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Review Article

2,4-Thiazolidinedione in Treating Diabetes-Review: A Comprehensive Overview - History, Chemistry, Advancements, Challenges and Future Perspectives

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ABSTRACT

Thiazolidinones are insulin-sensitizing agents used in the management and treatment of diabetes mellitus. Saturated at 5 positions, the thiazolidinedione compound is more active than the corresponding unsaturated compound. In some cases, 2,4-oxazolidinedione derivatives have shown superior anti-diabetic activity compared to 2,4-thiazolidinediones. Hydrophobic interactions between the N-alkyl group and the tail group of the aromatic ring of the TZD ligand and the receptor have been identified as crucial for the potent anti-hyperglycemic activity observed. This group of chemicals, called TZDs, includes indole, benzofuran, imidazopyridine, purines, pyridines, benzimidazole, phthalazinone, and benzoxazinone. The modification of the ether linker with ketone, alcohol olefin, amine, and acyl linker demonstrates modern to high anti-diabetic activity. Dual PPARα/γ agonists have the advantage of treating hyperglycemia and hyperlipidemia associated with T2DM. Unlike TZDs, which only bind and activate the PPARα/γ protein, phenyl propionic acid compounds have dual PPARα/γ agonist activity. Non-thiazolidinedione (non-TZD) compounds that activate PPARs are essential for managing hyperglycemia in diabetic patients. Drug development has targeted PPARs to treat diabetes mellitus and obesity, anti-inflammatory and cardiovascular disease. However, while glitazones have shown efficacy, they have also been linked with adverse drug reactions such as weight gain, hepatotoxicity, osteoporosis and increased myocardial risk.

INTRODUCTION

Diabetes represents a significant global public health challenge, with over 463 million people affected in 2019. Between 2000 and 2016, the prevalence of diabetic patients increased by 5%. According to forecasts from the International Diabetes Federation (IDF), the global population of individuals with diabetes is projected to rise to 578 million by 2030 and reach 700 million by 2045.[1] Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder marked by persistently high blood sugar levels. It results from insufficient insulin secretion by the pancreas, insulin resistance, or a combination of these factors.[2] T2DM arises from a combination of inadequate insulin production and insulin resistance, which are often influenced by various lifestyle factors, including obesity, diet, stress, and insufficient physical activity. To manage this condition, a range of oral hypoglycemic medications have been developed. These medications work in different ways: some enhance insulin action (known as insulin sensitizers), others slow down the absorption of glucose, and some increase insulin secretion (referred to as secretagogues).[3] A group of insulin sensitizers known as 2,4-thiazolidinediones (TZDs), also known as glitazones, is utilized in the treatment of T2DM. These medications have anti-hyperglycemic, anti-hypoglycemic, and anti-lipidemic

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actions, and they are well-known for their anti-diabetic qualities. TZDs transactivate peroxisome proliferator-activated receptors (PPARs) more frequently. They focus on PPAR-γ, which is the subtype that has been studied the most in the context of treating diabetes. These receptors are crucial nuclear receptors that help regulate genes involved in glucose and lipid metabolism, making them significant targets for TZDs. Takeda Laboratories in Japan first developed these receptors in 1975 and synthesized 71 analogs to find more potent fibrate hypolipidemic drugs.[4] However, a number of adverse effects caused the early TZDs to be taken off the market. Thiazolidinediones contain two carbonyl groups with a five-member heterocyclic ring and they are potent PPAR agonists. Despite the setbacks with early versions, TZDs gained widespread recognition in the late 1990s.[3] In summary, TZDs are primarily appreciated for their hypoglycemic effects and their ability to activate PPARγ, as reported in various studies.

History

In 1982, Takeda launched a TZD anti-diabetic agent known as substituted-2,4-thiazolidinediones, which demonstrated potential for lowering blood glucose levels in diabetic models but not in non-diabetic rats. Among this series, ciglitazone was identified as a compound that effectively enhanced insulin action in diabetic and/or obese rats.[5] Later, liver toxicity led to the discontinuation of ciglitazone, despite its initial promise.[6] Daiichi Sankyo developed troglitazone, another thiazolidinedione, in Japan and launched it in the USA in March 1997 as the first oral hypoglycemic agent in its class. However, Phase 3 clinical trials revealed a high incidence of acute liver failure, with 797 cases per 1 million patients per year, a rate more than 240 times higher than expected, leading to its market withdrawal.[7] In 1999, GlaxoSmithKline launched rosiglitazone, marketed under the trade name Avandia, as an anti-hyperglycemic medication for the treatment and management of diabetic patients.[8,9] Despite its effectiveness, the EU, New Zealand, and South Africa withdrew rosiglitazone from their markets between 2010 and 2011, citing its association with cardiovascular risks, including heart failure, myocardial infarction, and stroke. In the United States, it remains available but carries a black-box warning.[10]

Takeda Pharmaceutical Company also introduced pioglitazone as Actos in 1999. It is ten times more potent than troglitazone in its glucose-lowering effect, and, while it has not been linked to severe hepatic dysfunction, its safety is still debated. Brief use of pioglitazone has not been associated with an increased risk of bladder cancer, but using it for over two years may elevate the likelihood of developing the condition. [11-14] The active TZD structure is shown in Fig. 1.

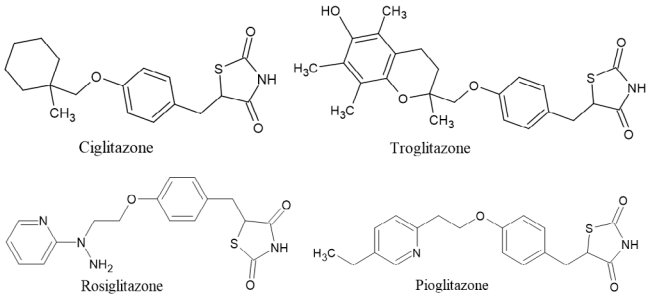

Fig. 1: PPARγ active drugs ciglitazone, troglitazone, rosiglitazone and pioglitazone

Glitazone Derivatives for T2DM

TZDs with 2 or 4-oxazolyl ring

The novel derivatives prepared by the pioglitazone 2-pyridyl ring are replaced by a 2 or 4-oxazolyl and evaluated for hereditary obesity and diabetes in mice. These derivatives show a significant hypoglycemic effect. Among the substances that were prepared is 5-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-2,4-thiazolidinedione (I) in Fig. 2, the most active molecule, had almost hundred-fold more activity than pioglitazone.[15]

TZDs with indole and azaindole moiety

Lohray BB *et al.*, prepared various indole and azaindole analogs and tested their anti-hyperglycemic efficacy. Compared to azaindole analogs, the indole (DRF-2189) exhibits the highest euglycemic and hypolipidemic action (Fig. 2). The substituents at carbon-2 and carbon-3 of indole significantly reduce the euglycemic and hypolipidemic actions.[16,17]

Darwish KM developed, produced, and tested a unique class of thiazolidinediones (TZDs) from benzhydrol and indole for their binding affinity to two receptors: PPAR-E and FFAR1, also known as GPCR40. There are three compounds that have a high affinity for both targets. *In-vivo*

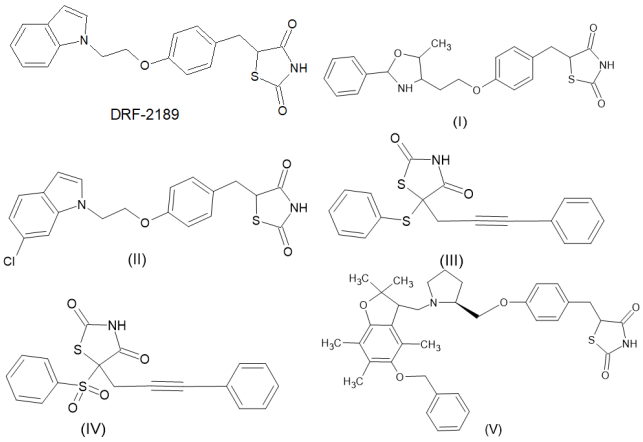

Fig. 2: Prominent TZD's compounds made from different heterocylic rings show antidiabetic activity

tests revealed that compound II shown in Fig. 2 exhibited significantly stronger hypoglycemic and hypolipidemic effects than the standard drug rosiglitazone.[2]

TZDs with arylsulfanyl and arylsulfonyl

In comparison to their sulfanyl thiazolidinedione analogs, the sulfonyl thiazolidinediones (IV)(Fig. 2) were more potent. By adding substituents to the 3-propynyl phenyl ring, one could create more powerful analogs. It wasn't clear what effects substituents had on the phenyl-sulfonyl (Ar) moiety of IV. However, adding a substituent to the fourth position of the aromatic phenyl ring did enhance its effectiveness in combating hyperglycemia. The 2-pyridine sulfonyl compounds demonstrated a remarkable level of effectiveness.[18]

TZDs with benzofuran moiety

TZDs with dihydrobenzofuran moiety had shown good hypolipidemic and euglycemic actions. The benzyl ether at 5-OH of dihydrobenzofuran is protected, resulting in improved pharmacokinetic properties, lowering blood sugar and improving drug delivery. Compound V in Fig. 2 is the most potent in the series of benzofurans containing thiazolidinediones.[16]

TZDs with imidazopyridine, purines, pyrimidinone and pyridines

Sakakibara S, *et al.,* developed and manufactured 2,4-thiazolidinedione containing imidazopyridine, and assessed its hypoglycemic action *in-vivo* on genetically diabetic KK mice, as well as its adipocyte differentiation activity *in-vitro* using a mouse preadipocyte cell line (3T3-L1). Future clinical trials selected Compound VI due to its promising characteristics.[19] TZDs with 6-substituted purines (VII) were less effective at building triglycerides in 3T3-L1 cells than rosiglitazone. On the other hand, 9 substituted-purine-6-yl derivatives (VIII) had much higher triglyceride-building activity. TZDs with the pyridine moiety (IX) and (X) were synthesized and evaluated for hypoglycemic activity. The modified pyridine derivatives worked better than the standard compound to stop the buildup of triglycerides in 3T3-L1 cells and lower blood sugar and cholesterol levels in KKAy mice.[20] The antidiabetic activity of pyrimidinone thiazolidinedione derivatives was tested in insulin-resistant mice models to assess their efficacy. In the study with animals, compound XI was better at lowering insulin, plasma glucose, and lipids than rosiglitazone and pioglitazone. The 28-day oral toxicity trial in Wistar rats demonstrated that the treatment had no adverse effects.[21] The structure of the compound from VI to XI is shown in Fig. 3.

TZDs with chromone ring moiety

Through Knoevenagel condensation and reduction with H2 gas and a palladium catalyst, a one-of-a-kind library of TZDs with chromone rings was made. Compounds

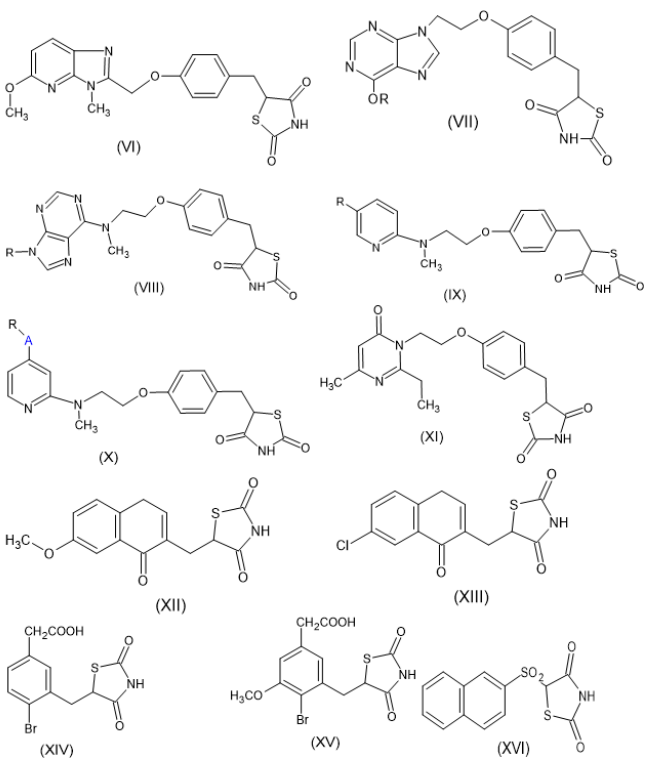

Fig. 3: TZD derivatives showing the promising blood glucose lowering effect with reduction in blood lipid level. TZD derivatives made with imidazopyridine, purines, pyrimidinone, pyridines chromone ring, phenoxy acetic acid and 2-naphthalene moiety

(XII) and (XIII) in Fig. 3 were 30% more effective than pioglitazone in lowering blood glucose levels. Derivative XII considerably boosted PPARγ gene expression (2.56-fold), leading to reduced insulin resistance and improved glucose metabolism, compared to the conventional medication pioglitazone. Derivative XII also exhibited significantly lower levels of toxicity.[22]

TZDs with phenoxyacetic acid

A series of 13 novel conjugates of phenoxyacetic acid and TZD was synthesized. Compounds (XIV) and (XV) are shown in Fig. 3 exhibited significant PPARγ transactivation and anti-hyperglycemic activity *in-vitro* cell line, comparable to std medicines, rosiglitazone and pioglitazone.[23]

TZDs with 2-naphthalene

A variety of naphthalenylsulfonyl with 2,4-thiazolidinediones are produced and tested for anti-diabetic activity in an insulin-resistant mice model. The anti-hyperglycemic action of naphthalene surpassed that of other groups, including the p-alkoxy phenyl group present in ciglitazone. The sulfonyl group linker between naphthalene and 2,4-thiazolidinedione resulted in maximum activity. The best analog of 2-naphthalenylsulfonyl thiazolidinedione is compound XVI (Fig. 3), which proved potent in two animal models.[24]

TZDs with oximes

Oximes paired with 2,4-thiazolidinedione underwent assessment for their impact on PPARγ activities and their ability to decrease blood glucose levels. Incorporating biphenyl and methyl groups, along with an ethylene bridge linking the oxime and phenoxy groups, boosts their effectiveness against diabetes. Notably, compounds (XVII) and (XVIII) surpass rosiglitazone in activating PPARγ and exhibit notable effectiveness in lowering blood glucose levels.[25] Compounds (XVII) and (XVIII) are shown in Fig. 4

TZDs with phthalazinone and benzoxazinone moiety

Studies on biological systems, demonstrated the superior hypoglcemic action of the phthalazinone analog. The greatest chemical in this series is compound XIX (Fig. 4), which outperformed troglitazone and pioglitazone in terms of *in-vitro* PPARγ transactivation potential.

In insulin-resistant db/db mice, compound (XIX) demonstrated superior triglyceride and plasma glucose-lowering action compared to troglitazone and pioglitazone, the conventional medications. Benzoxazinone DRF-2519-containing TZDs exhibited strong PPAR-α and -γ activation.[26]

TZDs with benzimidazole moiety

A series of compounds featuring thiazolidinediones (TZDs) with benzimidazole were synthesized and subjected to testing for their agonist activity on PPARγ or FFAR1 receptors. Docking studies suggest that polar-polar interactions with the hydrogen bonding at the sites of PPARγ play an important role in receptor activation According to docking studies, polar-polar interactions and hydrogen bonding at PPARγ sites are crucial for receptor activation. Additionally, the benzimidazole moiety of these TZD engages in hydrophobic interactions within the receptor pocket. XX, an allyl derivative from the benzimidazole series, showed significantly higher intrinsic activity than rosiglitazone. XX demonstrated a 55-fold increase in activation potency. These results show that compounds in this series, especially XX, could be powerful activators of PPARγ or FFAR1. They suggest that these compounds could be used to make new medicines.[27]

A new drug called rivoglitazone (XXI) is a thiazolidinedione compound that contains benzimidazole and selectively activates the site of the receptor (PPARγ) in Fig. 4. Rivoglitazone is an effective and well-tolerated TZD that improves glycemic control in T2DM. Rivoglitazone better controls the levels of glucose and lipids in the patient compared with placebo and pioglitazone treatment patients.[28,29]

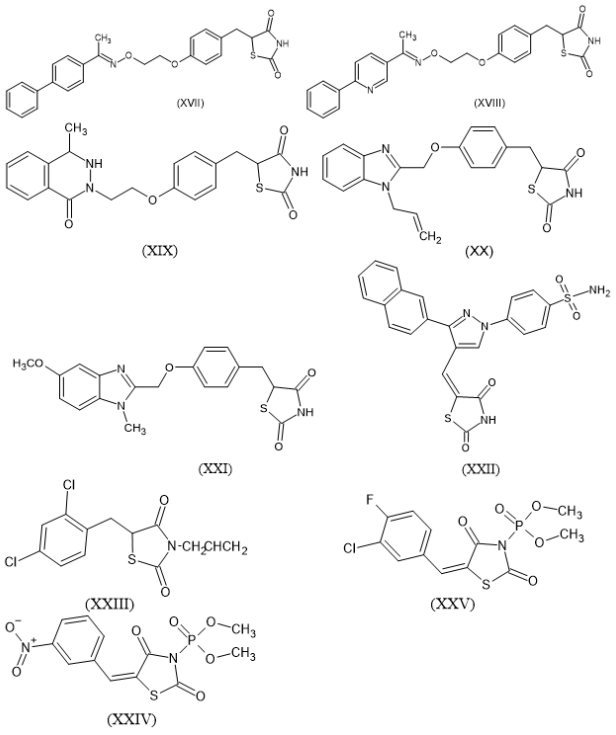

Fig. 4: TZD associated with oxime, phthalazinone and benzoxazinone, benzimidazole, sulphonamide moiety show the significant antidiabetic activity in different animal diabetic model

TZDs with sulphonamide moiety containing pyrazole trunk

In 2018, Mohd. Javed Naim studied thiazolidinedione derivatives with a sulphonamide moiety and a pyrazole trunk, which showed promising glucose-lowering activity. Biological studies showed that XXII stood out among the compounds studied because it had strong PPAR-γ transactivation, reaching 61.2% and causing gene expression to increase by an amazing 1.9 times. Molecular docking studies further elucidated XXII's favorable interactions, demonstrating robust hydrogen bond interactions with key amino acids. Notably, derivative XXII in Fig. 4 exhibited an absence of hepatotoxicity and showed no indications of weight gain, suggesting a favorable safety profile. These findings highlight the potential therapeutic efficacy of compound XXII in managing glucose levels, while its favorable safety profile underscores its promise as a candidate for further development in diabetes treatment.[3]

TZDs without aryl moiety at tail

A series of thiazolidinedione compounds synthesized had no alkyl or aryl moiety at the tail but were substituted at the trunk benzyl ring with methoxy, =hydroxyl, chloro, and nitro groups. The anti-diabetic activity results indicate that halogen-containing compounds demonstrated superior efficacy compared to others, particularly those with a chloro group at the ortho and para positions. All the derivatives are less active than reference pioglitazone. The compound (XXIII) had the strongest anti-diabetic effect of all the derivatives.[31] Phosphonates with thiazolidinedione were synthesized and tested for their anti-diabetic potential. Docking studies were conducted to examine their interactions with ligands targeting the human PPARγ protein, a crucial target in diabetes

therapy.[30] The compounds XXIV and XXV (Fig. 4) were synthesized and evaluated hypoglycemic activity through an amylase inhibition assay and showing promising inhibition of α-amylase compared to the pioglitazone. These results emphasize the potential of these compounds as potent α-amylase inhibitors, suggesting their usefulness in diabetes management.[31]

TZDs with ether linker modified by ketone, alcohol, olefin moiety

Pfizer's approach to identifying new, potent euglycemic agents focused on finding a sterically and biologically similar functional group to replace the ether group found in ciglitazone and englitazone. Groups such as sulfur, nitrogen, and carbonyl modified the 2-benzylbenzopyran ether oxygen. While the sulfur and nitrogen analogs displayed slightly lower potency, cyclic as well as alicyclic ketone, exhibited comparable activity. The cyclic ketone has lacked an effect on the tetralone (XXVI); the cyclic structure would offer no benefit compared to the alicyclic analog (XXVII) shown in Fig. 5.[32] In KKAy mice, the ketone derivative of TZD (XVIII) exhibited anti-hyperglycemic activity.[33]

Ketones of rosiglitazone and pioglitazone are poor PPARγ binders as compared to rosiglitazone and pioglitazone. The EC_{50} values for pioglitazone ketone (EC_{50} = 0.657 μM) and rosiglitazone ketone (EC_{50} = 0.961 μM) show that they are 7 to 10 times more active than pioglitazone and 80 to 100 times more active than rosiglitazone. Ketone derivatives of rosiglitazone and pioglitazone exhibit good anti-hyperglycemic activity.[34]

TZD derivatives contain an ether linker modified with three carbon ketones and were assessed for hypoglycemic activity using the diabetic-induced animal model and blood glucose was monitored.

The compound (XXIX) (Fig. 5) shows promising anti-diabetic activity among all synthesized compounds.[35]

Ether linker modified with cyclic amines

Thiazolidinedione derivatives having cyclic amine linker has been synthesized and evaluated *in-vivo* for oral glucose tolerance tests in mice. Different cyclic amines, like (S)-prolinol, piperidine, morpholine, 3-carbinolpiperidine, and piperazine, were used to make the unsaturated TZD (XXX). This was easy to do by reacting 2-chloropyridine with (S)-prolinol, and it had very good effects on lowering blood sugar and cholesterol. Other cyclic amines, like piperidine or piperazine, had much less effective effects on these conditions. However, the morpholine cyclic linker compound (XXXI), showed significant antidiabetic and hypolipidemic actions (Fig. 5). Among all the options considered, 2-(S)-prolinol emerged as the best linker for the TZD series.[36] *In-vivo* studies revealed that the cyclic amine imidazopyridine, substituting the linker ether, exhibited notable glucose-lowering activity. Additionally, *in-vitro* experiments demonstrated euglycemic activity

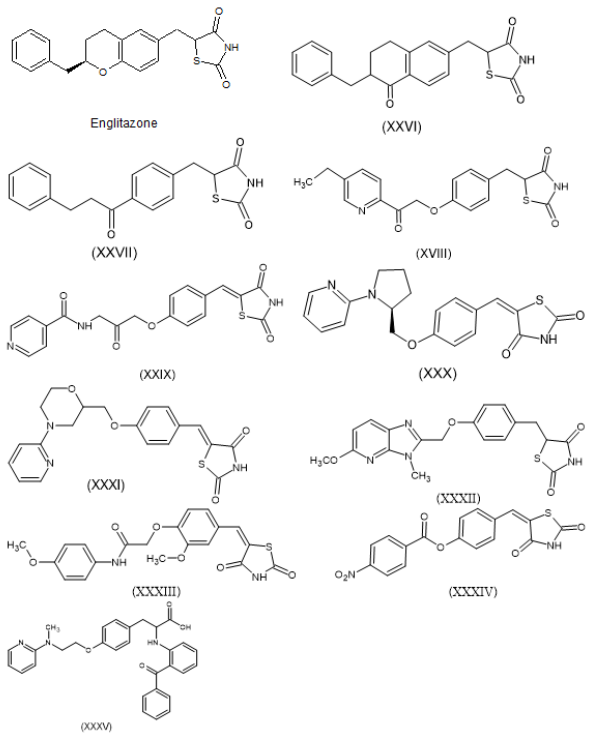

Fig. 5: TZD with ether linker modified by ketone, alcohol, olefin, cyclic amines, acyl and esters

in the 3T3-L1 cell line. These compounds serve as conformationally restricted analogs of TZDs. Among them, Compound XXXII emerges as the most potent molecule within this new series.[19]

Ether linker modified with acyl linker

Nanjan *et al*. synthesize the derivative of TZDs, which includes the acyl linker between the trunk and tail. The key structural prerequisite for anti-diabetic action is the amide (-NHCOCH2-) two-carbon linker. The most active molecule in this group is (XXXIII) in Fig. 5 which has a benzyloxy truck replaced with 3-methoxy group and an amide linker connection to p-anisidine as part of the hydrophobic tail.[37] Prashanth Kumar *et al.,* created an analogous type of new TZD with anti-diabetic properties by attaching an acyl linker between the head of thiazolidinedione and the tail aromatic/acyclic amines of glitazone. This series' chemicals demonstrated moderate to considerable glucose uptake activity.[38-41]

Ether linker modified with ester linker

Santosh Chhajed and colleagues synthesized novel thiazolidinedione derivatives with ester linkers. Among them, XXXIV depicted in Fig. 5 emerged as the most promising active molecule in glucose uptake assays. In molecular docking studies, compound TZD4 demonstrated significant hydrogen interactions with amino acids and carbonyl groups, as well as pi-interactions with amino acids Glu259 and Ile341. [42]

2,4-thiazolidinedione ring replace with tyrosine (or opening of thiazolidinedione ring)

A gripping narrative unfolds around a new lineage of N-(2-benzoylphenyl)-L-tyrosine derivatives, showcasing their robust efficacy as selective PPARγ agonists. The substitution of the tyrosine nitrogen with the 2-benzoylphenyl moiety emerges as a striking revelation, amplifying their potency. These compounds claim to be better than other thiazolidinedione diabetes medicines, which suggests a new way of binding with the PPARγ receptor that needs to be explored. The β-phenylpropionic acid part also works well as an isosteric substitute for the benzyl 2,4-thiazolidinedione ring. Notably, within this series, compound (XXXV) present in Fig. 5 stands as the pinnacle of potency and promise.[43]

2,4-thiazolidinedione replace with 2,4-oxazolidinedione

In the realm of diabetes prevention, 2,4-oxazolidinediones have shown superior performance compared to their 2,4-thiazolidinedione counterparts. Prashantha Kumar carefully studied the ability of 2,4-oxazolidinediones to treat diabetes in animals that had a genetic tendency to be overweight and diabetic. One of these, compound (XXXVI) shown in Fig. 6, which is a derivative of 2,4-oxazolidinedione, was ten times more effective at treating diabetes than pioglitazone.[44]

Along with that, Prashantha Kumar described a wide range of new TZD compounds, including ring structures of thiazolidinedione, oxazolidinedione, and rhodanine. Although compound XXXVII is the potent oxazolidinedione of this series, the compounds of this series exhibited varying levels of glucose uptake activity, with only a few showing significant effects.[45]

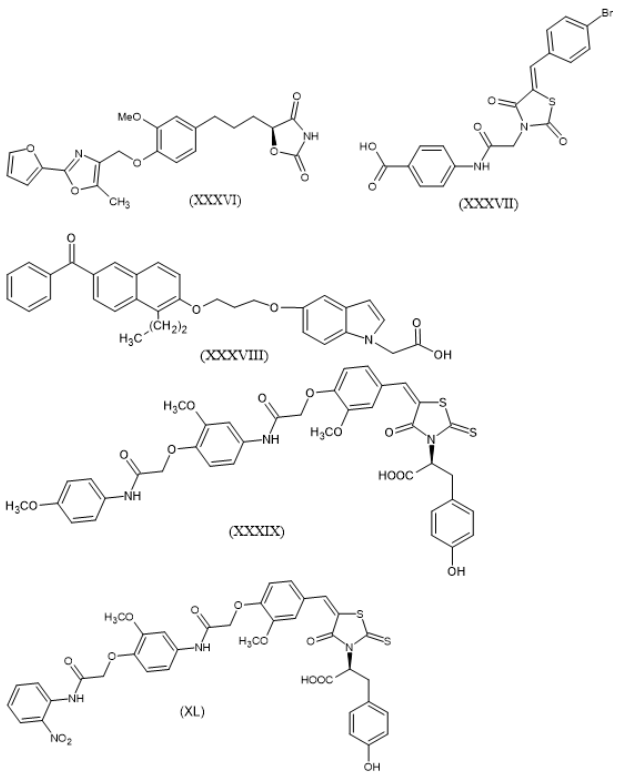

Fig. 6: A novel glitazone derivatives design by TZD replace with oxazolidinedione and indole acetic acid

2,4-thiazolidinedione modified with indol-1yl acetic acid

Substituting the 2,4-thiazolidinedione ring with indol-1-yl acetic acid yields a novel series of compounds, culminating in the emergence of a highly potent PPARγ agonist, denoted as XXXVIII (Fig. 6), surpassing the efficacy of the reference drug rosiglitazone. This potency is attributed to robust hydrophobic interactions facilitated by the hydrophobic tail of 6-benzoylpropylnaphthalene.

More information from molecular docking studies shows that the 5-substituted indole moiety places the acidic group perfectly in relation to the linker, making sure that the ligand and PPARγ receptor are at the right distance for interaction. These results provide insight into the complex molecular processes, increased affinity, and activity of these substances in PPARγ function modulation.[46]

TZDs incorporated with amino acid and peptide

A variety of compounds that incorporated 2,4-thiazolidinedione with amino acids were synthesized and evaluated for their antidiabetic properties *in-vitro*. The six most promising compounds were chosen for additional testing in Wistar rats, primarily to determine how well they lower glucose and triglycerides *in-vivo* to prevent insulin resistance and hyperlipidemia brought on by dexamethasone. Notably, out of this series, compounds (XXXIX) and (XL) in Fig. 6 were the most active.[47]

Subsequently, scientists synthesized a new set of compounds based on 5-acetic acid-thiazolidinedione, incorporating various amino acids and peptides. This series involved substituting hydrophobic tail amino acids (such as phenylalanine, leucine, and methionine) as well as less hydrophobic ones (like tyrosine and glycine) with highly hydrophobic counterparts. These compounds were screened for both antidiabetic and cardioprotective properties.

When compared to the standard pioglitazone, six of the 14 substances evaluated showed significant drops in blood glucose levels and improved antioxidant activity. Notably, compounds XLI, XLII, and XLIII presented in Fig. 7 consistently demonstrated substantial decreases in blood glucose levels on both the 7th and 14th day of the animal anti-diabetic studies. Furthermore, compounds T1 and T7 were found to have a cardioprotective effect in mice, as evidenced by ECG wave pattern analysis, suggesting that they assist the diabetic heart in functioning almost akin to a normal heart.[48]

Phenoxyalkyl linker modified with benzoxazole ring

A novel series of thiazolidinedione compounds incorporating benzoxazole was synthesized and

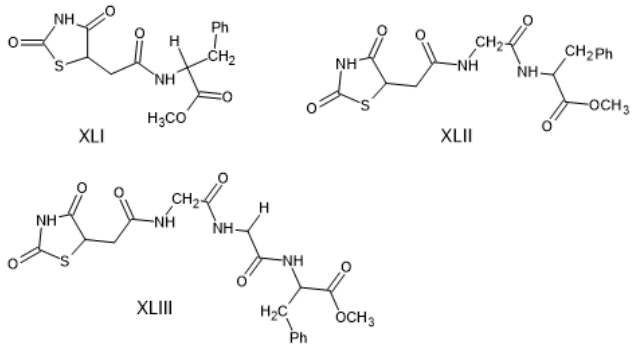

Fig. 7: TZDs incorporated with various amino acid and peptide develop new hypoglycemic agent

subjected to *in-vivo* evaluation for anti-diabetic activity. These benzoxazole-2,4-thiazolidinedione derivatives demonstrated robust efficacy in obese and diabetic yellow mice. Remarkably, the most potent compounds within this series, namely XLIV, XLV, and XLVI (as shown in Fig. 8), displayed activity levels surpassing the standard by a staggering factor of 100. This underscores the potential of these novel derivatives as promising candidates for combating diabetes effectively.[49]

Thiazolidinone with pyrazole ring

A novel series of thiazolidinedione derivatives was ingeniously designed, incorporating the substitution of phenoxyalkyl with a pyrazole ring. After making 15 different molecules from this design, they were put through a lot of tests to see if they could lower blood sugar in a model of diabetes in rats and turn on PPAR-γ. Among these compounds, XLVII presented Fig. 8 stood out because it had a PPAR-γ transactivation of 51.30%, which was higher than the standard drugs rosiglitazone (85.30%) and pioglitazone (65.22%). The effectiveness of compound XLVII led to more research, which showed that PPAR-γ gene expression increased 2.35 times more than it did with pioglitazone, which increased 1.6 times. These results show that compound XLVII in this series has a lot of potential for changing PPAR-γ activity. It should be studied more to see what therapeutic effects it might have on diabetes management. [50]

TZDs with pyrazole trunk series are synthesized and screened for antidiabetic activity in the diabetic rate model. The 2,4-thiazolidinedione with $-CH_2CONH_2$ moiety containing pyrazole ring in the series derivatives contributed one additional hydrogen bond interaction with the ILE 281 amino acid in the PPARγ active pocket, which may contribute to better anti-diabetic activity in the series. Compounds of the amide series exhibited significant anti-diabetic potency, among which compound XLVIII in Fig. 8 showed the most potent anti-diabetic activity. Compound XLIX 6c (Fig. 8) shows no sign of hepatotoxicity without any weight gain.[51]

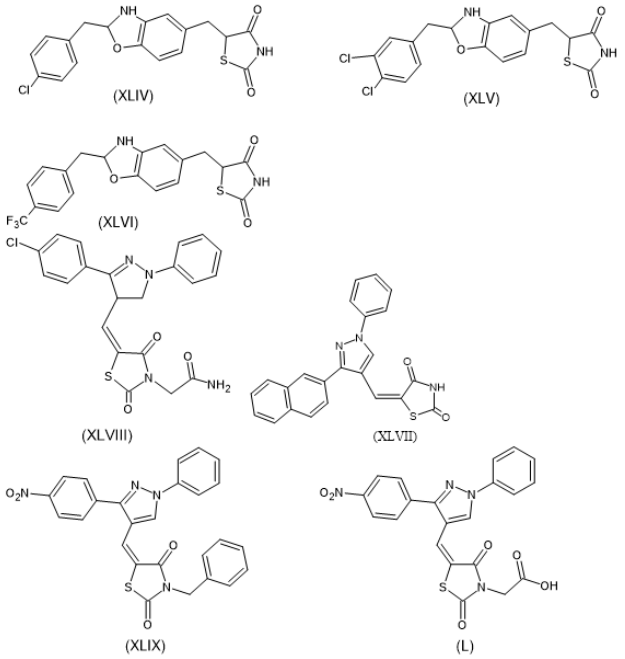

Fig. 8: 2,4-thiazolidinedione with benzoxazole and pyrazole active derivatives for effective reduction in serum glucose level

Additionally, compound L exhibited notable anti-inflammatory properties, demonstrating efficacy in the reduction of inflammatory markers such as TNF-α, IL-β, and MDA. Moreover, it displayed significant antioxidant activity, complementing its anti-inflammatory effects. In addition to being unique, compound L showed strong antidiabetic activity, which showed its wide range of therapeutic potential in conditions linked to inflammation and diabetes.[52]

TZD with carboxylic acid substituted at N-3

Thiazolidinedione with a carboxylic acid ester substituted at N-3 of the TZD ring was developed and produced by Prasanna Datar *et al*. The hypoglycemic effect was assessed with a model loaded with sugar. Compounds (LI) and (LII) present in Fig. 9, in this class exhibit significant anti-diabetic properties.[53]

Saturated and unsaturated TZDs

Lohray, BB and colleagues undertook the preparation of both saturated and unsaturated TZD derivatives, aiming to compare their pharmacological profiles. Notably, the unsaturated TZDs showed very strong effects on lowering blood sugar and cholesterol, which were especially clear at a higher dose (100 mg/kg/day). Conversely, the saturated TZDs displayed exceptional euglycemic activity at a lower dose (30 mg/kg/day), yet their hypolipidemic effects were entirely absent.[36] In a related study, Gurram R. Madhavan and co-researchers conducted a comparison between saturated and unsaturated benzoxazinone-containing thiazolidinedione derivatives. Here, the researchers observed that the *in-vitro* potency of saturated TZDs,

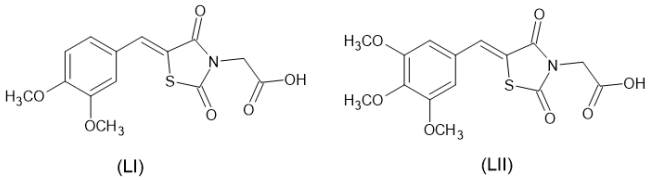

Fig. 9: TZD derivatives with carboxylic acid at N-substitution showing significant hypoglycemic activity

represented by LIII (Fig. 10), was notably inferior to that of their corresponding unsaturated counterparts. These results shed light on the different pharmacological profiles of saturated and unsaturated TZD derivatives. They show how molecular saturation has a complex effect on how well they work as medicines.[26]

Avupati and colleagues embarked on the synthesis of 24 unsaturated TZD compounds, aiming to assess their anti-hyperglycemic activity. The hypoglycemic activity was conducted by streptozotocin-induced diabetes rat models. Out of all the derivatives that were made, a new one called LIV (Fig. 10) stood out as especially promising. It had much stronger blood sugar-lowering effects than the standard drug, rosiglitazone. This finding emphasizes LIV's potential as a candidate for further investigation in the management of hyperglycemia associated with T2DM.[54]

SAR of Glitazone Derivatives

Rosiglitazone is a thiazolidinedione (TZD) derivative that interacts with its receptor in a hydrophobic way through its N-alkyl group and aromatic tail. These interactions are very important for its strong effects against hyperglycemia.[50] The core structure of TZD derivatives includes an 2,4-thiazolinedione group linked to a lipophilic cyclic and heterocyclic group by a phenoxyalkyl chain.[51] Removing the acidic group by N-substitution results in a loss of activity, highlighting its importance. The thiazolidinedione ring can be substituted with other groups, such as oxazolidinediones and α-substituted carboxylic acids, leading to strong antidiabetic agents, though replacements with α-substituted carboxylic acids may lack selectivity for PPAR-γ.[52-54] The activity of these compounds is higher when the linker between the TZD and the phenoxyalkyl group is saturated rather than unsaturated. Modifications to the benzene ring of the phenethyl segment do not affect the activity, and the optimal linker for activity is a two-carbon ether.[52] Additionally, while lengthening the N-alkyl chain decreases activity, adding aromatic and heteroaromatic groups to the lipophilic tail increases activity. Replacing the 2-pyridyl group with 2- or 4-oxazolyl or 2- or 4-thiazolyl groups significantly boosts the anti-diabetic efficacy *in-vivo*.[55]

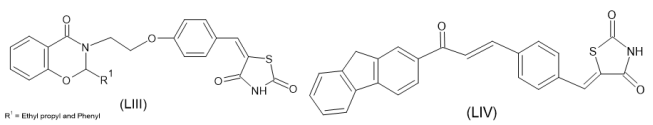

Fig. 10: Unsaturated TZD derivatives showing significant anti-hyperglycemic activity

PPARα/γ Dual Agonist

Diabetes mellitus (T2DM) is marked by elevated blood glucose levels, insulin resistance in adipocyte tissue, and low insulin secretion, often accompanied by dyslipidemia, hypertension, and obesity. PPARα/γ dual agonists target both hyperglycemia and hyperlipidemia in T2DM.[56,57] KRP-297 (Fig. 11) was first reported PPARα/γ dual agonist, developed jointly by Kyorin Pharmaceuticals and Merck but it was discontinued in phase 3 trials. AZ-242 (Fig. 11), developed by AstraZeneca, is a more potent PPARα/γ dual agonist, particularly effective at the PPARγ receptor. It significantly reduced blood glucose levels and triglyceride levels in diabetic mice.[58-60] Dr. Reddy's Research Foundation developed ragaglitazar and other α-ethoxy-β-phenylpropanoic acid derivatives. Ragaglitazar, in particular, is more effective than rosiglitazone in hypoglycemic activity and lowering triglyceride levels in diabetic mice and demonstrating good oral bio-availability.[61] Other developments include DRF-2519, a potent benzoxazinone 2,4-thiazolidinedione compound that improved glucose and lipid levels in animal models.[62] Liu, K. G., *et al*. reported potent PPARα/γ activities in α-isopropoxy-β-phenylpropanoic acid derivatives. The compound (LV) has high potencies at PPARα and PPARγ**.** Several compounds of this series showed partial PPARγ agonist.[63] Eli Lilly and Ligand Pharmaceuticals reported novel agents 'LY510929' and Devasthale *et al*.'s report muraglitazar (Fig. 11) both showed potent dual agonist activity and efficacy in animal models. Merck's research into 3-phenylbenzisoxazoles and 5-arylthiazolidinediones revealed compounds with promising antidiabetic and anti-hyperlipidemic effects, enhancing the therapeutic options for managing T2DM.[64-67]

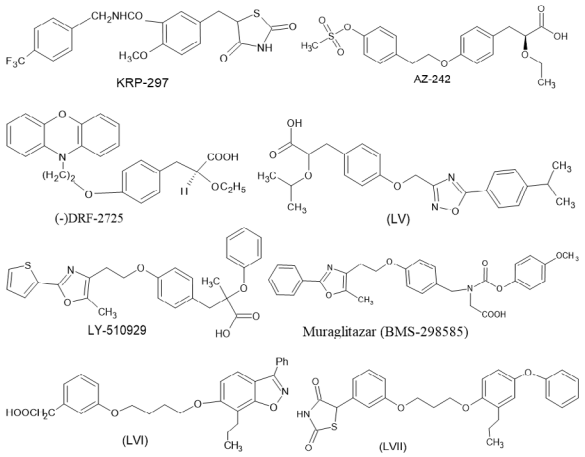

Fig. 11: PPARα/γ dual agonist effective in hyperglycemia and hyperlipidemia and target diabetes, dyslipidemia, hypertension, and obesity

Non-TZDs PPARγ Agonist Ligands

PPARs and are pivotal in modulating the hyperglycemic state in diabetic patients. New α-alkoxy and alkylthio carboxylic acid compounds were synthesized, characterized, and assessed for their potential in treating diabetes. Substituting the thiazolidinedione ring with a carboxylic acid, a novel family of derivatives was created to exhibit acceptable activity while mitigating the associated toxicity of TZDs. Among these, compounds LVIII, LIX, and LX present in Fig. 12 demonstrated notable activity, showing potency comparable to TZD derivatives.[60] Additionally, N-(2-benzoylphenyl)-L-tyrosine derivatives, as non-TZDs compounds, were identified as selective PPARγ agonists and robust anti-diabetic agents.[64] α- phenyl propanoic acid derivatives with oxadiazole manifested dual agonist activity on PPARα as well as PPARγ receptors.[66] Furthermore, benzoylphenyl with L-tyrosine derivatives exhibited strong and selective PPARγ agonist properties. Notably, among these, propanoic acid derivatives LXI (Fig. 12) emerged as the most active within this series. Compound LXI's ethyl side chain was modified to produce strong, specific PPARγ molecular receptor agonists with improved water solubility.[64]

Clinical and Under Clinical TZDs Agents

Rosiglitazone

Rosiglitazone is an anti-hyperglycemic thiazolidinedione (TZD) drug that was launched in 1999 by Takeda in Japan for the treatment of diabetes mellitus. However, it was introverted in Europe in 2010 due to an analysis of an increased risk of untreatable myocardial diseases.[8] Rosiglitazone, similar to other TZDs, enhances insulin action primarily through the stimulating action of the PPAR-γ (PPAR-gamma). Adipose tissue, skeletal muscle, and the liver are the primary locations for this receptor. When PPAR-gamma is activated in these tissues, it enhances insulin's effects. Rosiglitazone may also influence other tissues that express PPAR-gamma. Unlike sulfonylureas and meglitinides, TZDs do not raise plasma insulin levels and do not cause glucose levels to drop to clinical hypoglycemia, which is why TZDs like rosiglitazone are classified as anti-hyperglycemic rather than hypoglycemic agents.[68]

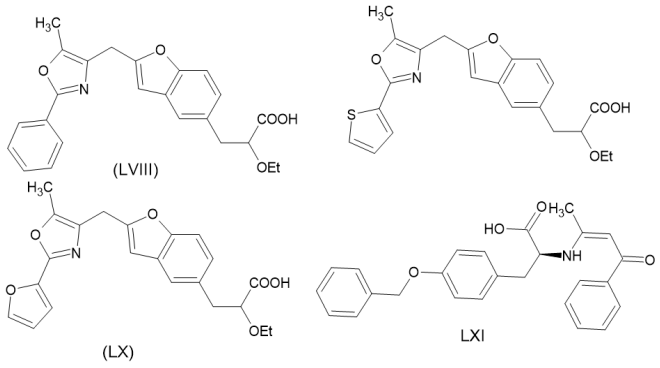

Fig. 12: Non-TZD compounds have dual agonist activity of PPARα and PPARγ molecular receptor

Pioglitazone

The second clinical PPARγ agonist drug, pioglitazone (Actos), was introduced to the market in 1999 by Takeda Pharmaceutical Company in Japan. Pioglitazone is ten times more potent than troglitazone in its glucose-lowering effects. Unlike troglitazone, no severe liver dysfunction reports associated with pioglitazone treatment. However, there has been controversy regarding its safety. Bladder cancer risk is not associated with the use of a for short duration, using it for more than two years may increase the likelihood of developing the condition.[69-72]

Rivoglitazone

Daiichi Sankyo has developed a fourth agent, rivoglitazone, which boasts a longer half-life than both pioglitazone and rosiglitazone. *In-vitro* studies indicate that rivoglitazone is more potent in activating PPAR-γ compared to the other two drugs. The most common side effects of rivoglitazone, which are dose-dependent, include peripheral edema and weight gain.[73]

Lobeglitazone

Lobeglitazone, developed by Chong Kun Dang Pharmaceuticals, is a powerful active glitazone with a less side effect profile. Its unique p-methoxyphenoxy group enhances hydrophobic interactions. *In-silco* docking studies indicates that lobeglitazone has high affinity for PPARγ compared with rosiglitazone and pioglitazone. Phase III clinical trials showed that lobeglitazone was as effective and safe as pioglitazone when used as an add-on treatment to diabetes. Lobeglitazone shows a favorable combination of efficacy and safety.[74-77]

Mitoglitazone

Metabolic Solutions Development Company developed a new generation insulin sensitizer, mitoglitazone. Phase IIb trials indicate that this PPARγ-sparing insulin sensitizer may offer a novel approach to addressing resistance to the insulin signaling pathway, which is crucial for preserving the β-cell in the diabetic. By activating the mitochondrial receptor, this drug improves insulin sensitivity and may have glucose-lowering effects comparable to pioglitazone. Mitoglitazone lacks the weight gain and edema side effects commonly associated with thiazolidinediones (TZDs).[78,79]

Saroglitazar

Sarglitazar launched in 2013 by Zydus Cadila Ltd. in India, saroglitazar (ZYH1) is used to treat diabetic dyslipidemia. It is a dual PPAR agonist, primarily targeting α and moderately affecting γ receptor. Clinical studies indicate that saroglitazar is safe and generally well-tolerated, with no notable side effects observed in single-dose trials.[80-82]

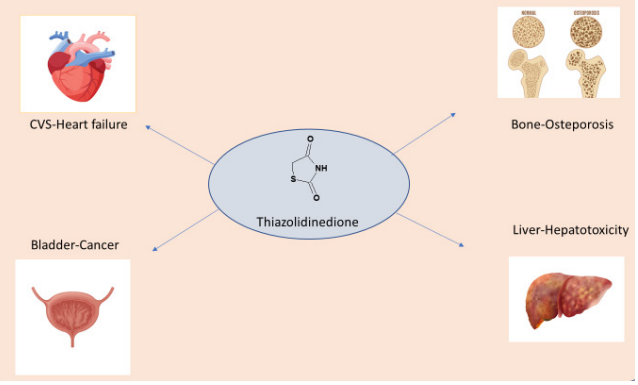

Fig. 13: Thiazolidinedione adversely affect the liver, CVS, Bone and Bladder on longer term uses

Adverse Effect of TZDS

The thiazolidinedione ring, a structural characteristic of TZD, has been linked to liver toxicity in humans. This suggests that TZD may have a harmful effect on the liver.[83] 1.9% of patients develop hepatotoxicity from troglitazone. In troglitazone trials, five patients had ALT levels over thirty times the normal limit, and several had levels over ten times the upper limit. While ALT elevations were not caused by a placebo, they are an important sign of potentially lethal hepatotoxicity.[7] Rosiglitazone was less harmful than troglitazone, according to Elcock *et al*.'s analysis of the two drugs' effects on the toxicity of cultured rat hepatocytes. These results suggest that troglitazone and hepatotoxicity are related, while thiazolidinediones are not.[61] Rosiglitazone may carry a cardiovascular risk, according to Nissen's examination of clinical study data.[9] The possibility of a heart failure warning was included by the USA FDA in the prescription instructions for both pioglitazone and rosiglitazone[84] Fig. 13 describes the adverse effect of TZD on various organs.

It was discovered that the incidence of peripheral edema in the pioglitazone side effect research was 3.6%. Because pioglitazone may enhance the reabsorption of salt, there may be a rise in the volume of blood in circulation, which could lead to edema and an increase in body weight.[84] Pioglitazone use was linked to bladder cancer in a clinical investigation, however short-term use did not raise the risk. Pioglitazone use for longer than two years, however, may marginally increase the risk of bladder cancer.[14] In the meantime, lobeglitazone use has significantly decreased because of its associations with an increased risk of cardiovascular problems and bladder cancer.[85] Thiazolidinediones have a major impact on bone development and can lead to osteoporosis, particularly in postmenopausal women.[86]

Conclusion and Future Perspective

Insulin sensitizers (TZDs) are used to treat type 2 diabetes. Through hypoglycemic, anti-hyperglycemic, and anti-lipidemic pathways, TZDs have been demonstrated to have antidiabetic effects. By increasing the transactivation of PPAR receptors, TZDs work effectively. Early TZDs that were clinically used were withdrawn or discontinued from the market due to a number of negative effects.

The second clinical PPARγ agonist drug is pioglitazone (Actos) introduced in the market in 1999 by Takeda Pharmaceutical Company in Japan. Thiazolidinedione derivatives prepared with the combination of a variety of cyclic and heterocyclic rings found miscellaneous results. The ether oxygen in the linker was substituted with sulfur, nitrogen, and carbonyl groups. Although the sulfur and nitrogen analogs showed slightly lower potency, both the ketone analog and the alicyclic ketone demonstrated comparable activity. The two-carbon linker is an important structural requirement for antidiabetic activity. 2,4-Oxazolidinediones exhibited better antidiabetic activity than 2,4-thiazolidinediones. Unsaturated TZDs showed appreciably good euglycemic and hypolipidemic activities but saturated TZDs showed excellent euglycemic activity. The PPARα/γ dual agonists have the advantage to treat hyperglycemia and hyperlipidemia associated with T2DM. Ragaglitazar (-) DRF-2725) is a phenyl propanoic acid derivative and is an α & γ dual potent agonist of the human PPAR receptors. Non-TZD compounds activate the (PPARs) and play an essential part in controlling the patient's hyperglycaemic state when they have diabetes. A series of molecules that eliminate the toxicity associated with TZDs while maintaining adequate activity is produced by substituting a carboxylic acid group for the thiazolidinedione ring. Pioglitazone is currently the only PPARγ agonist available on the market. A novel TZD mitoglitazone completed the clinical trial phase II for the treatment of diabetes and Alzheimer's. Lobeglitazone is equally effective as pioglitazone with reduced side effects. Non-TZD saroglitazar was launched in 2013 by Zydus Cadila Health Care having more PPARα effect than PPARγ effect. The need for new TZD with high potency, devoid of the adverse effects associated with TZDs.

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