



Review Article

A REVIEW ON THIAZOLIDINEDIONES: A POTENT BIOLOGICAL AGENT

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ABSTRACT

Cardio vascular risk associated with the metabolic syndrome and the state of being subject to death in patients are the serious concerns in clinical exercise. Thiazolidinedione's act as supporting medium of the peroxisome proliferator receptor (γ) improving blood glucose control by reducing insulin reluctance. The use of thiazolidinedione's (TZDs) in the management of type 2 diabetes mellitus (T2DM) has been associated with an increased risk of peripheral edema. TZD's although help to regulate blood glucose levels, however, recent statistical procedure describes limitations of TZD's such as rosiglitazone in controlling CVS disorders by combining data from multiple studies. In this article we have depicted the role of Thiazolidinedione's on other phenomenal pharmacological activities other than anti-diabetic.

Keywords: Thiazolidinedione's, Cardiovascular, Peroxisome, Rosiglitazone, Anti-diabetic.

INTRODUCTION

Thiazolidinedione's (TZDs) have been the subject of extensive researches because of their deep involvement in the regulation of different physiological processes. Thiazolidinedione derivatives have been shown to possess potent immune stimulatory property, antiarthritic Activity as well as oncostatic activity ⁽¹⁾. TZDs such as Troglitazone, Pioglitazone, and Rosiglitazone are potent reducer of plasma glucose level *in vivo*. Besides their anti-diabetic potency, these TZDs have been shown to exert anti-inflammatory effects on vascular cells ⁽²⁾. TZDs were also found to inhibit the production of inflammatory cytokines and the expression of inducible nitric oxide synthases in monocytes macrophages ^(3, 4). It has been shown that TZDs suppress the growth of several cancer cell lines including colon, breast, and prostate *in vivo* and *in vitro* ⁽⁵⁻⁷⁾. TZDs were also found to inhibit angiogenesis ⁽⁸⁾. Some thiazolidinedione derivatives also showed Cu²⁺ mediated lipid-peroxidation inhibitory activity ⁽⁹⁾ and were found to inhibit serum ALT, AST as well as c-GTP levels significantly during treatment in patients with type 2 diabetes. TZDs are also potential cancer chemo preventive agents against colon, breast, tongue, and gastric carcinogenesis. Ciglitazone is the first thiazolidinedione that was found to exhibit anti-hyperglycemic activity ⁽¹⁰⁾. Analog synthesis and *in vivo* screening over a period of 20 years led to the identification of thiazolidinedione's with increased potency. Examples of thiazolidinedione's that have progressed to clinical evaluation are Englitazone, Pioglitazone, Rosiglitazone and Troglitazone. Their molecular mechanism of action is thought to be related to the activation of PPAR γ , a receptor subtype highly expressed in adipocytes and shown to induce adipocyte differentiation. Structure and activity analysis of thiazolidinedione's as antihyperglycemic agents has indicated that benzyl thiazolidinedione analogs are about 100-fold more active than their benzylidene counterparts. In contrast,

benzylidene analogs are more potent than their benzyl counterparts in inhibiting 15-PGDH. The concentrations of thiazolidinedione's needed to activate PPAR γ and to inhibit 15-PGDH are comparable ⁽¹¹⁾. Thiazolidinedione's are known to have marked adipogenic effects on pre-adipocytes and dramatic anti-diabetic effects in animal models of non-insulin-dependent diabetes mellitus. One of the thiazolidinedione's, rosiglitazone, was also found to inhibit adipocyte 11 β -hydroxysteroid dehydrogenase Type I expression and activity. The ability of rosiglitazone to reduce visceral adipose tissue hypertrophy and insulin resistance may result, at least in part, from its ability to inhibit expression of this dehydrogenase activity and, as a result, decrease the level of active glucocorticoid within adipocytes⁽¹²⁾.

The Thiazolidinedione's (TZDs), increases both circulating adiponectin concentrations and mRNA expression in adipose tissue. Thiazolidinedione's (TZDs), including rosiglitazone (RGZ) and pioglitazone (PGZ), are synthetic high affinity ligands for PPAR γ and new anti-diabetic drugs that attenuate insulin resistance in type 2 diabetes⁽¹³⁾.

THIAZOLIDINEDIONES: MECHANISM OF ACTION AND DURABLE GLYCEMIC CONTROL

TZDs reduce hyperglycemia by improving insulin sensitivity. Rosiglitazone and Pioglitazone are the only 2 drugs in this class currently available in the United States. TZDs bind to the nuclear peroxisome proliferator-activated receptor- γ (PPAR- γ), subsequently activating genes that encode proteins involved in the metabolism of glucose and lipids. This leads to an increase in glucose uptake in skeletal muscle and adipose tissue, a reduction in hepatic glucose output, and finally, an increase in free fatty acid uptake. These factors combine to lower glucose levels and can decrease HbA1c levels over time. A number of studies have shown that TZDs provide long-term glycemic

control in patients with diabetes. Monotherapy with rosiglitazone has been shown to decrease HbA1c by 1.2% to 1.5% compared with placebo after 26 weeks of therapy. An open-label study compared the effects of rosiglitazone and glyburide on glycemic control. Fasting plasma glucose decreased by 50 mg/dL and 25 mg/dL after 8 and 52 weeks of therapy, respectively, with rosiglitazone; durable glycemic control was maintained for 52 weeks. Notably, twice as many patients achieved levels of HbA1c below 7% when treated with rosiglitazone compared with glyburide after 52 weeks of therapy. Pioglitazone also effectively decreases both HbA1c and fasting plasma glucose in patients with type2 diabetes. Pioglitazone 15 to 45 mg daily decreased HbA1c levels by 1.0% and 1.6%. Fasting plasma glucose decreased as well by 74.5 mg/dL, 42.0 mg/dL, and 43.7 mg/dL in patients treated with pioglitazone 45 mg, 30 mg, and 15 mg, respectively. The TZDs are as efficacious as sulfonylureas in achieving glycemic control. One possible explanation for the lower fasting glucose may be the enhanced insulin sensitivity provided by TZD therapy⁽¹⁴⁻¹⁶⁾.

Another advantage of TZDs is their ability to improve measures of β -cell function. The homeostasis model assessment (HOMA) has been utilized as a research tool to evaluate measures of β -cell function and insulin resistance⁽¹⁷⁾.

Although epidemiological associations relating inflammation to T2D or obesity can be traced back to the late 1950s and 1960s⁽¹⁸⁾, when fibrinogen and other acute-phase reactants concentration were found to be on a higher side in circulating blood.⁽¹⁹⁻²¹⁾ These investigations, however, failed to confirm the manner of development of a disease. Recently though extensive studies confirmed the concept by studying analysis of the patterns of fibrinogen, C-reactive protein (CRP), sialic acid etc. in circulating blood and effects of these markers on health and disease conditions in defined population having increase concentration of TZD's.⁽²²⁻²³⁾ Markers and inflammation due to them show drastic decline by following healthy life patterns as adipose tissue kept on decreasing and it is proved adipose tissue has a sole marker stored in it has named as TNF- α which is involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction.⁽²⁵⁻²⁹⁾

PHARMACOLOGICAL ACTIVITY OF THIAZOLIDINEDIONES OTHER THAN ANTI-DIABETIC

- Recent experimental studies have demonstrated that thiazolidinedione's (TZDs) Therapy inhibits proliferation and migration of vascular smooth muscle cells, accelerates endothelium reparation and attenuates neointimal hyperplasia. It implies that TZDs therapy may have beneficial effects on in-stent restenosis (ISR). Several small-sample clinical trials have evaluated the effect of TZDs therapy on ISR; however, the results were inconsistent across trials. In clinical studies, TZDs therapy decreases carotid intima media thickness in diabetic and non-diabetic patients, which is a strong predictor of myocardial infarction and stroke. It implies that TZDs may have beneficial effect on ISR. Several small-sample clinical trials have evaluated the effect of TZDs therapy on ISR; however, the results were inconsistent across trials. In this study, we performed a met analysis of all relevant randomized controlled trials (RCTs) to evaluate the effect of TZDs therapy on ISR after coronary stenting⁽³⁰⁾
- Thiazolidinedione's (TZDs) have broad spectrum of actions, including immunomodulation effects that are dependent or

independent of the target nuclear receptor, peroxisome proliferator activated receptor-gamma (PPAR-g).

- In addition to their roles in insulin sensitization and adipose cell differentiation, TZDs have also been implicated in modulating macrophage functions or the immune system. It has been reported that PPAR-g is expressed on peripheral blood monocytes and tissue macrophages. Furthermore, TZDs showed inhibitory effect on the production of monocyte inflammatory cytokines and monocyte activity via PPAR-g-independent pathway. Based on these demonstrations of their anti-inflammatory effects, TZDs may be good candidate drugs to suppress the phagocytic activity of RES or macrophages⁽³¹⁾.

Side effects associated with Thiazolidinedione's

- Troglitazone causes severe liver injury by opening of the pores of Mitochondria wall thus leading to drug induced liver injury. This was the sole reason it was withdrawn from the market. Similar studies were also found for Ciglitazone; however, Rosiglitazone and Pioglitazone don't penetrate through Mitochondria wall and hence are less hepatotoxic.⁽³²⁾
- Thiazolidinedione-related fluid retention and congestive heart failure**⁽³³⁾

In animal models, TZDs improve contractility and systolic performance, enhance diastolic performance and decrease cardiac hypertrophy independent of loading conditions⁽³⁴⁻³⁶⁾. Similarly, RCTs have demonstrated that PPAR γ agonists do not directly affect left ventricular systolic or diastolic function and may even be beneficial^(16, 37). However, data from the large scale outcome trials and from the recently published meta-analyses^(38, 39) consistently indicate that treatment with TZDs significantly increase the risk of congestive heart failure (CHF), raising the possibility that these agents, by their well-known effects on salt and water retention, might simply unmask previously undiagnosed cardiac dysfunction without itself having any direct impact on heart muscle. Erdmann and Wilcox have recently emphasized the apparent lack of any long term mortality consequences and a relative improvement in outcomes associated with TZD-induced HF. The pathophysiology of TZDs-related fluid retention and CHF includes several potential mechanisms such as increased vascular permeability, decreased urinary sodium excretion, increased sympathetic tone and altered interstitial ion transport^(40, 41).

Table 1: Side-effects of Thiazolidinediones

| Side Effect | Relative Frequency |
|---------------------------|--------------------|
| Weight Gain | +++ |
| Raised LDL-cholesterol | ++ |
| Fluid retention | + |
| Drug Interactions | + |
| Hepatotoxicity | + |
| Cardiac hypertrophy | ? |
| Induction of colon polyps | ? |

Because of tumors-inducing effects in a murine model for familial adenomatous polyposis and sporadic colon cancer, these drugs should not be prescribed for people from families with adenomatous polyposis coli. Long-term studies should monitor effects on the development of sporadic colon tumors. Fluid retention, haemodilution, and the induction of preload-induced cardiac hypertrophy—all serious side-effects seen in animal studies—should also be looked for. Clinically, however, the rise in plasma volume seems not to be associated with an increase in

left-ventricular mass. Nevertheless, glitazones are contraindicated in patients with New York Heart Association class III or IV cardiac status. Another word of caution concerns drug interactions. Troglitazone and pioglitazone, but not rosiglitazone, induce the cytochrome P450 isoform CYP3A4, which is partly responsible for their metabolism. Safety and efficacy could be affected when these new agents are Co-administered with other drugs metabolized via this enzyme, such as erythromycin, astemizole, calcium channel blockers, cisapride, corticosteroids, cyclosporine, statins, tacrolimus, and triazolam. Blood-glucose should also be monitored more carefully in patients receiving these antidiabetic drugs in combination with inhibitors of CYP3A4 such as ketoconazole or itraconazole. Finally, time will tell whether obesity, and eventual secondary drug resistance, is a serious issue⁽⁴¹⁾.

CHEMISTRY OF THIAZOLIDINEDIONE'S

Thiazolidinedione's have 2,4- diones and have nitrogen and Sulphur in the ring structure which possess various pharmacological activities such as Antibacterial, antifungal, antiviral, diuretic, anti-tuberculostatic, anti-HIV, antihistaminic, Anticancer, anticonvulsant, anti-inflammatory and analgesic properties.

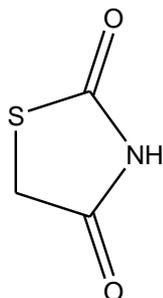


Figure 1: The chemical structure of thiazolidinedione

Chemically, the members of this class are derivatives of the parent compound thiazolidinedione, and include Rosiglitazone (Avandia), Pioglitazone (Actos) and Troglitazone (Rezulin). Experimental agents include netoglitazone, an antidiabetic agent, rivoglitazone⁽³²⁾.

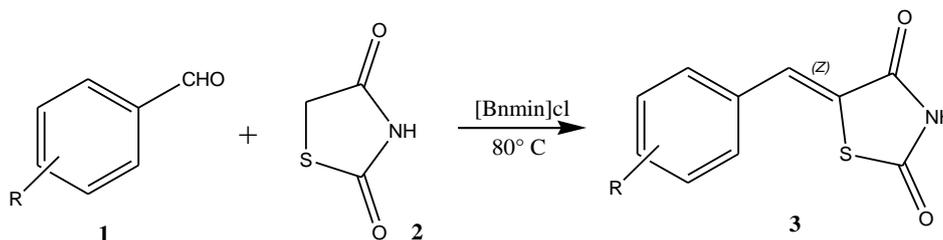


Figure 5: Synthesis of derivatives Thiazolidine-2,4-diones

Pattan Shashikant R, Kekare Prajact, NS Dighe, SB Bhawar, Nikalje Ana, Pati Ashwini and MB Hole synthesized 2, 4-thiazolidinedione by following means:

In a 250 mL three necked round-bottomed flask was placed solution containing (56.4 gm, 0.6 mol) of chloroacetic acid (1) in 60 mL of water and (45.6 gm, 0.6 mol) of thiourea (2) dissolved in 60 mL of water. The mixture was stirred for 15 min to form a white precipitate, accompanied by considerable cooling. To the contents of the flask was then added slowly 60 mL of

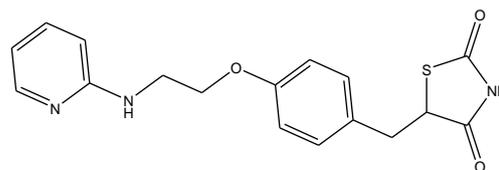


Figure 2 Rosiglitazone

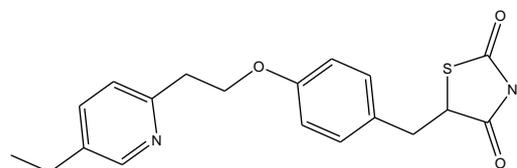


Figure 3 Pioglitazone

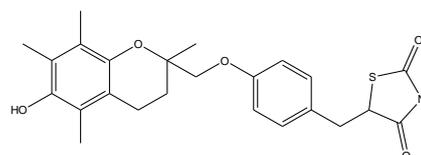


Figure 4 Troglitazone

SYNTHESIS OF VARIOUS THIAZOLIDINEDIONES DERIVATIVES

K.F. Shelke, S.B. Sapkal, B. R. Madje, B. B. Shingate and M. S. Shingare synthesized 5-arylidene-2,4-thiazolidinedione by following means:

A mixture of aromatic aldehyde (1 mmol) (1), 2,4-thiazolidinedione (1 mmol) (2) and [bnmim] Cl (0.5 mmol) were taken in single neck round bottom flask. The reaction mixture was stirred at 80°C in an oil bath for the appropriate time. The progress of reaction was monitored on TLC. After completion of reaction, the mixture was cooled to room temperature and the product was extracted from diethyl ether (2 × 20 mL), leaving behind [bnmim] Cl. Organic layer washed by brine (2 × 10 mL) and dried over sodium sulfate and removed the solvent on rotary evaporator under reduced pressure. The solid obtained was recrystallized by ethanol to get pure product (3)⁽⁴²⁾.

concentrated hydrochloric acid from a dropping funnel, the flask was then connected with a reflux condenser and gentle heat applied to effect complete solution, after which the reaction mixture was stirred and refluxed for 8-10 hrs. at 100-110°C. On cooling the contents of the flask solidified to a cluster of white needles. The product (3) was filtered and washed with water to remove traces of hydrochloric acid and dried. It was purified by recrystallization from ethyl alcohol.

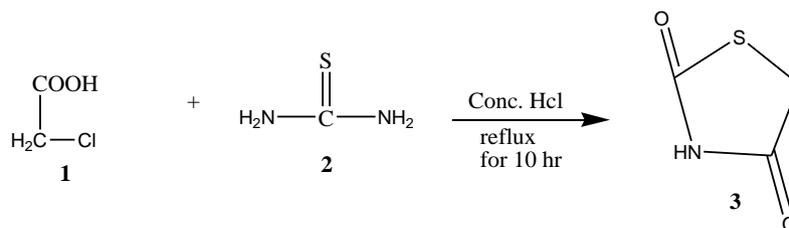


Figure 6: Synthesis of Thiazolidine-2, 4-diones

Prashantha B. R., Nanjan, M. J., Suresh, B., Karvekar, M. D.; Adhikary synthesized thiazolidinedione derivative by Microwave technique. Chloroacetic acid, thiourea, water were transferred into long necked vial and stirred under ice cold conditions for about 15min to form a white precipitate of 2-imino-thiazolidine-4-one as intermediate. Irradiation with microwave is carried out at 250W power for 5 min. They cooled the reaction mixture, collected the solid and filtered the impurities and washed with water to give white crystals of thiazolidine-2,4-dione⁽⁴²⁾.

PHARMACOLOGICAL ACTIVITIES OF DERIVATIVES OF THIAZOLIDINEDIONES

Hypoglycemic activity

3-Benzyl-5-[3'-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione.

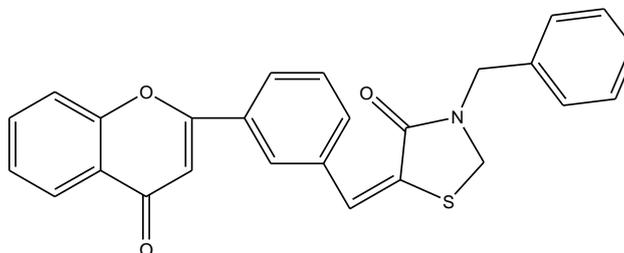


Figure 7

3-(4-Chlorobenzyl)-5-[3'-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4 thiazolidinedione.

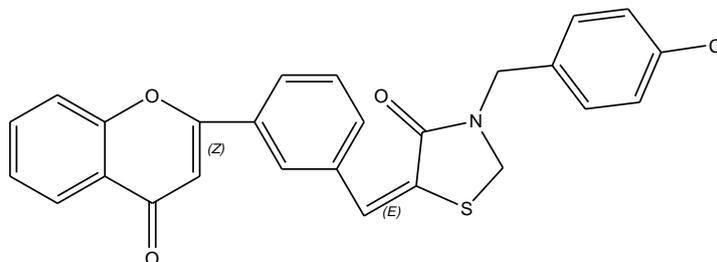


Figure 8

3-(4-Bromobenzyl)-5-[3'-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione.

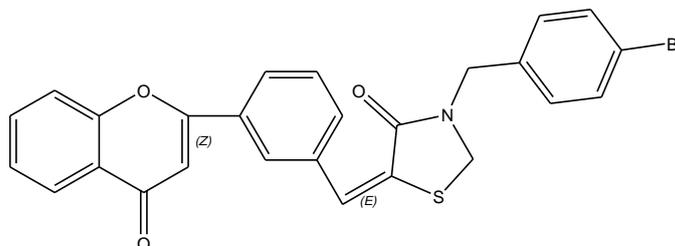


Figure 9

3-(4-Fluorobenzyl)-5-[3'-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione

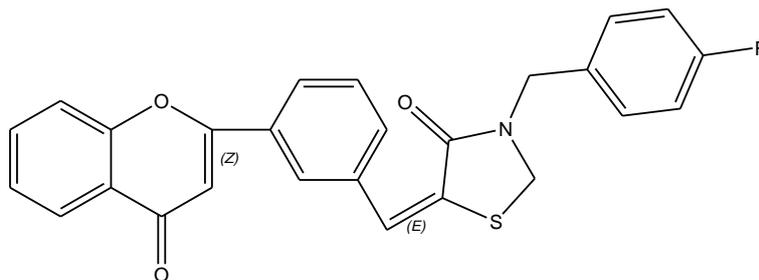


Figure 10

3-(4-Nitrobenzyl)-5-[3'-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione.

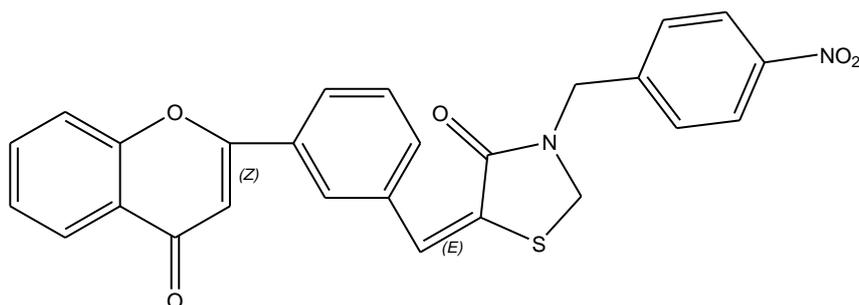


Figure 11

MeralTunc,bilek, OyaBozdog˘-Du˘ndar, Gu˘lgu˘nAyhan-Kılcıgil, Meltem Ceylan, Abdul˘ Waheed, Eugen J. Verspohl, Rahmiye Ertan synthesized the above derivatives. They underwent hypoglycemic activity by measuring insulin release by incubating half-confluent cells in micro-wells with KRBH as buffer. They were latter assayed using rat insulin as a standard measure insulin secretion.⁽⁴³⁾

Anti-microbial activity

3-(4-Chlorophenacyl)-5-[3'-(4H-4-oxo-1-benzopyran-2-yl)benzylidene]-2,4-thiazolidinedione.

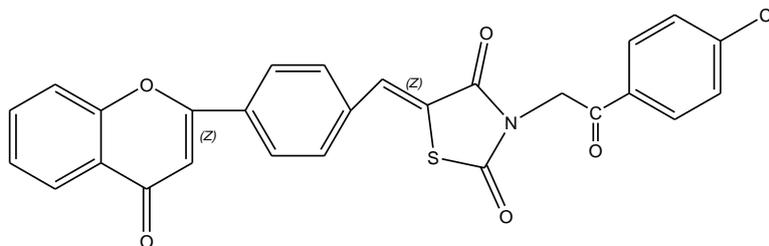


Figure 12

3-(4-Nitrophenacyl)-5-[3'-(4H-4-oxo-1-benzopyran-2-yl)benzylidene]-2,4-thiazolidinedione.

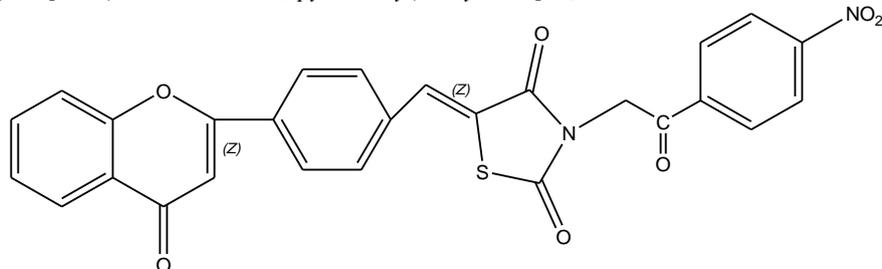


Figure 13

3-(4-Methoxyphenacyl)-5-[3'-(4H-4-oxo-1-benzopyran-2-yl)benzylidene]-2,4-thiazolidinedione.

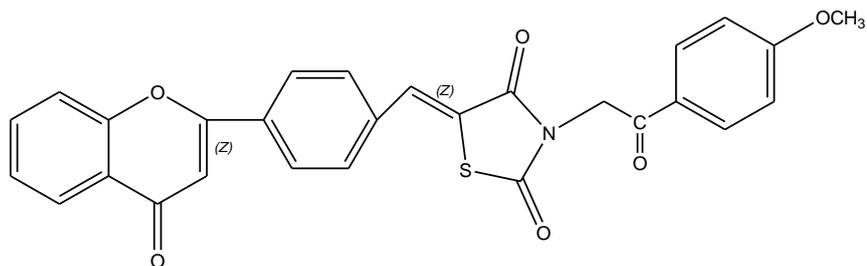


Figure 14

3-(2,5-Dimethoxyphenyl)-5-[4-(4-methoxyphenyl)benzylidene]-2,4-thiazolidinedione.

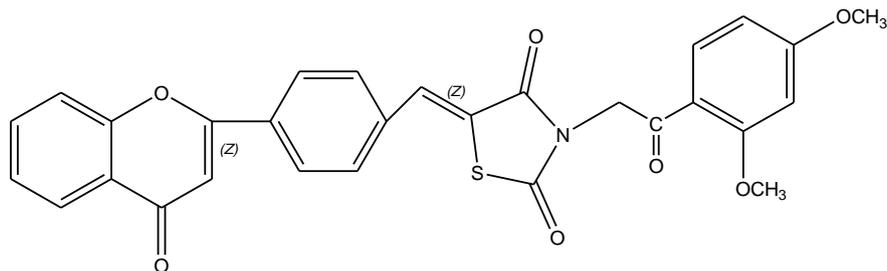


Figure 15

MeralTunc bilek, NurtenAltanlar tested all the compounds *in vitro* by the tube dilution technique, the compounds and solvents were dissolved in DMSO and MIC was calculated. All the compounds showed potent Anti-microbial activity. ^(44, 45)

Antibacterial and antifungal activity

6-phenyl-2-(3,4,5-trimethoxyphenyl)imidazo[2,1-b]-[1,3,4]thiadiazole-carbaldehyde.

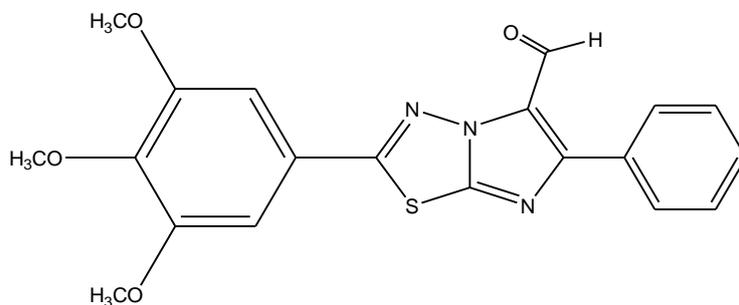


Figure 16

6-(4-methylphenyl)-2-(3,4,5-trimethoxyphenyl)imidazo[2,1-b]-[1,3,4]thiadiazole-5-carbaldehyde.

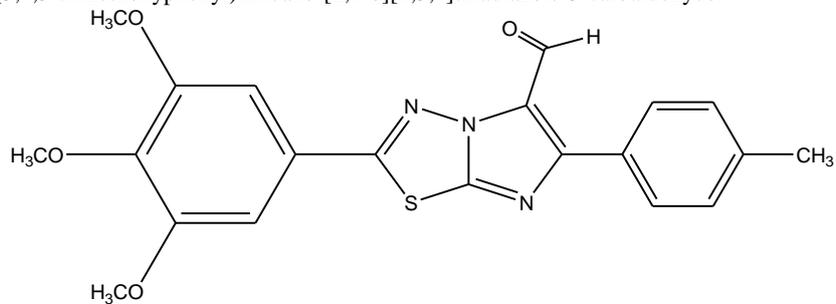


Figure 17

6-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)imidazo[2,1-b]-[1,3,4]thiadiazole-5-carbaldehyde.

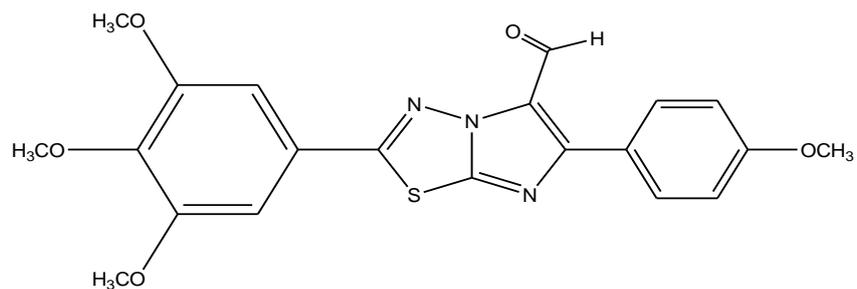


Figure 18

6-(4-nitrophenyl)-2-(3,4,5-trimethoxyphenyl)imidazo-[2,1-b][1,3,4]thiadiazole-5-carbaldehyde.

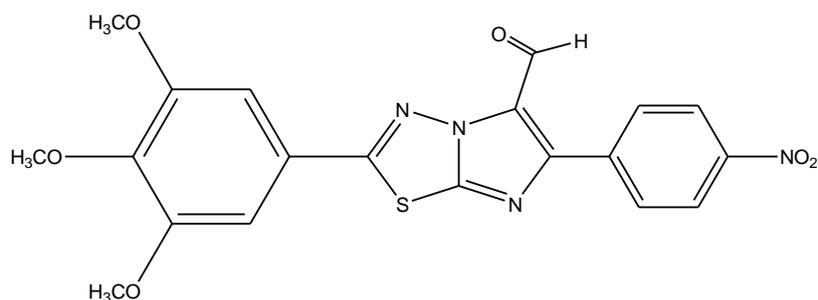


Figure 19

6-(4-bromophenyl)-2-(3,4,5-trimethoxyphenyl)imidazo-[2,1-b][1,3,4]thiadiazole-5-carbaldehyde

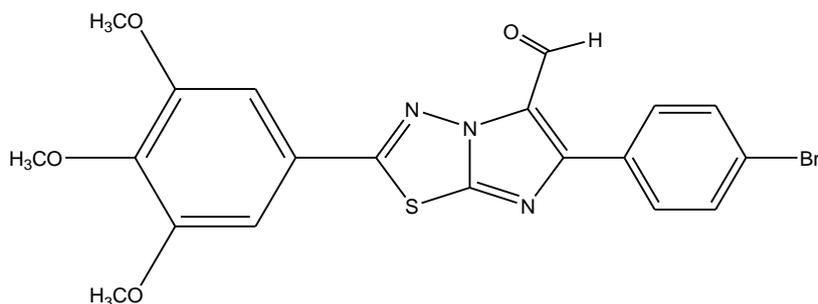


Figure 20

6-(4-chlorophenyl)-2-(3,4,5-trimethoxyphenyl)imidazo-[2,1-b][1,3,4]thiadiazole-5-carbaldehyde.

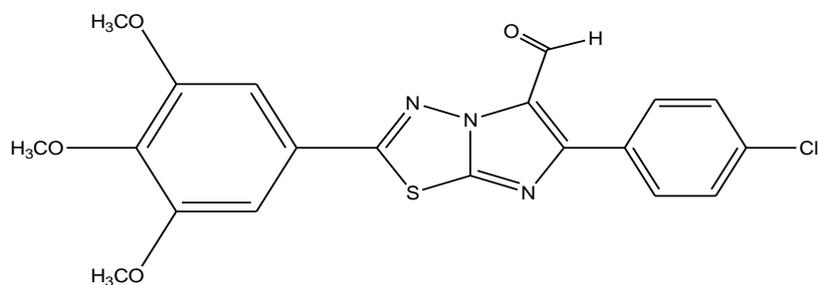


Figure 21

6-(2,5-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)imidazo[2,1b][1,3,4]thiadiazole-5-carbaldehyde.

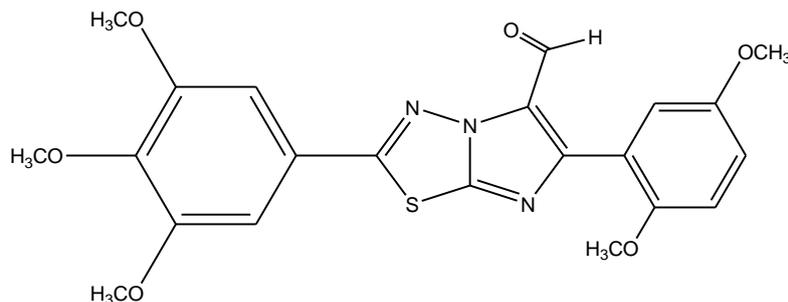


Figure 22

For the antibacterial and antifungal activity, the compounds were tested by **Kallanagouda R. Alagawadi, Shankar G. Alegaon** by dissolving them in dimethyl sulfoxide (DMSO). Dilutions of the compounds and standard drugs in the test medium were prepared with Mueller–Hinton broth and Sabouraud dextrose broth. ⁽⁴⁶⁻⁴⁸⁾.

MARKETED FORMULATIONS ⁽⁴⁹⁻⁵⁴⁾

- **Pioglitazone:** Actos.
 1. In combination with Glimepride: Duetact
 2. In combination with Alogliptin: Oseni
 3. In combination with Metformin: ActoPlus Met, Actoplus XR
- **Troglitazone:** Rezulin
- **Rosiglitazone:** Avandia
 1. In combination with Glimepride: Avandryl
 2. In combination with Metformin: Avandamet

CONCLUSION

Thiazolidinediones are the privileged structure motif having variety of pharmacological activities like anti-microbial, anti-inflammatory, analgesic, anti-diabetic etc.

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