

THIAZOLE DERIVATIVES AS POTENTIAL ANTIDIABETIC AGENTS

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ABSTRACT

Various molecules showing pharmacological activities consist of thiazole as a core structure having heteroatom as sulfur and nitrogen. Thiazole is present in many naturally occurring compounds, along with vitamin B1 and penicillin. Thiazole is used in different biological fields, and it is also known as a wonder nucleus. Thiazole moieties are contained in many new compounds, and hence it is one of the essential areas of research. Diabetes is one of the life-threatening diseases and has become a pandemic presently more than 400 million people are suffering from this and likely to be double by the next ten years. Noncompliance, hypoglycemia, and obesity can be caused by most diabetic drugs. As a result, new antidiabetic drugs with thiazole moieties were synthesized with improved efficacy and minimized side effects. Considering the prominence of the past as well as the latest developments in drugs as an antidiabetic drug having thiazole ring as an antidiabetic drug and its significance, is this described in the present review.

Keywords: Thiazole, Diabetes, Antidiabetic

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INTRODUCTION

The most common form of the disease is Type 2 diabetes which accounts for approximately 90% of cases.¹ Among the well-known bioactive scaffolds, the heterocyclic compounds five-membered heterocyclic compounds were extensively explored in organic and pharmaceutical chemistry.² The most common five-membered heterocyclic compound is the thiazole ring, namely 1, 3-thiazole, which incorporates both nitrogen and sulfur. Thiazole is a pale yellow liquid having an odor similar to pyridine, and its molecular formula is C_3H_3NS . From the penicillin, the nucleus of which showed diverse activity of its different derivatives such as antimicrobial (sulfazole), antiretroviral (ritonavir),³ antifungal (abafungin),⁴ anti-thyroid, and antihistaminic activities,⁵ the versatility of thiazole scaffold has been described. Due to the extensive applications offered by thiazoles in the field of drug design and discovery, they occupy an important place in ongoing medicinal chemistry. Thiazoles are also used as an anti-ulcer agent (nizatidine), a cancer treatment drug (tiazofurin), an anti-depressant drug (pramipexole), HIV/AIDS drug (ritonavir), and an anti-inflammatory drug (meloxicam). Compared to the five-membered heterocycles such as oxazole, thiophene, furan, isoxazole, and isothiazole, thiazole is a more regular essential of FDA-approved pharmaceuticals. Apart from many different beneficial effects, insulin is regulated by GLP-1 in a strictly glucose-dependent manner.⁶ Pyrazolines are found to be useful as antioxidant composition in polymers.⁷ On the other hand, the process of photocatalysis widely uses the metal complexes of thiazole. Using 1,3-thiazoles, many fused heterocyclic compounds such as imidazothiazoles, thiazolopyridine, thiazolopyrimidine were synthesized. When 1,3-thiazoles undergo a separate set of reactions. After the work of Hofmann and Hantsch⁸ on thiazole, the chemistry of thiazole and its derivatives progressively emerged. A significant contribution to expanding the importance of the thiazole ring in synthetic and biological chemistry was made by Bogert⁹ and further Mills.¹⁰ Recently, many reviews on diverse biological activities on thiazole and its derivatives have been published.¹¹ Considering the prominence of the past and the latest developments, the biological importance of the thiazole nucleus and its derivatives as antidiabetic agents has been described in the present review. Many different classes of drugs as antidiabetic, such as sulfonylureas, biguanides, insulin and insulin analogs,

have been happening for many years. However, most drugs are associated with metabolic disorders such as noncompliance, hypoglycemia, and obesity. Therefore, the requirement is to have a new antidiabetic drug with improved compliance and reduced side effects.

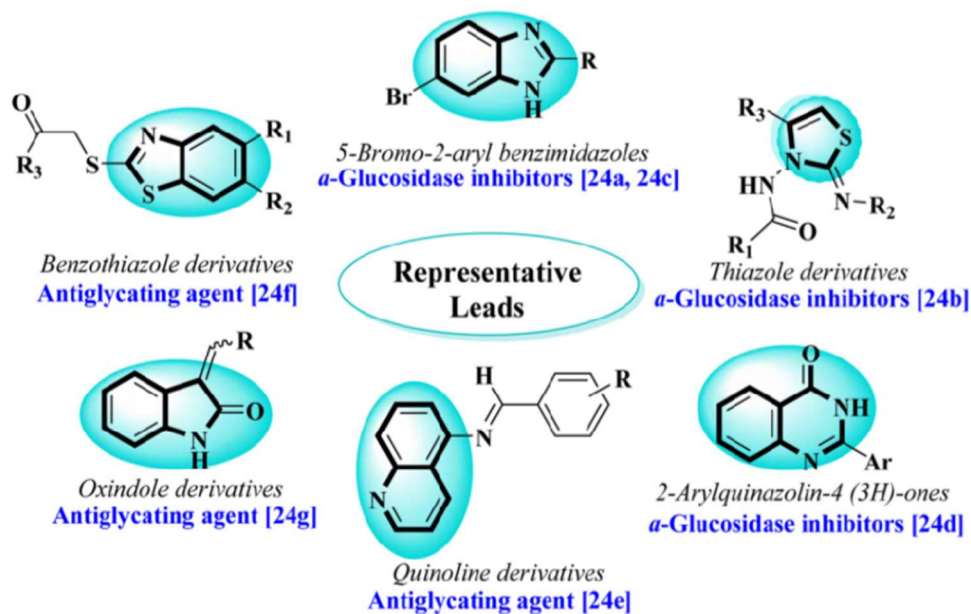


Fig.-1: Representative Leads of Thiadiazole Derivatives

Thiazole Derivatives as Antidiabetics

1. A series of sixteen different thiazole-containing derivatives were synthesized as dipeptidyl peptidase IV (DPP-IV) inhibitors. The study of all thiazole derivatives was done for their blood glucose level decreasing activity through a rat oral glucose tolerance test (OGTT). The results of this study showed that two compounds 14 and 15 displayed good hypoglycemic activity to decrease the blood glucose level at % inhibitory rate 24.9 and 19.2 (at 100 mg/kg dose) respectively, and were equally potent to gliclazide; this signifies the importance of these derivatives as a promising lead for the treatment of type II diabetes (DM)¹²

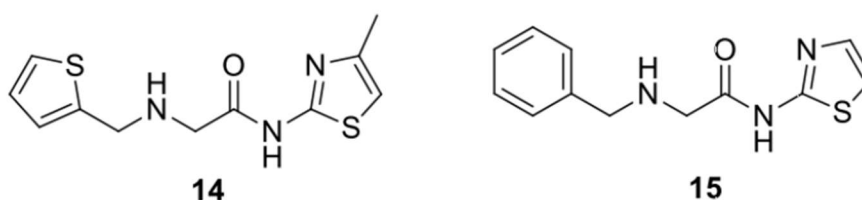


Fig.-2: Thiazole Derivatives as dipeptidyl peptidase IV (DPPH-IV) inhibitors

2. A vital scaffold, Isatin, was explored with thiazole as a potential α -glucosidase inhibitor. Among them, compound 22 was most potent with $IC_{50} = 5.36 \mu M$ in the *in vitro* α -glucosidase inhibitory activity. Further, the consistency of results on *Saccharomyces cerevisiae* α -glucosidase enzyme (3AJ7) was shown by molecular docking study as well. The binding affinity with the energy of -10.1 kcal/mol at the binding site of the α -glucosidase enzyme was shown by Compound 22. The hydrogen bonding of 22 with Glu-276 and Asp-68 amino acid residues along with 2-fluorophenyl form hydrophobic interaction with Phe-157, Leu-176, Leu-218, and Pro-240 amino acid residues was shown by the in-depth analysis.¹³

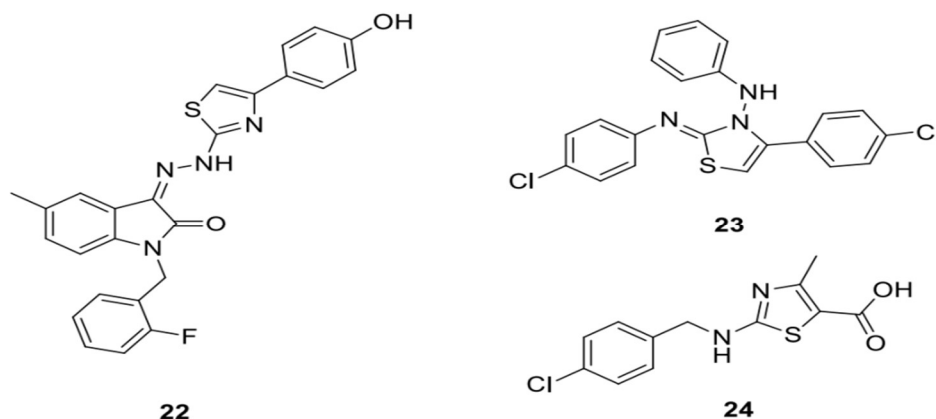


Fig.-3: Thiazole Derivatives as a potential α -glucosidase inhibitor

Pharmacological Activities of Thiazolidinedione

1. Various new analogs of thiazolidinedione containing different heterocyclic rings such as thiazole, triazole, and oxadiazole were synthesized and evaluated for antidiabetic and hypolipidemic properties. Among all these synthesized compounds, a compound containing thioethoxy linkage with triazole and oxadiazole showed excellent results among all the synthesized compounds.¹⁴

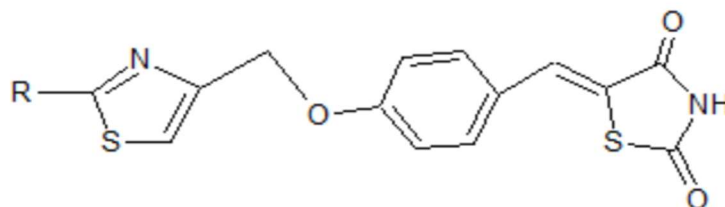


Fig.-4: Thiazolidinone Derivatives as antidiabetic agents

2. Various compounds for the inhibition of Aldose reductase (ARI) were synthesized and their *in vitro* inhibiting properties for aldose reductase were reported. It was observed that compounds with various substituted 2,4-thiazolidinedione analogs were best among all the synthesized compounds as aldose inhibitors. It was concluded that noncarboxylic acid compounds consisting of 5-arylidene-2,4-thiazolidinediones were potent at low-micromolar doses.¹⁵

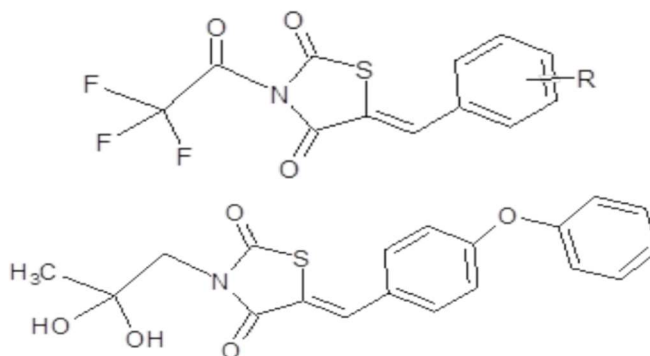


Fig.-5: Thiazolidinedione Derivatives as aldose reductase inhibitors

Mechanism of action of Thiazolidinediones (TZDs)

Due to triggering particular nuclear receptor peroxisome proliferator-activated receptor gammas (PPAR γ),¹⁶ TZDs doubtlessly stimulate actual transcriptional events in adipocytes. The extraction of

PPAR γ was done from white and brown adipocytes cell. PPAR γ forms complexes with X receptor of the retinoid present in the nucleus.¹⁷ TZDs are lipophilic, due to which they get into cell easily and hold together to PPAR γ with great attraction.¹⁸ In the PPAR γ -RXR complex, a conformational change is caused by this, which replaces a co-repressor and authorizes the stimulation of controlling sequences of DNA, which thereby commands the extraction of specific genes. Insulin controls some of these genes. Hence, amplification or imitation of definite genomic effects of insulin on adipocytes is done by TZDs. In this way, enhancement of extraction of genes computing enzymes such as lipoprotein lipase and the fatty acid transporter protein (FATP) can be done using TZDs. However, other enzymes such as the adipocyte requisite protein (aP2), fatty synthase, glucokinase can also be done through the same. In consequence, an enhancement in fatty acid uptake and lipogenesis is the major biological effect of TZDs on adipocytes. The alteration regards preadipocytes (and other non-terminally differentiated cultured cells) into adipocytes¹⁹ is also promoted by TZDs. It is believed to bring change to obesity.²⁰ Later, it has been noticed after persistent intake of TZDs, apparently, the drugs employ some other route *in vivo* that brings excessive adipogenesis. Lipogenesis gets diminished as there is an elevation in the concentration of englitazone.²¹ It further observed that there is a significant decrease in the concentration of blood glucose level and lipid profile within the transgenic aP2/DTA mice absence of white and brown adipose tissue when treated with troglitazone. Since most of the expression for PPAR γ receptor has been shown by tissue present in the skeletal muscle along with the liver tissue, therefore it can be stated as the target of TZDs. Apart from these, it has also been observed the low affinity for TZDs within other muscles and some parts of the liver may result in different biological actions within adipocytes cells. Due to this different or opposite action, the complete differentiation for its classification is not justified. Apart from these, TZDs tend to prove the relation between PPAR γ and its blood-lowering properties.²² it has also been observed that troglitazone increase the blood glucose utilization and its transportation, especially in the isolated soleus muscle with more effects than expected for its transcriptional effect.²³ The may reason explained that it may be because of an increase in the glycogen formation and anaerobic glycolysis apart from these it also enhances glucose utilization and formation that shoes similar process outcome muscle contraction and low oxygen effects and that is different from the effect of insulin.²⁴ However, it has not shown any effect on the impairment in the utilization of glucose.²⁵ with This result, it was observed that any change in PPAR γ present in the liver and adipose tissue has no major contribution in lowering the blood sugar level in the adipose-free transgenic aP2/DTA. Therefore it can be stated that troglitazone has a complete indifferent procedure to lower the blood sugar level in transgenic aP2/DTA mice

CONCLUSION

Thiazole ring has been considered as a potential scaffold in drug discovery and development, proving its potential in the pharmaceutical field. The study and exploration of thiazole, benzothiazole and thiazolidinedione derivatives have been recently very well done in the area of diabetes. These compounds showed potential antidiabetic activity and proved to be useful in diabetic complications. Thiazole derivatives such has rosiglitazone, pioglitazone, troglitazone etc mainly target the PPAR. Recently, it was identified that other enzymes and receptors that play an important role in the pathogenesis of diabetes such as α -amylase, α -glucosidase, SGLT2, dipeptidyl peptidase IV (DPP4), 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), etc. have also been targeted by these thiazole derivatives. Thus, these thiazole derivatives could be further employed to find out the better drug molecule to combat the increasing drug resistance in the treatment of diabetes and diabetic complications.

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