylamine and dichloromethane as an starting material **(Scheme 13).** All the synthesized compounds evaluated for their antidiabetic activity against PPAR-y agonist. Potential compound 2,2′-[{8-[(2-{4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)methyl]phenoxy}- ethyl)(methyl)amino]-8-oxooctane-1,3-diyl}bis(thio)]bis(2-oxo-ethanaminium) showed significant activity against PPAR-y agonist. [73]

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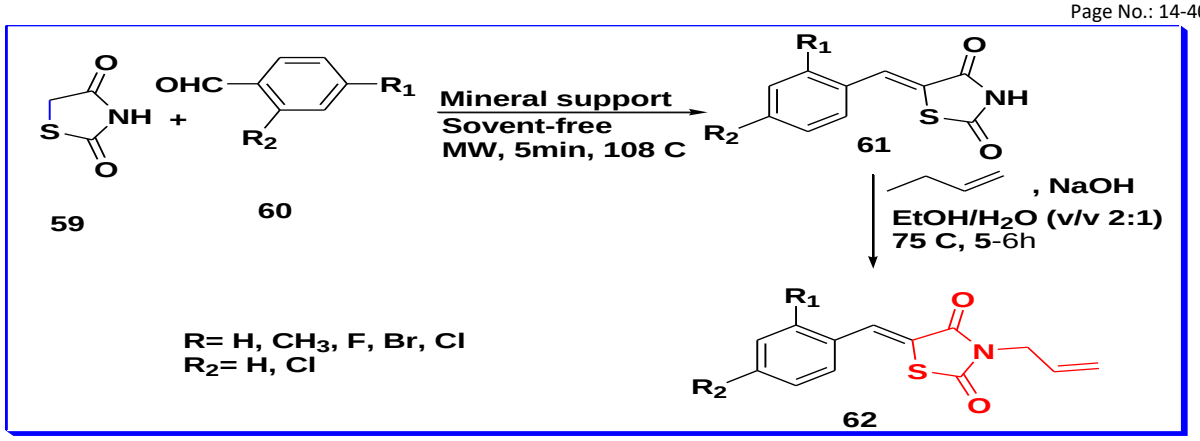
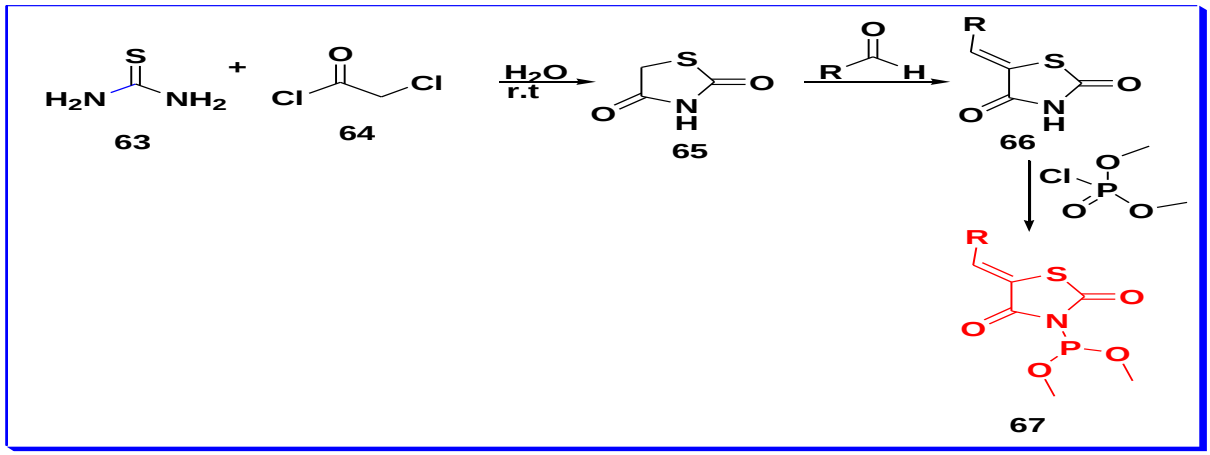


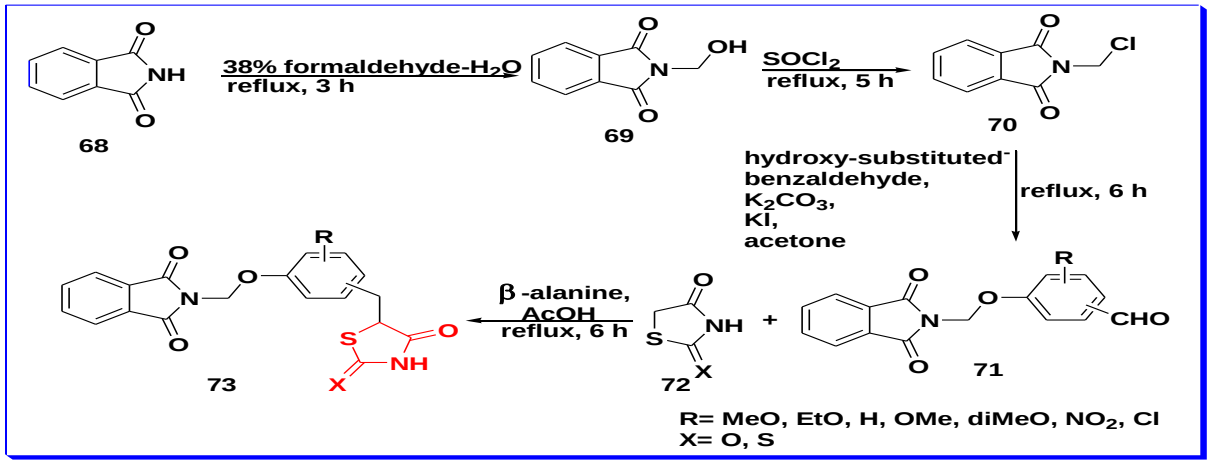
Scheme 14: synthesis of 2,4-thiazolidinediones

Saad Fettach, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from thiazolidine-2,4-dione **(59)** reacted with substituted benzaldehyde in the presence of mineral support as an starting material **(Scheme 14)**. All the synthesized compounds evaluated for their antidiabetic activity against alpha amylase and alpha glucosidase. Potential compound 3-Allyl-5-(2,4-dichlorobenzylidene)thiazolidine-2,4- dione showed significant activity against alpha amylase and alpha glucosidase. [74]



Scheme 15: synthesis of 2,4 thiazolidinedione

Bogiri Sujatha, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from thiourea **(63)** reacted with chloro-acetyl-chloride in the presence of water as an starting material **(Scheme 15)**. All the synthesized compounds evaluated for their antidiabetic activity against PPARy. Potential compound (Z)-dimethyl 5-((5-methoxypyridin-2-yl)methylene)-2,4-dioxothiazolidin-3-ylphosphonate showed significant activity against PPARy. [75]



Scheme 16: synthesis of 2,4-thiazolidinedione

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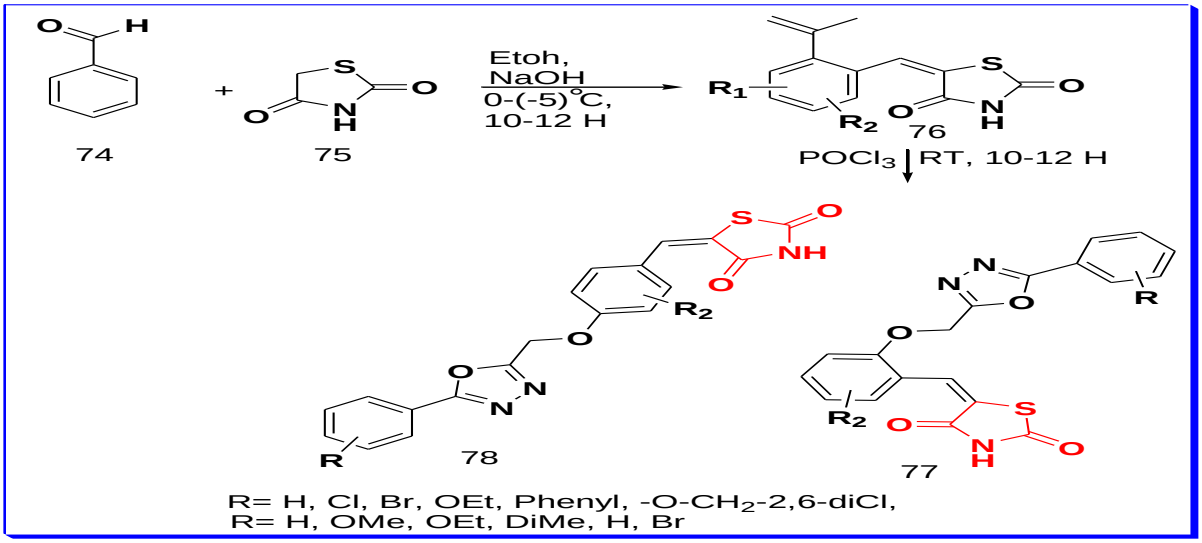
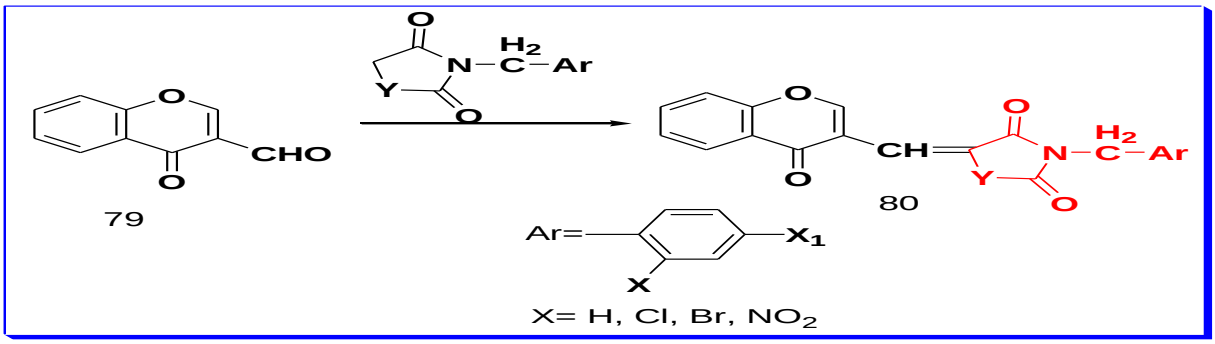
Guang-cheng Wang, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from isoindole1,3-dione **(68)** in the presence 38% formaldehyde-H_2O as an starting material **(Scheme 16)**. All the synthesized compounds evaluated for their antidiabetic activity against that they inhibit alpha-glucosidase activity. Potential compound (Z)-2-((2-Chloro-4-((4-oxo-2-thioxothiazolidin-5-ylidene)- methyl)phenoxy)methyl)isoindoline-1,3-dione showed significant activity against that they inhibit alpha-glucosidase activity. [76]



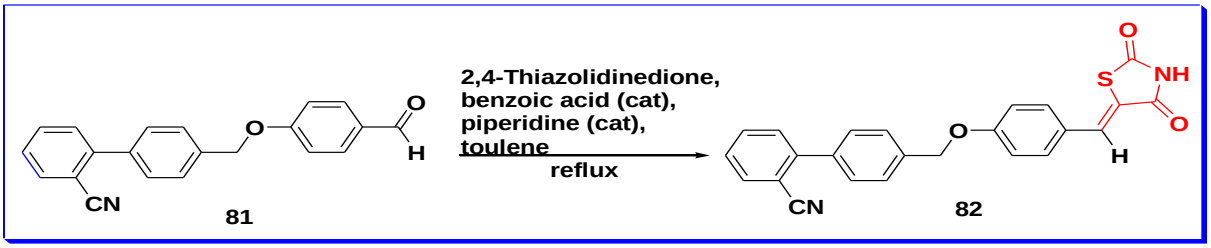
Scheme 17: synthesis of 2,4-thiazolidinediones

Syed Nazreen, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from benzaldehyde **(74)** reacted with thiazolidine-2,4-diones in the presence ethanol and sodium hydroxide as an starting material **(Scheme 17)**. All the synthesized compounds evaluated for their antidiabetic activity against that they increase PPAR-y gene expression. Potential compound 5-[2-[[5-{(2,4-Dichlorophenoxy)methyl}-1,3,4-oxadiazol-2- yl]methoxy] benzylidene]thiazoli dine-2,4-dione showed significant activity against that they increase PPAR-y gene expression . [77]



Scheme 18: synthesis of 2,4-thiazolidinediones

Oya Bozdag˘-Dündar, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from **(79)** reacted with substituted thiazolidine-2,4-diones as an starting material **(Scheme 18)**. All the synthesized compounds evaluated for their antidiabetic activity against INS-1 cells. Potential compound 3-(4-Bromo-benzyl)-5-(4-oxo-4H-chromen-3- yl-methylene)-thiazolidine-2,4-dione showed significant activity against INS-1 cells. [78]



Scheme 19: synthesis of 2,4-thiazolidinediones

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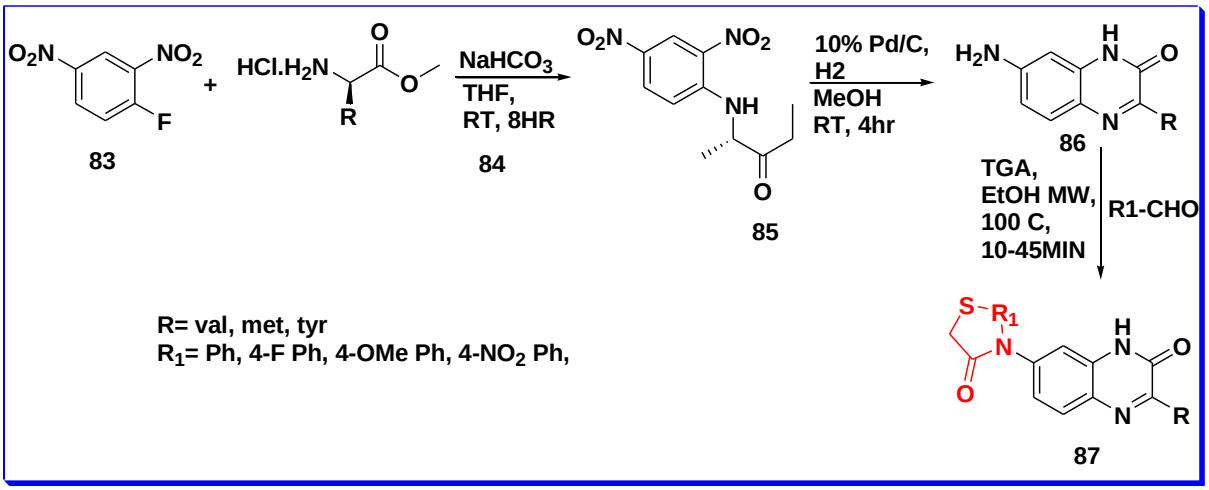
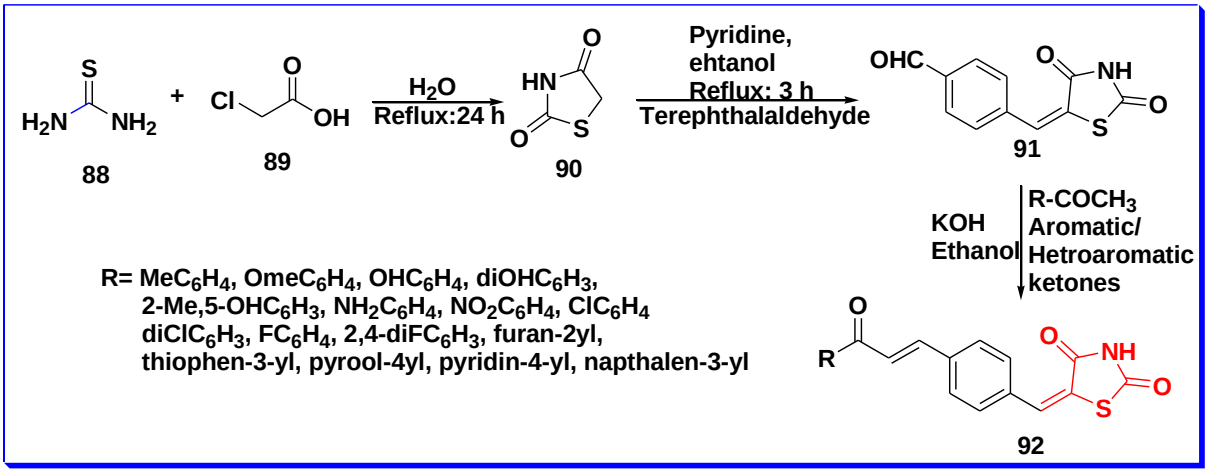
Sergio Hidalgo-Figueroa, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from 3-[4-(4-Formyl-phenoxymethyl)-phenyl]-2-methyl-penta-2,4-dienenitrile **(81)** reacted with thiazolidine-2,4-diones in the presence of benzoic acid, piperidine and toulene as an starting material **(Scheme 19)**. All the synthesized compounds evaluated for their antidiabetic activity against that they increasing in the mRNA expression of PPAR a, PPAR c, and also GLUT 4. Potential compound 4′-({4-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl]phenoxy}methyl)-1,1′-biphenyl-2-carbonitrile showed significant activity against that they increasing in the mRNA expression of PPAR α, PPAR β, and also GLUT 4. [79]



Scheme 20: synthesis of 2,4-thiazolidinedione

Suhas A. Shintre, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from 1-Fluoro-2,4dinitro-benzene **(83)** reacted with substituted amino-acetic acid methyl ester in the presence of sodium bicarbonate and tetrahydrofuran as an starting material **(Scheme 20)**. All the synthesized compounds evaluated for their antidiabetic activity against that they show α amylase and α glucosidase inhibitory activity. Potential compound 3-(4-Hydroxybenzyl)-7-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)quinoxalin-2(1H)-one showed significant activity against that they show α amylase and α glucosidase inhibitory activity. [80]



Scheme 21: synthesis of 2,4-thiazolidinedione

Divakara Laxman Somayajulu Nori, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from thiourea **(88)** reacted with substituted chloro-acetic acid in the presence of water as an starting material **(Scheme 21)**. All the synthesized compounds evaluated for their antidiabetic activity against that they show α glucosidase inhibitory activity. Potential compound (Z)-5-(4-((E)-3-(2-fluorophenyl)-3-oxoprop-1-enyl)benzylide ne)-1,3-thiazolidine-2,4-dione showed significant activity against that they show α glucosidase inhibitory activity. [81]

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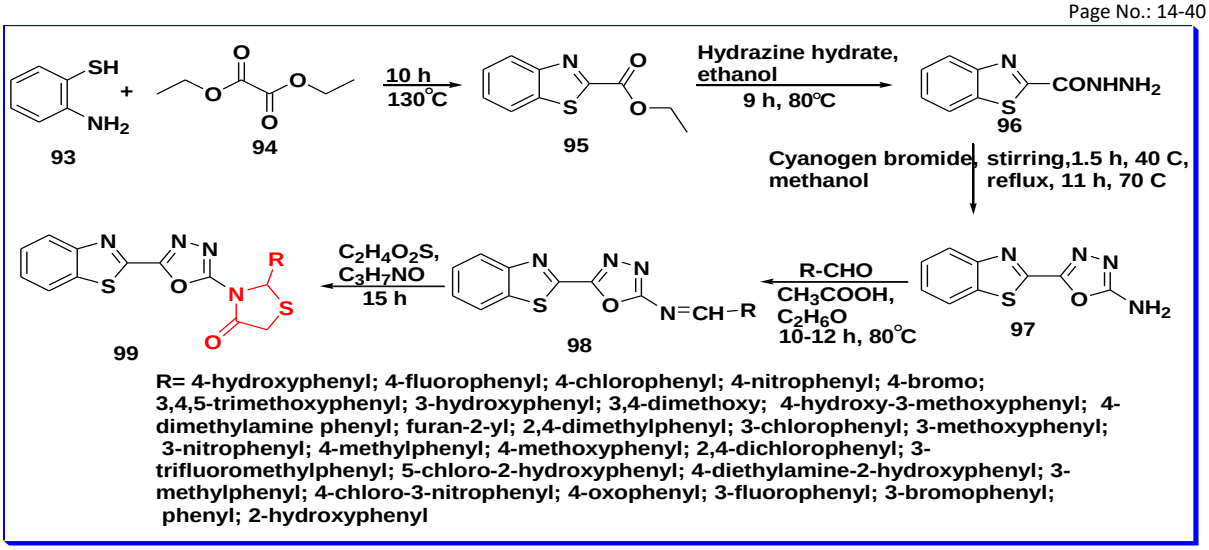
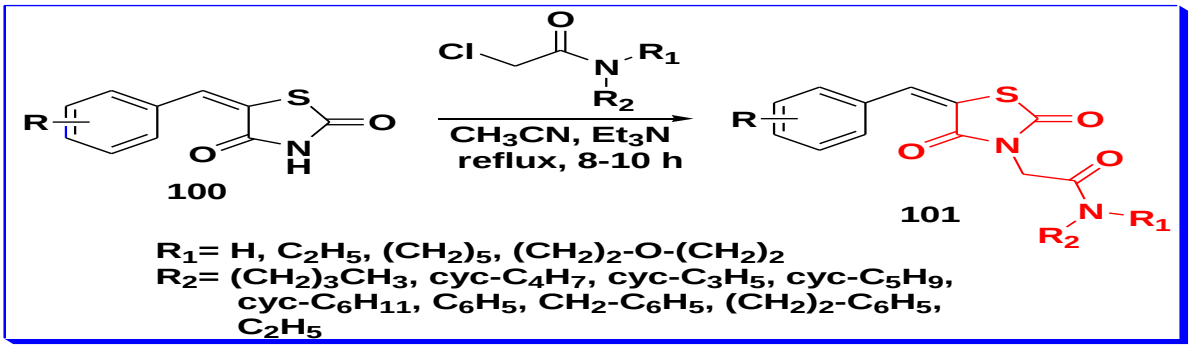


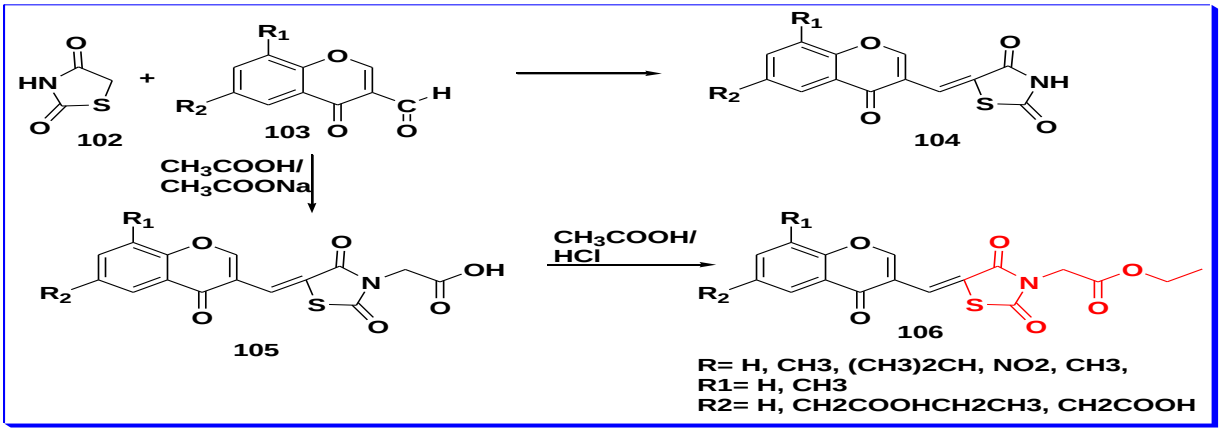
Scheme 22: synthesis of 2,4-thiazolidinedione

Rubina Bhutani, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from 2-amino-benzenethiol **(88)** reacted with oxalic acid diethyl ester for 10 h at 130°c as an starting material **(Scheme 22)**. All the synthesized compounds evaluated for their antidiabetic activity against that they show α glucosidase inhibitory activity. Potential compound 3-[5-(benzo[d]thiazol-2-yl)-1,3,4-oxadiazol-2-yl]-2-(4- diethylamino-2-hydroxyphenyl) thiazolidin-4-one showed significant activity against that they show α glucosidase inhibitory activity. [82]



Scheme 23: synthesis of 2,4-thiazolidinedione

Sabina Yasmin, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from substituted benzylidene-thiazolidine-2,4-dione **(100)** reacted with substituted 2-chloro-acetamide in the presence of methyl cyanide and triethylamine as an starting material **(Scheme 23)**. All the synthesized compounds evaluated for their antidiabetic activity against that they exhibited selectivity towards PPAR-γ. Potential compound 2-(5-Benzyldene-2,4-dioxo-thia1zolidine-3-yl)-N,N-dimethyl-acetamide showed significant activity against that they exhibited selectivity towards PPAR-γ. [83]



Scheme 24: synthesis of 2,4-thiazolidinedione

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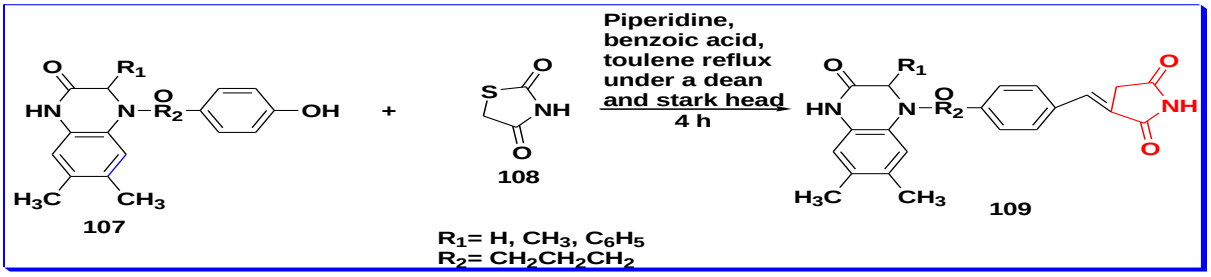
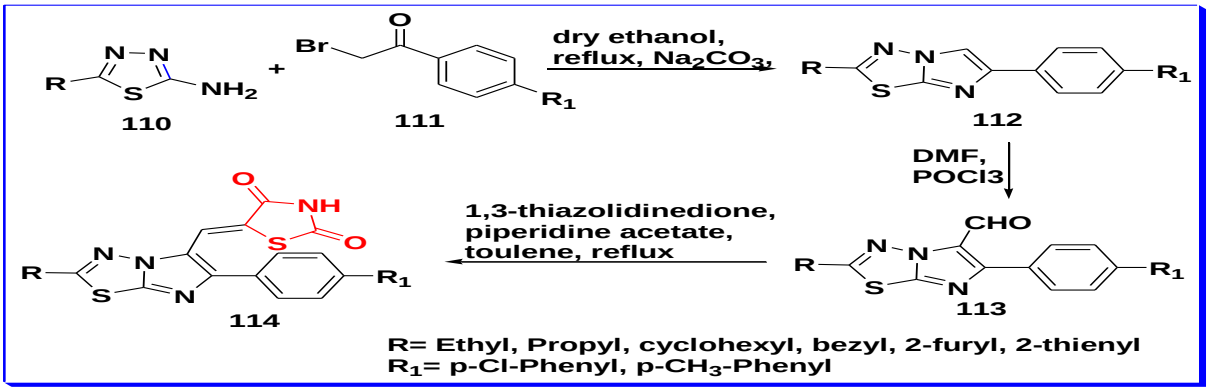
Oya Bozdag-Du ˘ ¨ndar, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from thiazolidine-2,4-dione **(102)** reacted with 4-Oxo-4H-chromene-3-carbaldehyde in the presence of acetic acid and sodium acetate as an starting material **(Scheme 24)**. All the synthesized compounds evaluated for their antidiabetic activity against that they inhibit AR. Potential compound {2,4-Dioxo-5-[(6-nitro-4-oxo-4H-chromen-3- yl)methylene]-1,3-thiazolidine-3yl}acetic acid showed significant activity against that they inhibit AR. [84]



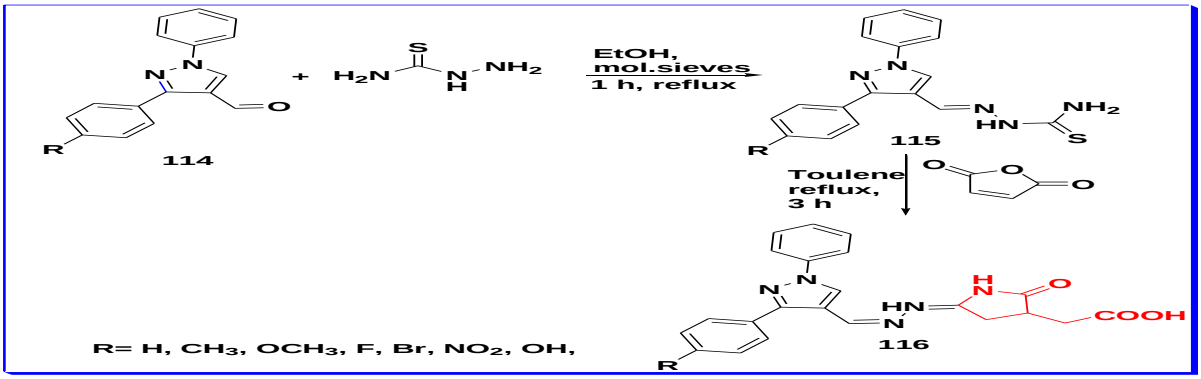
Scheme 25: synthesis of 2,4-thiazolidinedione

Dipti Gupta, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from substituted 4-(4-hydroxy-benzyl)-6,7-dimethyl-3,4-dihydro-1H-quinoxalin-2-one **(107)** reacted with thiazolidine-2,4-dione in the presence of piperidine, benzoic acid and toluene as an starting material **(Scheme 25)**. All the synthesized compounds evaluated for their antidiabetic activity against that they decrease plasma glucose. Potential compound 5-[4-[2-(6,7-dimethyl-1,2,3,4-tetrahydro-2-oxo-4-quinoxalinyl)ethoxy]phenyl]-methylene]thiazolidine-2,4-dione showed significant activity against that they decrease plasma glucose . [85]



Scheme 26: synthesis of 2,4-thiazolidinedione

Mohammed Iqbal A. Khazi, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from substituted [1,3,4]thiadiazol-2-ylamine **(110)** reacted with substituted 2-bromo-1-phenyl-ethanone in the presence dry ethanol and sodium carbonate as an starting material **(Scheme 26)**. All the synthesized compounds evaluated for their antidiabetic activity against that they show PPAR-y agonist. Potential compound 5-{[2-Cyclohexyl-6-(4-methoxyphenyl)imidazo [2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1, 3-thiazolidine-2,4-dione showed significant activity against that they show PPAR-y agonist . [86]



Scheme 27: synthesis of 2,4-thiazolidinedione

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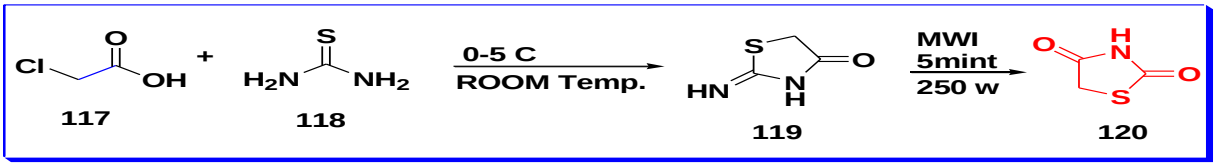
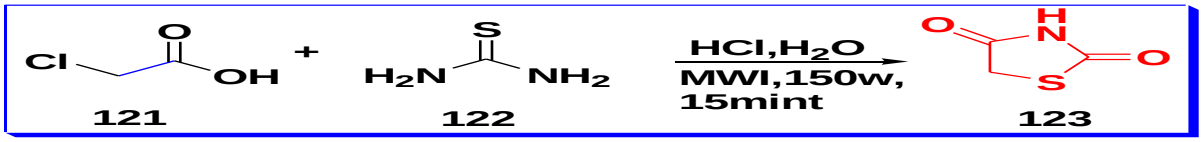
Manisha R. Bhosle, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from substituted 3-(4-substitutedphenyl)-1- phenyl-1H-pyrazole-4-carbaldehydes **(114)** reacted with thiosemicarbazide in the presence ethanol as an starting material **(Scheme 27)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y agonist. Potential compound 2-(4-(1-phenyl-3-4-nitrophenyl-pyrazol-4-yl) methylene-2-hydrazolyl) -1,3-thiazolidin-5-yl-acetic acid showed significant activity against that they are PPAR-y agonist. [87]



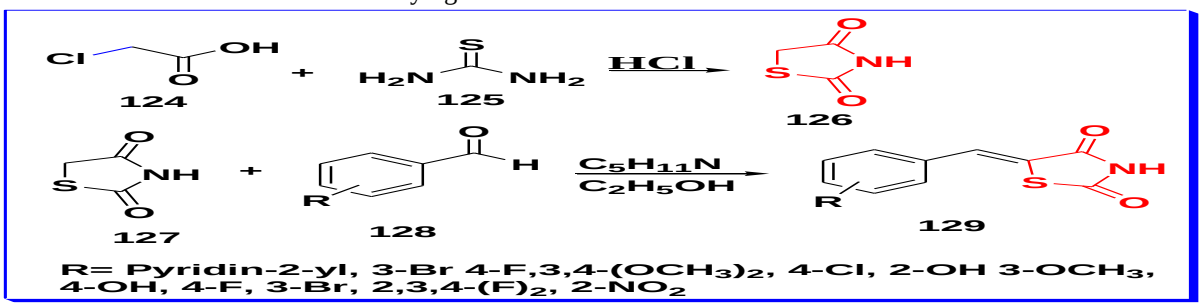
Scheme 28: synthesis of 2,4-thiazolidinedione

Kumar, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from chloroacetic corrosive **(117)** reacted with thiourea at room temperature as an starting material **(Scheme 28)**. All the synthesized compounds evaluated for their antidiabetic activity against with 93% yield. Potential compound (Z)-5-Benzylidene-thiazolidine-2,4-dione showed significant activity against with 93% yield. [88]



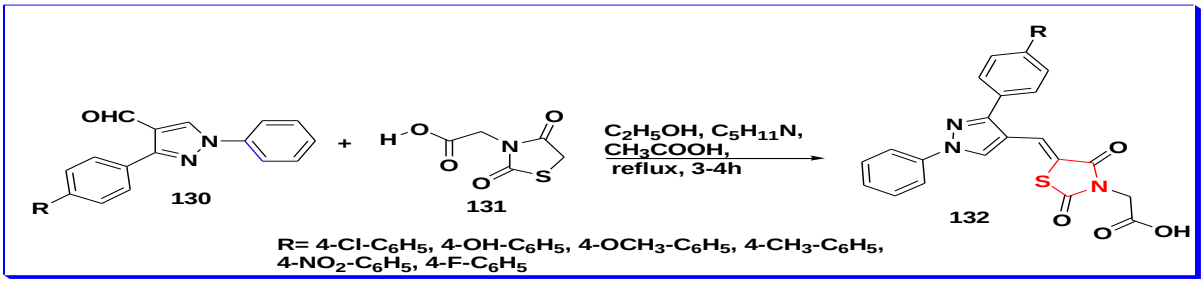
Scheme 29: synthesis of 2,4-thiazolidinedione

Marc, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from chloroacetic acid **(121)** reacted with thiourea in the presence of water and hydrochloric acid as an starting material **(Scheme 29)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y agonist. Potential compound 5-(3-methoxy-4-(2-oxo-2-phenylethoxy)benzylidene)- 3-(2-oxo-2-phenylethyl)thiazolidine-2,4-dione showed significant activity against that they are PPAR-y agonist. [89]



Scheme 30: synthesis of 2,4-thiazolidinedione

Pardeshi, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from thiazolidine-2,4-dione **(127)** reacted with benzaldehyde derivative in the presence of piperidine and ethanol as an starting material **(Scheme 30)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y agonist. Potential compound 5-(2,3,4-trifluorobenzylidene) thiazolidine-2,4-dione showed significant activity against that they are PPAR-y agonist. [90]



Scheme 31: synthesis of 2,4-thiazolidinedione

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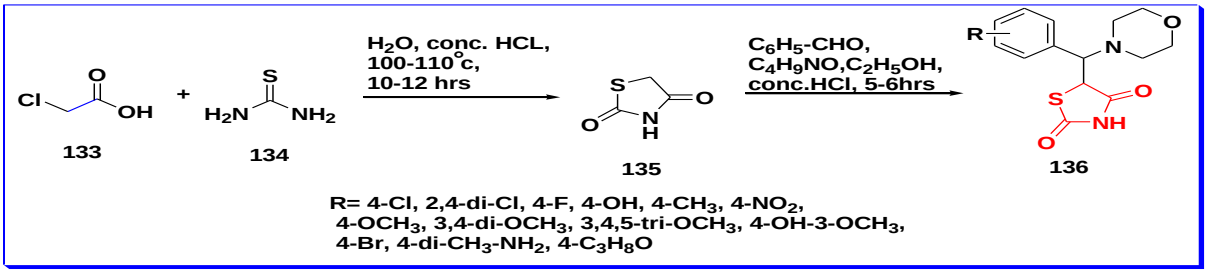
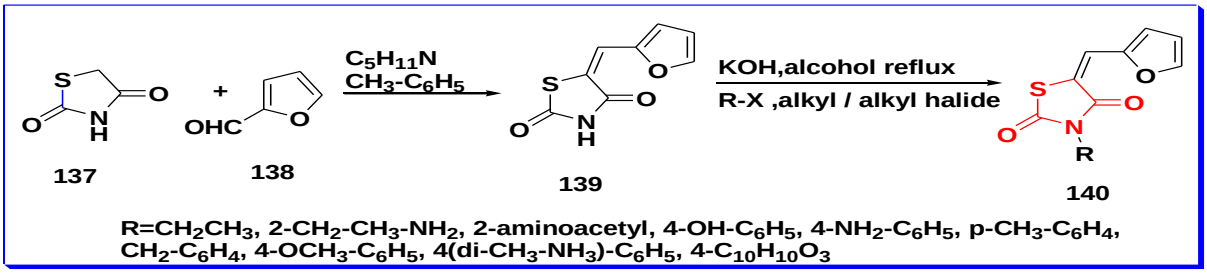
Bansal, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from 1,3-Diphenyl-1H-pyrazole-4-carbaldehyde derivative **(130)** reacted with (2,4-Dioxo-thiazolidin-3-yl)-acetic acid in the presence of piperidine, glacial acetic acid in ethanol as an starting material **(Scheme 31)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y agonist. Potential compound 2-(5-((3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)- 2,4-dioxothiazolidin − 3-yl)acetic acid showed significant activity against that they are PPAR-y agonist. [91]



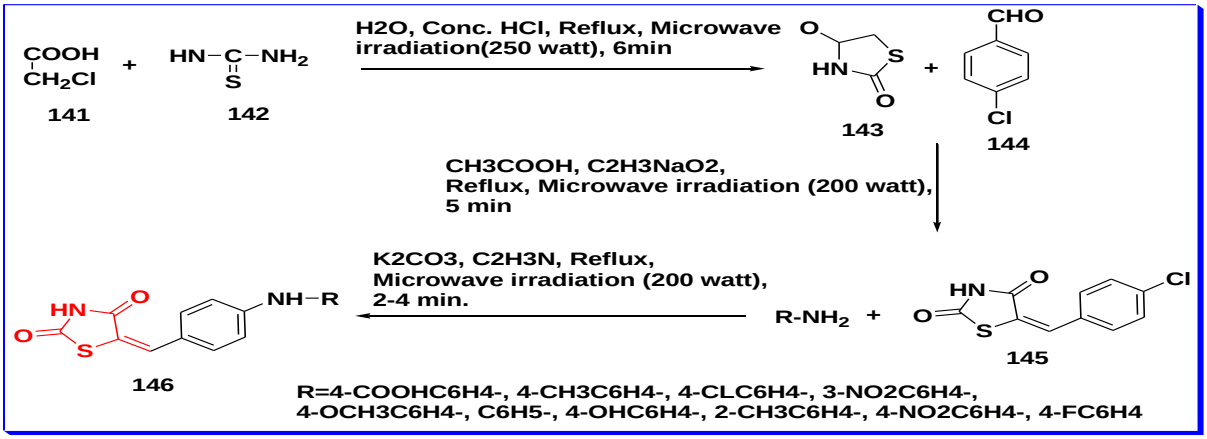
Scheme 32: synthesis of 2,4-thiazolidinedione

Karumanchi, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from chloro-acetic acid **(133)** reacted with thiourea in the presence of water and conc. hydrochloric acid as an starting material **(Scheme 32)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y protein. Potential compound 5-[(3,4-dimethoxyphenyl)-morpholin-4 yl-methyl]- thiazolidine-2,4-dione showed significant activity against that they are PPAR-y protein. [92]



Scheme 33: synthesis of 2,4-thiazolidinedione

Kumar, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from thiazolidine-2,4-dione **(137)** reacted with Furan-2-carbaldehyde in the presence of piperidine in toulene as an starting material **(Scheme 33)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y protein. Potential compound -(4-hydroxyphenyl)-5-[(furan-2-yl)-methylene]-thiazolidine-2,4-dione showed significant activity against that they are PPAR-y protein. [93]



Scheme 34: synthesis of 2,4-thiazolidinedione

Patel, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from chloro-acetic acid **(141)** reacted with thiourea in the presence of water and conc. Hydrochloric acid as an starting material

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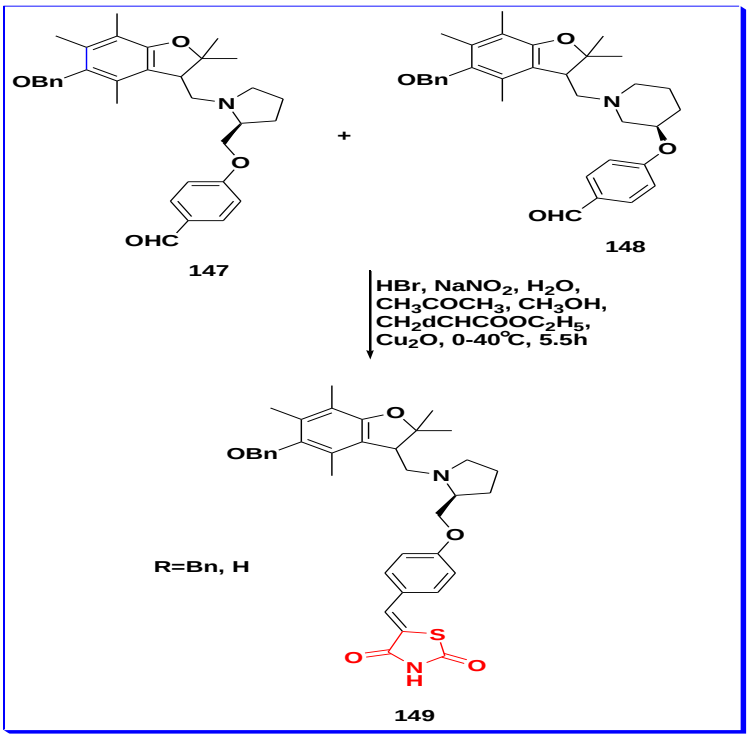
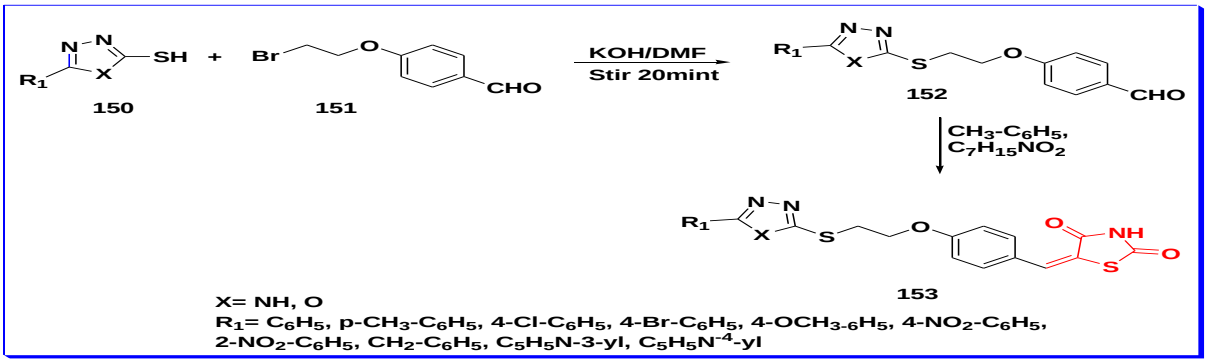
(Scheme 34). All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y protein. Potential compound 5-[4-(4-amino anisole) benzylidene] thiaolidine-2,4-dione showed significant activity against that they are PPAR-y protein. [94]



Scheme 35: synthesis of 2,4-thiazolidinedione

Reddy, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from 4-[1-(5-Benzyl-2,2,4,6-tetramethyl-2,3-dihydrobenzofuran-3-ylmethyl)-pyrrolidin-2-ylmethoxy]-benzaldehyde compound with inorganic neutral compound **(147)** reacted with 4-[1-(5-Benzyl-2,2,4,6,7-pentamethyl-2,3-dihydro-benzofuran-3-ylmethyl)-piperidin-3-yloxy]-benzaldehyde with inorganic compound in the presence of halogen, sodium nitrite and water as an starting material **(Scheme 35)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y protein. Potential compound 5-[4-[N-[3(R/S)-5-benzyloxy-2,3-dihydro2,2,4,6,7-pentamethylbenzofuran-3-ylmethyl]-(2S)-pyrrolidin-2-ylmethoxy] phenylene]-thiazolidine-2,4-dione showed significant activity against that they are PPAR-y protein. [95]



Scheme 36: synthesis of 2,4-thiazolidinedione

Iqbal, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from substituted thiazole, triazole and oxadiazole **(150)** reacted with dominant phenyl ring in the presence of water and conc. Hydrochloric acid as an starting material **(Scheme 36)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y protein. Potential compound 5-[4-(2- {[5-(4-Methoxyphenyl)-4H-1,2,4-triazol-3-yl] thio} ethoxy) benzylidene]-1,3-thiazolidine-2,4-dione showed significant activity against that they are PPAR-y protein. [96]

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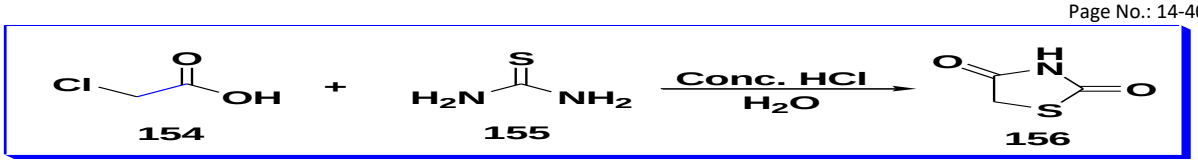
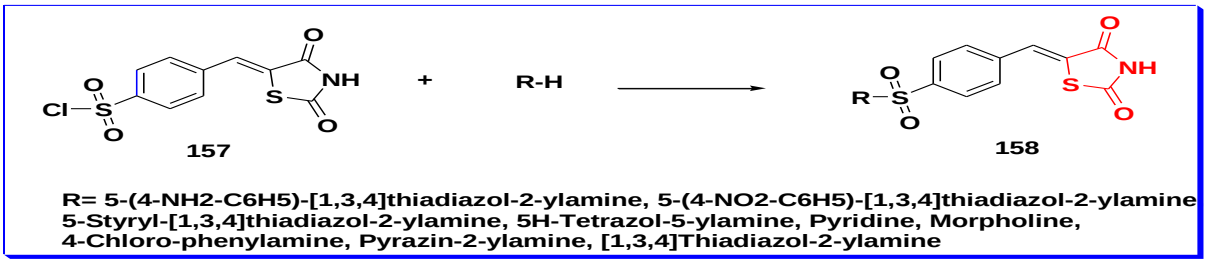


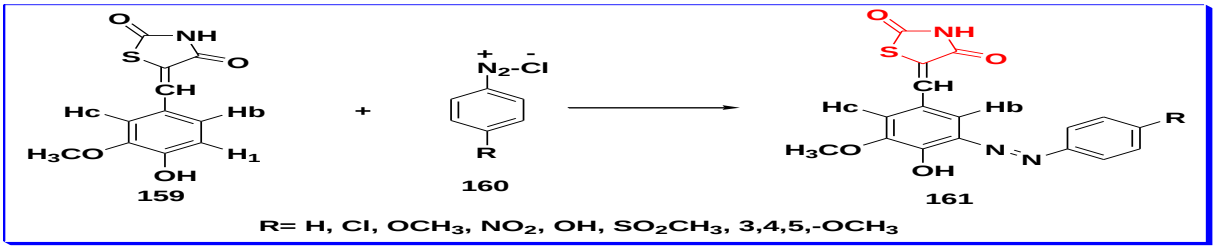
Scheme 37: synthesis of 2,4-thiazolidedione

Mishra, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from chloroacetic acid **(154)** reacted with thiourea in the presence of water and water and concentrated hydrochloric acid as an starting material **(Scheme 37)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y protein. Potential compound 2,4-thiazolidinedione showed significant activity against that they are PPAR-y protein. [97]



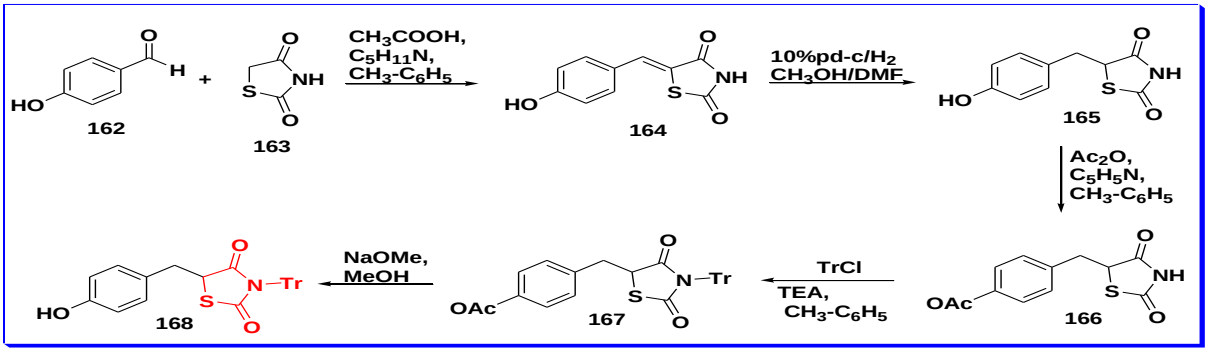
Scheme 38: synthesis of 2,4-thiazolidinedione

Pattan, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from -(2,4-Dioxo-thiazolidin-5-ylidene-methyl)-benzenesulfonyl chloride **(157)** reacted with substituted hydrogen in the presence of water and water and concentrated hydrochloric acid as an starting material **(Scheme 38)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y protein. Potential compound N-[5-(4-Amino-phenyl)- [1,3,4] thiadiazol-2- yl]-4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-benzenesulfonamide showed significant activity against that they are PPAR-y protein. [98]



Scheme 39: synthesis of 2,4-thiazolidinedione

Kadium, *et al.,* described that 2,4-thiazolidinediones derivatives were developed from thiazolidine-2,4-dione ligands that were fused from (z)-5(4-hydroxy-3- methoxybenzylidine)-2,4-thiazolidinedione **(159)** reacted with diazonium salt derivative as an starting material **(Scheme 39)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y protein. Potential compound 5-((E)-4- hydroxy-3-methoxy-5-((Z)-(4(methylsulfonyl)phenyl) diazenyl) benzylidene) thiazolidine showed significant activity against that they are PPAR-y protein. [99]



Scheme 40: synthesis of 2,4-thiazolidinedione

Jeon, *et al.*, described that 2,4-thiazolidinediones derivatives were developed from 4-Hydroxy-benzaldehyde **(162)** reacted with Thiazolidine-2,4-dione in the presence of benzoic acid, piperidine in toluene as as an starting material **(Scheme 40)**. All the synthesized compounds evaluated for their antidiabetic activity against that they are PPAR-y protein. Potential compound 5-[4-[2-(Benzoxazol-2-yl-alkylamino) ethoxy] benzyl] thiazolidine-2,4-diones showed significant activity against that they are PPAR-y protein. [100]

CONCLUSION

Based on the issued data, we can conclude that Thiazolidine-2,4-dione derivatives are highly versatile compound with various therapeutic potentials including anti-inflammatory, anti-proliferative, anti-microbial, antiviral, anticonvulsant, etc. In this review, we summarized synthetic approaches for the creating of new Thiazolidine-2,4-dione analogues under various reaction conditions and highlight information on their pharmacological activities. Given their broad clinical application and pharmacological applications, especially regarding PPAR-α, PPAR-γ, as well as other pharmacological effects, the therapeutic benefits of 2,4-thiazolidinediones warrant further investigation. The review also discusses the synthesis of Thiazolidine-2,4-dione derivatives with different scaffolds and their structure-activity relationships. It aims to guide researchers in exploring these compounds for potential treatments for diabetes and other diseases.

LIST OF ABBREVATION

3T3 = 3-day Transfer PPAR

PPAR = Peroxisome Proliferator-activated Receptors

PPAR α = Peroxisome Proliferator-activated Receptors Alpha

CONSENT FOR PUCLICATION

Not Applicable.

CONFLICT OF INTREST

The authors declare no conflict of interest, financial or otherwise.

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