International Journal of Pharmaceutical Research and Applications
Volume 9, Issue 2 Mar-Apr 2024, pp: 2077-2095 www.ijprajournal.com ISSN: 2456-4494

A Review on Thiazolidine Derivatives in the Treatment of Diabetes Type II: Its Derivatives, Adverse Effects, Partial PPAR Agonism and Bioisosteric Replacements.

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Submitted: 20-04-2024 Accepted: 30-04-2024

ABSTRACT: Four drugs make up the well-known therapeutic class of insulin sensitizers known as thiazolidinediones, which was first introduced in the late 1990s: pioglitazone, rosiglitazone, troglitazone, and ciglitazone. They provided a fresh approach to improving glycemic control in people with type 2 diabetes mellitus as a particular PPAR-γ agonist. Nevertheless, this class of drugs has shown adverse effects that are both drug- and class-specific. The first medication in this class, ciglitazone, was first available in 1982 and showed promise in reducing glucose and lipids. But because it was toxic to the liver, it was taken off the market. Thiazolidinediones have been used as anti-diabetic agents due to their intriguing TZD framework, but they have also been investigated for a number of other therapeutic uses, including aldose reductase inhibition, anti-cancer, anti-microbial, and anti-arthritis. Troglitazone was the first medication the USFDA approved in 1997; however, because of its severe hepatotoxicity, it was taken off the market in 2000. In 1999, Rosiglitazone and Pioglitazone were subsequently launched, demonstrating comparatively lower hepatotoxicity. PPAR Partial agonism and Bio isosteric replacement have shown promising results to minimize these adverse effects and increase sensitization of insulin.

KEYWORDS: TZD rings, adverse effects, glitazones, partial agonism, PPAR gamma agonist, bio isosteric replacements.

I. INTRODUCTION

[1]Thiazolidinediones, a well-known therapeutic category of insulin sensitizer medications introduced in the late 1990s, comprises four drugs: ciglitazone, Troglitazone, Rosiglitazone, and Pioglitazone. As a specific agonist for PPAR-γ, they offered a new avenue for enhancing glycemic control in type 2 diabetes mellitus. However, this drug class has exhibited both class-specific and drug-specific adverse effects. Ciglitazone, the pioneer drug of this category introduced in 1982, demonstrated promising effects in lowering lipids and glucose. However, it was withdrawn from the market due to liver toxicity.[2]Because of its intriguing TZD framework, thiazolidinediones have not only been utilized as anti-diabetic agents but have also been explored for various therapeutic purposes such as anti-cancer, anti-microbial, anti-arthritis, and aldose reductase inhibition. Troglitazone was the inaugural drug approved by the USFDA in 1997, yet it was withdrawn from the US market in 2000 due to severe hepatotoxicity. Subsequently, Rosiglitazone and Pioglitazone were introduced in 1999, exhibiting relatively lower hepatotoxicity but associated with fluid retention, leading to edema and precipitation of congestive heart failure (CHF). Despite these concerns, Rosiglitazone and Pioglitazone, being comparatively safer, continue to be utilized in anti-diabetic therapy. This review will primarily focus on the anti-cancer and anti-diabetic applications of TZD-containing molecules, along with their toxicity issues, efforts to mitigate toxicity through structural modifications around the TZD framework, and bioisosteric replacement of the TZD ring. Darglitazone and ciglitazone were discontinued due to observed cataractogenic effects in rats. Some thiazolidinediones have exhibited mitochondrial dysfunction, with Troglitazone causing a decrease in membrane potential and ATP levels in HEPG2 cells, while Ciglitazone induced significant changes in membrane potential and accelerated oxy-radical production in glioma cells and astrocytes.(Article: Mitochondrial impairment by PPAR agonists & statins identified by immunocaptured OXPHOS complex activities and respiration).Pioglitazone has also been observed to impact cellular mitochondria, potentially leading to cytotoxicity by inhibiting ATP production.[3]Rosiglitazone has additionally demonstrated uncommon side effects such as

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Volume 9, Issue 2 Mar-Apr 2024, pp: 2077-2095 www.ijprajournal.com ISSN: 2456-4494

headache, upper respiratory tract infection, and injury. Reported side effects also include anemia and edema . (Article: A review on rosiglitazone in type2 diabetes mellitus Amy werner). It has also been noted that the use of rosiglitazone for 12 months in patients with glucose intolerance and type 2 diabetes increases the risk of myocardial infarction and heart failure without a rise in cardiac mortality.[4] Another member of the thiazolidinedione class, troglitazone, exhibited hepatotoxicity as a significant side effect. Although pioglitazone is a preferred drug within this therapeutic category, common side effects include weight gain, peripheral edema, decreased bone density, onset of congestive heart failure in patients at risk, elevated levels of HDL, diabetic macular edema, and anemia due to reduced hematocrit and hemoglobin levels.[5]There is an observed association between the use of pioglitazone and bladder cancer, leading to its withdrawal in most European countries. In the United States, patients with a history of bladder cancer or active bladder cancer are generally not recommended this drug. The mechanism underlying the development of bladder cancer with pioglitazone use remains unclear. Additionally, when rosiglitazone is included in glucose-lowering therapy for type 2 diabetes mellitus, there is a risk of heart failure and bone fractures, particularly in women. However, the effects on other cardiovascular conditions such as myocardial infarction remain uncertain .[6]Numerous clinical trials have been conducted on this drug class to evaluate metabolic and cardiovascular outcomes. [7]Since PPARγ is involved in cell proliferation processes, the TZD nucleus can potentially be used in anticancer combination therapy. However, associated side effects with this treatment have not been fully elucidated. Liver toxicity associated with this drug class depends on factors such as the chemical nature of the TZD ring, which may be a major contributor to toxicity but has not yet been definitively proven. Additionally, metabolites may inhibit the bile salt export pump, disrupting organic transport of polypeptides, leading to intracellular calcium ion imbalance and hepatic apoptosis, resulting in alterations in biochemical reactions such as oxidative stress, glutathione depletion, and PPARγ activation. [8]While various therapeutic agents such as insulin analogues, sulfonylureas, and biguanides are used for treating this disorder, thiazolidinediones have become popular due to their lack of hypoglycemia compared to other antidiabetic drugs. However, other antidiabetic agents like Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide agonists, and sodium-glucose co-transporter inhibitors not only reduce blood glucose levels but also do not exhibit adverse effects commonly associated with glitazones, such as weight gain, hepatotoxicity, and cardiovascular side effects. Nevertheless, these agents do not provide prolonged activity in glycemic control .[9]Recent studies have suggested that partial PPARγ agonists offer improved safety profiles compared to full PPARγ agonists, prompting efforts to promote these partial agonists for clinical development.[10]Rivoglitazone, another glitazone derivative currently in phase III clinical studies, has not been associated with adverse drug reactions such as cardiotoxicity or hepatotoxicity; however, the risks associated with its use have not been fully assessed, and therefore, the drug is not yet in use . [11]Hulin et al. synthesized a biotin conjugate called Darglitazone, a selective PPARγ agonist found to be associated with TZD-induced bone marrow adipogenesis and bone loss on cancellous and endocortical surfaces. However, it also increased periosteal bone formation in mice, indicating the involvement of PPARγ in the regulation of bone resorption and demonstrating surface-specific effects of PPARγ agonists on bone. Englitazone was discontinued due to poor efficacy and hepatotoxicity after phase II clinical trials.

II. DOCUMENTED ADVERSE EFFECTS OF THIAZOLIDINE DERIVATIVES:

[12]Thiazolidinedione derivatives are widely recognized for their diverse toxicity-related effects, despite exhibiting effective antihyperglycemic activity. One contributing factor to these effects is metabolism, as they have demonstrated both enzyme induction and inhibition, potentially resulting in various interactions. Metabolic pathways include N-demethylation, hydroxylation, and phase II metabolism involving sulfate, glucuronide, and glutathione conjugation .[13]The three primary glitazones—troglitazone, rosiglitazone, and pioglitazone—are recognized for their association with various serious side effects, despite their efficacy in managing hyperglycemia. As these drugs are PPARγ agonists, their full agonism may contribute to drug-induced toxicity. Troglitazone, extensively studied in this context, notably demonstrated severe hepatotoxicity, leading to its market withdrawal due to factors such as high dosage requirements (ranging from 200-600 mg/day), enzyme induction and inhibition

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(including CYP3A4 induction and inhibition of enzymes such as CYP2C8, CYP2C9, and CYP2C19), accumulation in the liver via enterohepatic circulation, and extensive protein binding capacity to albumin, mainly around 99%. Additionally, TGZ sulfate may contribute to toxicity by damaging mitochondria and inhibiting bile salt excretion, particularly risky in patients with a history of cholestasis. Troglitazone metabolism involves several pathways in human liver microsomes, resulting in four major metabolites: troglitazone glucuronide, troglitazone sulfate, troglitazone glutathione, and chromane ring oxidation. Chromane ring oxidation generates a stable, electrophilic O-quinone methide derivative that binds covalently with cellular proteins, predominantly responsible for hepatotoxicity. Furthermore, the quinone derivative's cytotoxic nature depletes glutathione levels via various redox reaction mechanisms.Rosiglitazone has been associated with cardiotoxicity and effects on bone mass and strength, particularly in postmenopausal women, although the exact mechanisms remain unclear.[14] In postmenopausal women, the utilization of rosiglitazone may lead to a heightened susceptibility to osteoporosis and bone fractures. [15] Reports suggest that drug-induced cardiac issues may be PPARγ receptor-independent or receptor-dependent. Studies indicate that, besides class-specific side effects, rosiglitazone may contribute to cardiac hypertrophy. However, the exact reasons behind this effect—whether metabolites, full agonism, or other factors—are not fully understood. After rosiglitazone administration, changes in cardiac gene expressions (such as changes in the chromatin network via H-3 phosphorylation) and increased risks of congestive heart failure have been observed, with fluctuations in atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels.

Long-term rosiglitazone treatment may lead to cumulative cardiotoxicity, primarily manifested as maladaptive cardiac hypertrophy and heart failure, independently of PPAR gamma activation. Reports also suggest that rosiglitazone induces cardiotoxicity by generating reactive oxygen species. While some studies propose overexpression of PPARγ in drug-induced toxicity, transcriptome studies suggest PPARγ-dependent cardiac dysfunction, although the association between metabolite formation and cardiac adverse effects remains unclear.

Pioglitazone is associated with increased incidences of bone fracture, bladder cancer, and cardiac side effects. The PROactive clinical trial suggests an increased risk of bladder cancer with pioglitazone use, although other studies do not consistently support this finding. The exact mechanism underlying pioglitazone-induced bladder cancer—whether through metabolites or agonism—is still unclear. Mechanisms proposed for pioglitazone-induced neurotoxicity and cardiotoxicity include changes in mitochondrial function, reactive oxygen species generation, and alterations in mitochondrial membrane structure. Recent studies also implicate GPR40 in PPAR-independent responses to TZDs in other cell types, suggesting involvement in osteocyte apoptosis and decreased bone mass via sclerostin expression induction. The Crystallurea hypothesis posits that pioglitazone use results in urinary solidification, leading to chronic bladder irritation and carcinogenesis. Pioglitazone is considered a causal risk factor for prostate and pancreatic cancers, with bladder cancer risk also possibly being receptor-independent, although the precise molecular mechanisms remain unclear.

Murglitazone has also been implicated in bone fracture and cardiovascular events. [16] In vivo metabolic pathways result in shorter accumulation times for rosiglitazone and pioglitazone, potentially reducing hepatotoxicity. [17] Long-term glitazone use has been associated with lower respiratory tract infections and serious pneumonia, although the mechanism remains elusive. [18] The chromane ring, known for its anti-neurodegenerative, anti-inflammatory, anti-cancer, and anti-diabetic properties, likely plays a significant role in troglitazone-induced hepatotoxicity. [19] In the case of rosiglitazone, the formation of active metabolites is relatively low and may contribute to adverse reactions.

III. TO ADDRESS THESE TOXICITY CONCERNS, MODIFICATIONS HAVE BEEN IMPLEMENTED IN THE FOLLOWING WAYS:

1.PARTIAL PPAR GAMMA AGONISM: [20]

The Rescue PPARγ agonists are classified as partial agonists, which cause less receptor activation at saturating concentrations than full agonists, and full agonists, which are traditionally represented by TZDs. Compounds with partial agonist activity are of interest because they provide a better understanding of PPARγ function through data from genetic studies involving humans and animals, as well as ligand studies. Reduced transcriptional activity and reduced binding affinity

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for responsive elements are the outcomes of the minor Ala allele of the human PPARγ2 polymorphism Pro12Ala.

[21]This idea underpins the idea that partial PPARγ agonists can both minimize the dose-dependent side effects of full agonists, like weight gain and plasma volume expansion, while preserving the advantages of PPARγ activation. Indeed, many compounds with weak agonist activity reduce these undesirable side effects without sacrificing their antidiabetic and insulin-sensitizing properties in animal models and clinical trials. They are also known as selective PPARγ modulators (SPPARγM) because of their capacity to distinguish between the functions of PPARγ in various tissues.

Differential binding pattern of partial/selective PPARγ agonists:

[22]Specific binding pattern of partial/selective PPARγ agonists: PPARγ is made up of five domains, A–E, spanning from the N-to the C-terminus. The activation function (AF1) of the N-terminal regulatory domain, which is composed of domains A and B, is involved in ligand-independent binding. The domain that binds DNA is called the C domain. The D domain, which is poorly conserved, serves as a flexible hinge that rotates the ligand-binding and DNA-binding domains. The nuclear receptor's largest and second most conserved domain is called the ligand binding domain (domain E), which is also known as the DNA binding domain. The ligand binding domain serves four primary purposes: (i) a coregulatory binding surface; (ii) ligand binding pocket; (iv) activation function 2 (AF-2). H1-H12 and H2' are the two 13α helices that make up the ligand binding domain. The ligand binding domain has a cavity with three branches that is shaped like a T or Y, according to crystallographic studies. H3, H5, H11, and H12 make up Branch I, which is hydrophilic in nature and serves as the interaction site for ligands with acidic head groups, like rosiglitazone. H2', H3, H6, and H7 make up Branch II, and Surro makes up Branch III.

INT 131

[23]Another effective selective PPAR gamma agonist that has been demonstrated by TZD to have no adverse effects is INT 131. Comparing the PPARγ receptor transactivation assay to the conventional medication rosiglitazone, a 49% response was noted, and the result was 83nM. Furthermore, when this drug was administered to ICR mice at doses of 10 or 30 mg/kg in addition to rosiglitazone for nine days, there was no increase in plasma volume; however, when rosiglitazone was administered, there was a 31.9 percent increase in plasma volume. In contrast to rosiglitazone, which was found to have an increased value, INT 131 did not increase plasma volume in ICR mice. Additionally, it was discovered that the pioglitazone-treated animals' epididymal fat mass had decreased, and INT-131 did not like the weight gain effect. Additionally, the osteocalcin level was determined using the ELISA test, and the results showed effects on bone architecture and bone mass density. While INT-131 did not exhibit any bone-related side effects, rosiglitazone carries the potential for such effects. INT-131 does not directly form an H bond with the Y473 residue or the AF2 helix. The only way that the sulfonamide moiety and the Y473 resid form an H-bond is when water is added. [22].Compared to standard drugs that are full PPARγ agonists, Balaglitazone Partial PPAR γ agonists (DRF-2593) have fewer side effects, such as fluid retention, heart enlargement, and no effect on bone formation. When balaglitazone and pioglitazone were compared, it was found that the former had better antidiabetic activity and a better safety profile due to the absence of side effects like myocardial infarction, peripheral oedema, and heart failure. Balaglitazone has demonstrated less fluid retention and no weight gain in phase II clinical trials when compared to other glitazones. Balaglitazones were found to exhibit less cardiac hypertrophy and fluid retention in clinical trials. Studies using the molecule balaglitazone on obese mice have revealed that the mice have not gained as much body weight. Following a 42-day course of treatment with pioglitazone and balaglitazone, pioglitazone caused an increase in water content, while balaglitazone did not cause this side effect. They have collected serum samples from the animals in order to monitor histomorphometry indices and assess the osteoclast biomarker for side effects related to bone.

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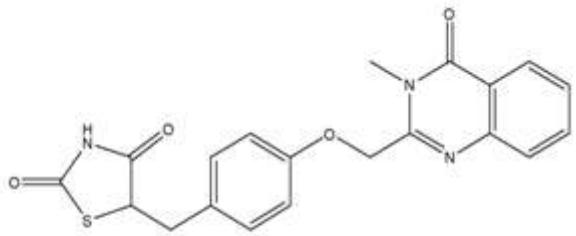
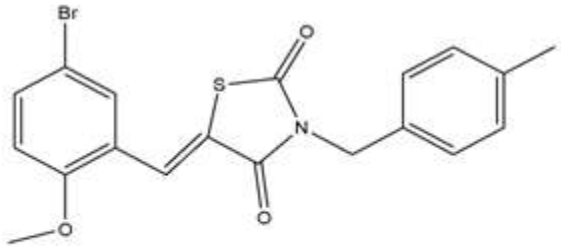


BALAGLITAZONE

[24]**GQ 16** ((5-(5-bromo-2-methoxy-benzylidene)- 3-(4-methyl-benzyl)-thiazolidine-2,4-dione) is a partial PPAR γ agonist that has been shown to have a distinct binding pattern and to inhibit Ser-273 phosphorylation at CDK5. The compound exhibited a better antidiabetic profile than rosiglitazone. It also showed no weight gain, which is the most common side effect related to the class, and less adipogenic edema. Transactivation assay results demonstrate that GQ-16 is partially an agonist of PPARγ, as it contributes to the AF2 binding region of the receptor's suboptimal induction.



GQ-16

[25]**PAR 1622** is a small molecule that the Dong-A research center synthesized. In contrast to rosiglitazone, which demonstrated 101 nM for the same assay, [(S)-2-ethoxy-3(4-(5-(4-(5-(methoxymethyl) isoxazol-3-yl) phenyl)-3-methylthiophen-2-yl) methoxy) phenyl) propanoic acid] is a non-TZD compound that is a partial agonist, demonstrating good PPARγ transactivation activity with an EC50 of 41 nM. and exhibit improved fluid retention and antihyperglycemic profile. A dose of approximately 10 mg/kg was administered to the db/db mice, which resulted in improved antihyperglycemic control. For nine days, they administered the same compound in addition to rosiglitazone to mice receiving 10 or 30 mg/kg ICR. They looked at the plasma's volume and related weight changes after nine days. Surprisingly, though, the weight of the ICR mice treated with PAR-1622 did not change; in contrast, the plasma volume of the ICR mice treated with rosiglitazone increased by 31.9 percent. Through in vitro assay, it demonstrates a 57% affinity for the PPARγ receptor. It was also less effective for the PPARα activity in PPAR γ and PPAR α, which is additional proof that this molecule is PPARγ selective.

[26] **T2384** is the compound that showed a unique binding pattern in the co-transfection assay, which used rosiglitazone. While rosiglitazone was found to activate the receptor 12 fold, the T2384 compound only activates it by about 3 fold, with an EC50 value of 0 point56 µM. This may also be one of the indicators that indicates a lower toxicity profile. When the molecule was given to KKy mice in addition to rosiglitazone, the mice receiving rosiglitazone displayed weight gain and a decrease in red blood

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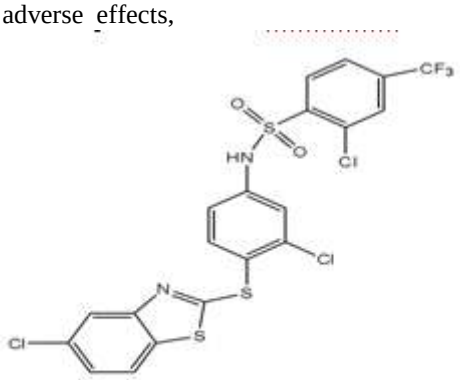
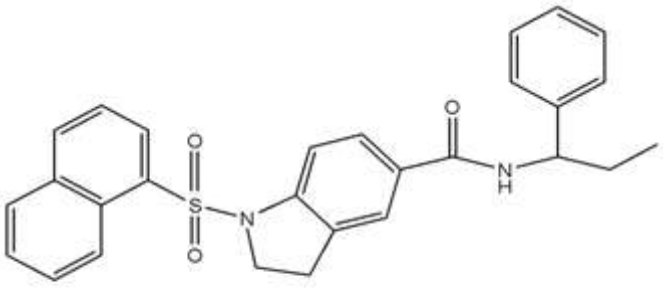
cells. However, animals treated with this molecule did not exhibit these side effects. Additionally, when combined with rosiglitazone, this compound can mitigate the drug's side effects without impairing insulin sensitivity or PPAR-γ binding activity. Compared to rosiglitazone, the compound showed superior antihypergycemic activity in KKY mice and was found to have no adverse effects, including weight gain, hemodilution, or anemia. T2384 exhibited a 3-fold partial activation of the receptor, while rosiglitazone demonstrated a 12-fold activity with an EC50 value of 0–56 µM. Furthermore, as anticipated, T2384 prevented PPAR transactivation when rosiglitazone was present.



T2384

[27]**SR2067**

A non-acidic partial PPAR γ agonist, SR2067 has demonstrated less transcriptional activation when compared to rosiglitazone. It has been discovered through kinetic studies that the non-acidic component is responsible for the hydrophobic stabilization. Studies on surface plasmone have also shown that this molecule has a lower affinity than rosiglitazone, which may lessen the toxicity related to the full agonism. With a transcriptional potency of about 60% less than rosiglitazone, SR2067 is classified as a partial agonist. Because SR2067 exhibits a transcriptional potency of approximately 60% when compared to rosiglitazone, it is classified as a partial agonist. (nonacidic gamma-agonist of PPAR).



SR2067

[28]**Compound 50**

Seto et al. synthesized a series of compounds that are 2,4,6-trisubstituted pyrimidine carboxylic acid derivatives and discovered that they have partial PPARγ agonist properties. Their binding pattern differs from that of a full agonist, and they exhibit superior anti-diabetic activity when compared to rosiglitazone, the standard medication; however, their potency is found to be lower than that of RGZ. In comparison to rosiglitazone, this compound has demonstrated 50–60% receptor affinity in both humans and mice. Additionally, it exhibited an antagonistic profile for the PPARγ receptor, with an IC50 value of 1 point79µM, whereas rosiglitazone demonstrated the same property at 1µM. This indicates that compound 50 is a partial PPARγ agonist.

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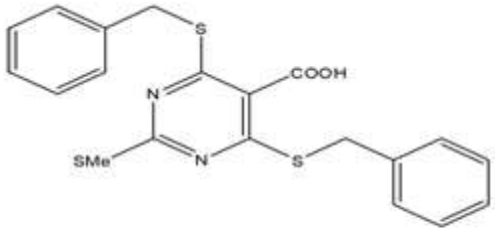
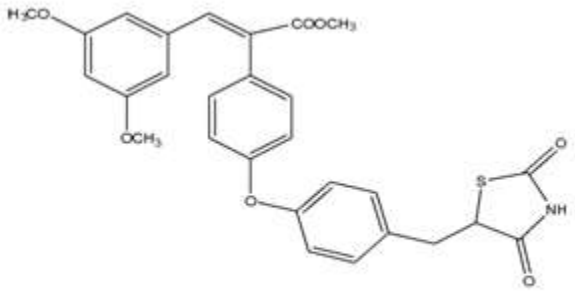


COMPOUND 50

[29]Natural occurring TZD from the genus Pterocarpus, **CLX-0921.** Dey et al. extracted it from the pterocarpous genus and found that it had a good antihyperglycemic effect when compared to rosiglitazone, coming from a natural source. In comparison to rosiglitazone (EC50-0.002µ mol/L), the compound has a lower potency (EC50–0.284µ mol/L). It also demonstrated good activity and fewer adipogenic effects in vivo when compared to rosiglitazone. There is less potential for receptor activity with this compound. The transactivation assay yielded an EC50 value of 0.284 ± 0.036 µmol/L for this compound, whereas rosiglitazone had an EC50 value of 0.009 ± 0.0007 µmol/L.



CLX-0921

[29]**FPFs-410** has been synthesized by Norisada et al., and their activity has been compared to that of pioglitazone, a commonly used medication. While showing less potency towards PPAR γ receptor activation, this molecule has demonstrated commendable antihyperglcemic, antidyslipidemic, and increased 3T3-L1 adipocyte differentiation when compared to PGZ. Additionally, weight gain in rodents that is specific to the TZD class is not demonstrated; however, there is a slight increase in adipogenesis. The PPARγ receptor has not been fully activated by the molecule under IB and DX conditions, although transactivation assays have not been carried out. (FPFS-410)

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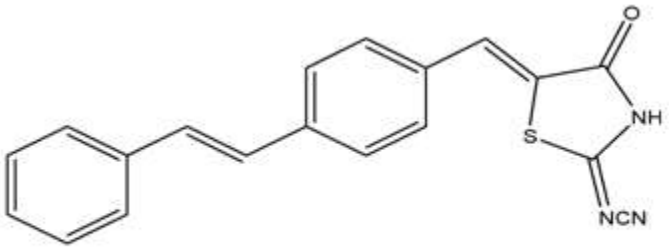
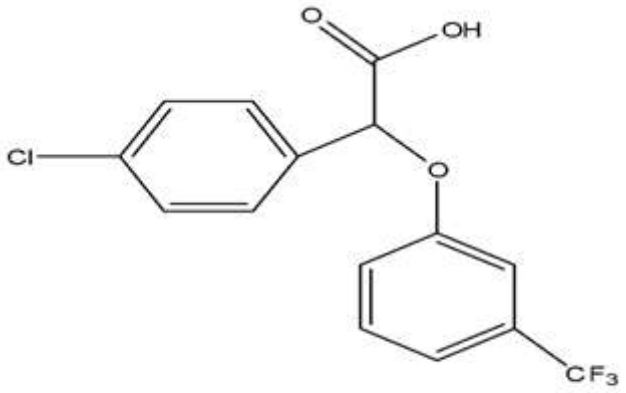


FPFS-410

[30]**MBX 102** acid is the (-) enantiomer of a halofenate derivative that has been shown through an in vitro transactivity assay to be a partial PPAR γ agonist in a dose-dependent manner. In ZF rats, this medication has also been tested in comparison to rosiglitazone. No adverse effects, such as weight gain or edema, were discovered. The 3T3-L1 human and murine adipocyte differentiation assay using rosiglitazone has also been carried out. The compound's adipogenic effect was found to be lessened. Additionally, they tested the compound with rosiglitazone on the human murine mesenchymal cell line C3H10 T1/2 and found that while MBX-102 acid did not inhibit retinoic acid-stimulated alkaline phosphatases, they did predict bone cell phenotype. This powerful insulin sensitizer has been investigated in vivo in rodent models in addition to in vitro. The results of a ligand binding assay were used to determine whether the molecule is a full or partial agonist of PPARγ. MBX-102 acid and rosiglitazone had EC50s of roughly 12 µM and 1 µM, respectively, for these two compounds.



MBX-102

[31]The molecule **L312** was identified by Xie et al. as a partial PPAR gamma agonist using PPAR gamma receptor studies and transactivation assay. When the current molecule was compared to pioglitazone, it was discovered that it had the same affinity as PGZ. The human murine 3T3-L1 pre-adipocyte cell lines have been treated with pioglitazone at a concentration of 10µM on L312. The molecule exhibits a better differentiation profile and has minimal lipid accumulation while having little effect on genes. In db/db mice, both male and female, this medication and pioglitazone were tested. The results showed that the female mice's cholesterol levels significantly decreased when treated with PGZ, but not when this molecule was used. Additionally, after a 14-day course of treatment, it was discovered that the pioglitazone group had significantly increased weight, while the

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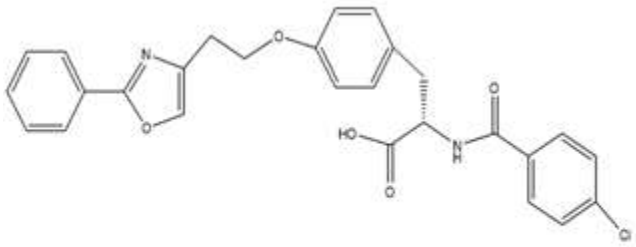
PGZ group had gained 50–60% less weight. Additionally, it was discovered that the substance inhibits the PPARγ receptor's CD5k phosphorylation in vivo in a dose-dependent manner. Additionally, PGZ-treated mice showed alterations in their epididymal white adipose tissues through the inhibition of f pSer273PPARγ; however, L312 molecule-treated animals did not exhibit this effect.



L312

[32]**F11 compund**, a pseudoginesoside derived from Panax quinquefolium L., was discovered by Wu et al. (ginseng from America). Pre-adipocyte 3T3-L1 cells are treated with the compound, and the same cells are also treated with rosiglitazone. Results showed an increase in lipid droplets, suggesting that this has some activity in 3T3-L1 adipocytes, albeit not as much as rosiglitazone. It is a novel partial PPAR γ agonist as a result. There is no report on the toxicity profile. The molecule may lessen the toxicity issues reported by TZDs since it did not demonstrate the same level of efficacy as rosiglitazone. An Luciferase assay was performed on the compound containing rosiglitazone, and the results showed that the molecule F11 had lower transactivation properties than rosiglitazon.

[33]Netoglitazone has been studied both in vivo and in vitro by Lazarenko et al. Neither a full agonist nor a partial agonist describes this substance. U-33/γ2 cells, which contain both osteoblasts and adipocytes under controlled expression of PPARγ2, were used to investigate the effects on osteoblasts and adipocytes. The analysis has demonstrated that netoglitazone considerably reduces osteoblastic activity as measured by osteoblastic gene expression, mineralization, and alkaline phosphatase activity. With 10µg/g/day, it demonstrated significant antihypergycemic activity and weak anti-osteblastic activity. It did not affect bone mass density, bone microarchitecture, or bone-related gene expression, as demonstrated by rosiglitazone at 20µg/g/day. Osteoblast cells that differentiate may overexpress Δ FosB cells, which could negatively impact the bone marrow's hemocrit composition, though this is still unclear. MCC555 Toxicological studies were conducted on male and female beagle dogs, with a planned daily dose of 6,67,20, and 40 mg/kg. The drug's toxicity profile for ophthalmoscopy, hematology, cardiac tissues, urine analysis, and organ weight charting has been studied.

[34]**PAM 1616**: Due to the notable partial activity of propanoic acid, a novel Non-Tzd derivative of the compound was synthesized. The molecule has partial PPARγ agonistic activity, according to the trans-activation assay (IC 50 value of 96nM). Research on the antidiabetic effect in male C57 BL/6J mice was conducted using rosiglitazone for three weeks, at a dose of 0.3–1 mg/kg/day, respectively. There are no weight changes seen in these mice when this compound is used. While rosiglitazone-treated mice exhibited a marked increase in GPT level and liver weight, db/db mice showed no change in GOT and GPT levels, weight changes, or alterations in the liver and heart tissues. The molecule has a higher affinity for the receptor than rosiglitazone, with an IC50 value of 133.9± 46.7 nM, compared to 24.1± 5.6 nM for the molecule. Even so, an in vitro transactivation assay reveals that it has a more potent receptor transaction assay than rosiglitazone (EC50= 83.6± 43.7 nM for this molecule and 113.6± 15.7 nM for rosiglitazone). Additionally, it has demonstrated concentration-dependent inhibition of 96nM rosiglitazone-induced activities. This indicates that it has PPARγ receptor selectivity, which accounts for the mol.

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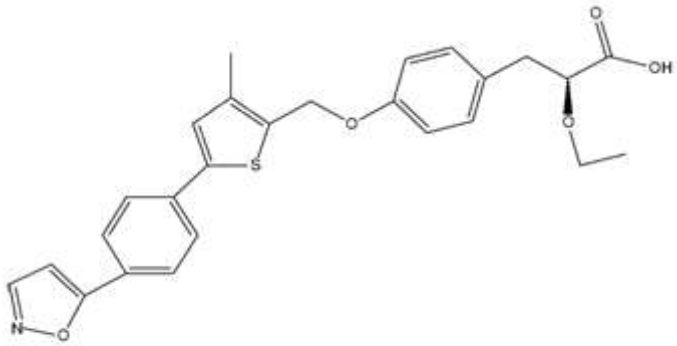
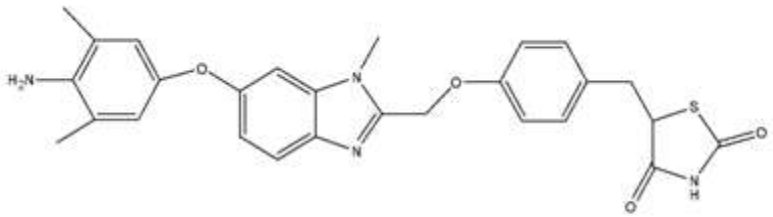


PAM -1616

[35]**Efatutazone** (CS- 7017/RS5444): Efatutazone (CS- 7017/RS5444) is a new PPAR γ receptor partial agonist with promising anti-cancer properties. It has shown anti-proliferative effects on various cancer cell lines, including pancreatic and colon cancer, anaplastic thyroid carcinoma, and tumors in nude mice, both alone and in combination with paclitaxel. Early phase clinical trials have shown that it can induce stable disease in liposarcoma patients, with a favorable safety profile. In phase II trials, it has been well tolerated in relapsed NSCLC patients in combination with erlotinib and in patients with metastatic colorectal cancer in combination with FOLFIRI. Some adverse effects, such as localized edema, have been observed in clinical studies, likely due to the compound's structural properties. Further research is ongoing to explore the full potential of efatutazone in cancer treatment.



Efatutazone

Netoglitazone is an additional partial PPARγ receptor that has antidiabetic properties. It has also demonstrated anticancer properties in a variety of cancerous cells, including prostate cancer tumors, colorectal cancer cells, pancreatic cancer cells, and myeloma cells Through a PPARγ dependent pathway, it also plays a role in the suppression of intestinal polyps.

[36**]Telmisartan**: Telmisartan: The molecule has been linked in preclinical studies to the apoptosis of human urological cancer cells and endometrial cells . demonstrated notable anticancer activity in prostate cancer cells , lung cancer cells , and triple breast cancer cells . Through the use of fluorescence energy transfer (FRET) and glutathione S transferase (GST), it is discovered that this molecule is linked to selective recruitment, making it a partial agonist of the PPARγ receptor. The pioglitazone from the oligo microarray assay exhibits a different gene expression profile from this molecule. This molecule is compared to rosiglitazone in the glutathione transferase assay. In the case of TZD, the recruitment of co-activators DRIP205 and TIF 2 resulted in a decrease in the amount of co-repressor NCoR; however, in the

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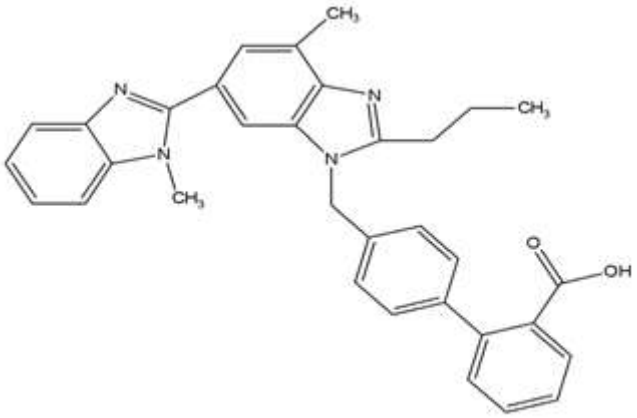
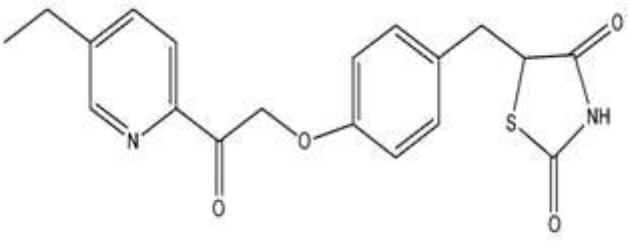
case of this ARB, there is no effect on this co-repressor and only a minor interaction with DRIP-205 and no interaction with TIF2. It is also observed that this causes a conformational change in the receptor. Furthermore, the molecule did not cause any negative side effects, such as weight gain, and it also helped mice's insulin sensitivity.

[37] Toxicity studies have been performed for 28 days for pioglitazone and telmisartan but there are no effects on biochemical parameters, weight changes also histopathology was done but there was no significant toxicological effects observed with telmisartan.



Telmisartan

[38]According to Ohashi M et al., α-benzyl phenylpropanoic acid is also a partial PPAR γ agonist. which, in dose-dependent manner (from 1 to 100μM), operate in human scirrhous gastric cancer cell lines to induce apoptosis. A partial PPARγ agonist found in antidiabetic therapy, mitoglitazone (MSDC-0160) is a derivative of pioglitazone developed by Metabolic Solutions Development Company, USA. This molecule differs structurally from pioglitazone only in that it has an additional carboxyl group, which makes it a selective PPARγagonist that causes fewer side effects in patients.



Mitiglitazone (MSDC-0160)

2. Bioisosteric Replacement

[39] Replacing the TZD ring with different alternatives offers a chance to alleviate the undesirable side effects linked to its adaptable framework. This deliberate substitution strategy seeks to improve safety profiles and address concerns regarding toxicity in glitazones. Potential bioisosteric substitutions encompass pyrolidinediones, isoxazolidinediones, oxazolidine-2,4-diones, tetrazoles,and tetrahydropyrimidones , Imidazolidinedione Derivatives ,Aryloxazolidinediones.

Saha et al. explored the role of sulfur in the TZD ring, identifying it as contributing to reactive metabolite formation. They synthesized compounds replacing the TZD ring with pyrrolidin-

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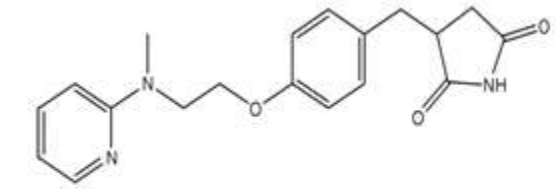
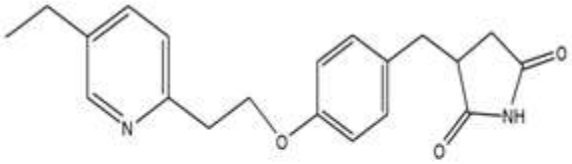
2,5-dione in troglitazone, rosiglitazone, and pioglitazone, resulting in reduced cytotoxicity, GSH depletion, and oxidative stress. Analogues of pioglitazone and rosiglitazone with pyrrolidin-2,5-dione were developed due to the toxic chromane ring. Comparative studies demonstrated lower cytotoxicity and reduced PPARγ binding in these analogues, which were less susceptible to ring opening and GSH adduct formation, thereby exhibiting decreased toxicity.

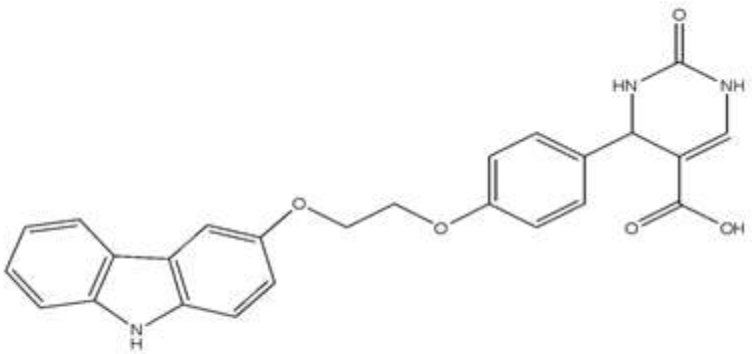


ROSISUCCINIMIDE



PIOSUCCINIMIDE

[40]Kumar et al. synthesized a compound library replacing the TZD ring with a pyrimidone ring, with 6e emerging as the most effective derivative. These compounds exhibited altered binding patterns to the PPARγ receptor, suggesting potential reduced toxicity compared to TZD-based compounds.



6e

[41]Sharon et al. synthesized PPAR gamma agonist molecules containing tetrazole and compared their transactivation assay with the standard drug, rosiglitazone. They observed lower affinity compared to rosiglitazone but significant antidiabetic activity in SD rats. However, toxicity studies were not conducted.

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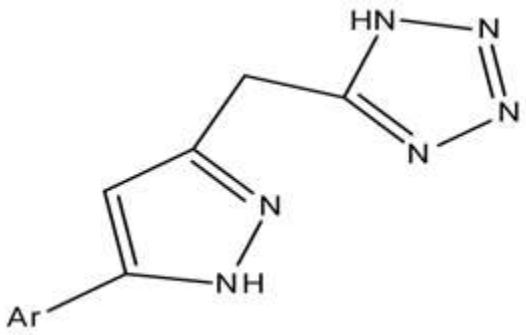
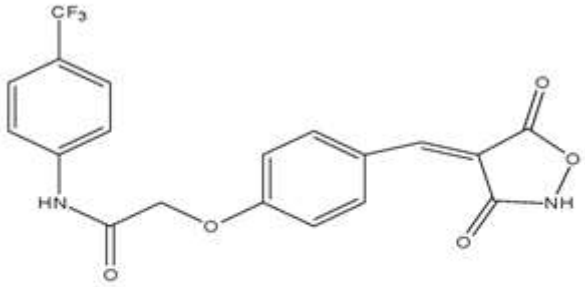
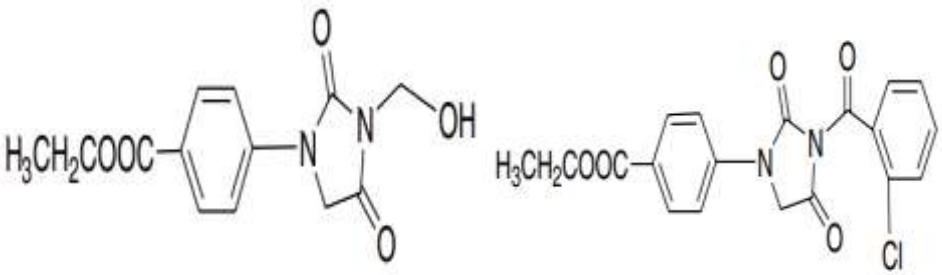


[42]Rupali et al. synthesized various compounds where the TZD ring was substituted with its bioisostere, the isoxazolidinedione ring, via an alkoxy linker and bezylidine hydrophobic trunk. Among these, 3b exhibited comparable activity to standard drugs rosiglitazone and pioglitazone in terms of both binding affinity and potency. Acute toxicity studies over 14 days showed no reported toxicity.



3b

[43]Maccari et al. highlighted 2,4-thiazolidinedione (2,4-TZD) derivatives as effective antidiabetic agents. Inspired by this, we developed a novel series of imidazolidinedione derivatives, substituting the thiazolidinedione ring. These derivatives effectively lower blood glucose levels short and long term, with notable antihypertensive activity observed in derivatives 3 (a, b, c)



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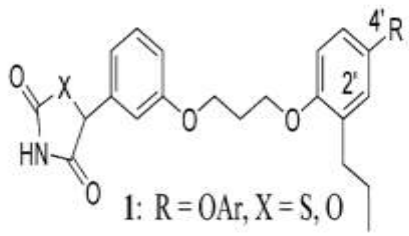
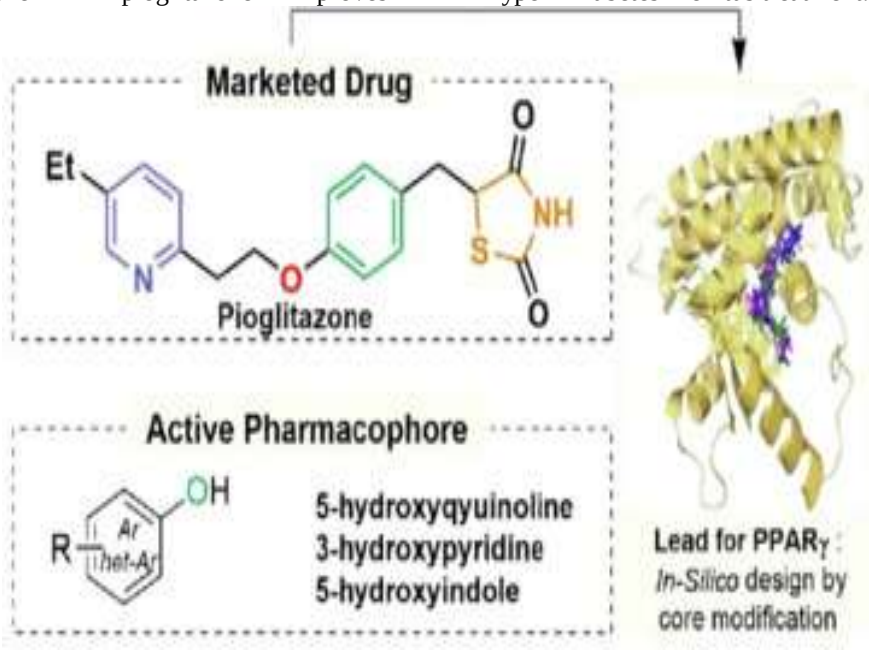


[44]Exploring a virtual molecular library reveals potential Type 2 Diabetes Mellitus treatments with compounds akin to thiazolidinediones (TZD), targeting PPAR-γ. Substituting the phenolic group with 5-hydroxyquinolone in pioglitazone improves affinity. Wang's discovery of chiral tetrahydrofuran-2-carboxylic acid inspires potent PPARγ ligands with promising in-silico binding affinity. Synthesizable via peroxide-free ipso-hydroxylation, these ligands hold promise for safer Type 2 Diabetes Mellitus treatment.



[45]Kyorin Pharmaceutical Co. introduced KRP-297, functioning as a dual PPARa and PPARg agonist, offering potential benefits in managing hyperglycemia and hypertriglyceridemia. Compound 1 spurred the exploration of aryl TZD analogues and oxazolidine-2,4-diones (OZDs). Structure-activity relationship studies identified compounds like 11 and 12, demonstrating significant efficacy in glucose and triglyceride reduction in rodent models. Additionally, research explored OZDs as TZD replacements, with compound 12 exhibiting notable dual PPARa/g agonist efficacy in vitro and in vivo.

[46]The study developed sixteen TZDs and RDs by modifying pioglitazone with pyrimidine. TZDs (7a, 7b, 7c, 29) reduced basal insulin while increasing glucose-stimulated secretion; RDs (33a–f) increased basal insulin. Glucose uptake improved, and molecular docking showed strong interactions with PPAR-γ, indicating potential as antidiabetic agents.

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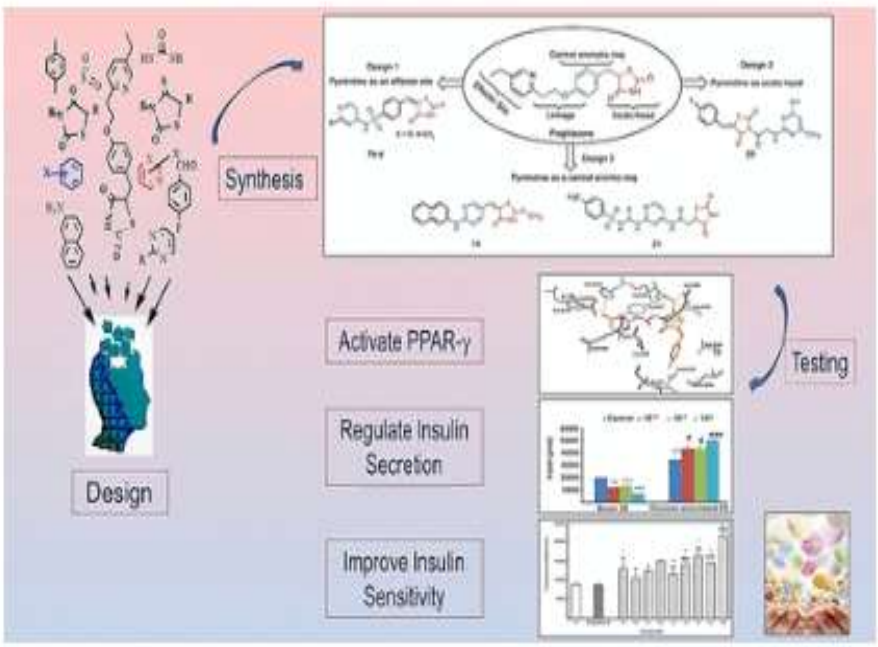

[47]Hardik et al. synthesized derivatives of hydroxycinnamic acid and ferulic acid with bioisosteric replacement of TZD. These synthesized derivatives were observed to interact with ArmIII and form hydrogen bonds with amino acid Ser342, along with hydrophobic interactions with Arm II, including Ile249, Ile281, Arg288, Leu330, Glu343, and Leu353. Cell viability assays conducted on non-transformed hepatocytes revealed that none of the compounds individually contributed to hepatotoxicity. Among the synthesized compounds, 3c, 4c, 3m, and 4m exhibited potent activity against K562 cell lines, with IG50 values below 50μM.

IV. CONCLUSION:

Glitazones are renowned for their efficacy in managing diabetes and other therapeutic benefits. However, the precise reasons behind the toxicity of TZD-induced drugs remain elusive. Numerous trials have been conducted on the standard glitazones, including troglitazone, rosiglitazone, and pioglitazone. Given the versatile nature of their scaffold, extensive efforts have been dedicated to mitigating their toxicity. While the association of these drugs with serious adverse effects and class-specific side effects is acknowledged, the mechanism underlying toxicity remains uncertain. Two assumptions have been proposed: toxicity may arise from the full agonism of the drugs or from factors related to the TZD ring or the formation of reactive metabolites.

Addressing these potential causes of toxicity, two approaches have been reported. Developing partial agonists with intact TZD rings has demonstrated reduced serious side effects and maintained good antihyperglycemic activity, as per reports. Additionally, substituting the TZD ring with various bioisosteres shows promise in controlling toxicity issues, although relatively fewer studies have explored this avenue. Alterations in the binding pattern to the PPARγ receptor while retaining the TZD ring may offer a promising alternative to mitigate side effects and toxicity.

Rivoglitazone, another glitazone derivative currently undergoing phase III clinical studies, has not been associated with adverse drug reactions such as cardiotoxicity or hepatotoxicity. However, the full risk associated with its use has not been thoroughly assessed, and thus, the drug is not yet in use (source: https://sci-hub.se/10.1345/aph.1R754). Hulin et al. synthesized a biotin conjugate known as Darglitazone, another selective PPARγ agonist found to be associated with TZD-induced bone marrow adipogenesis and bone loss on cancellous and endocortical surfaces, while also increasing periosteal bone formation in mice. This suggests the involvement of PPARγ in regulating bone resorption and demonstrates surface-specific effects

of PPARγ agonists on bone.Englitazone was discontinued due to poor efficacy and hepatotoxicity after phase II clinical trial

REFERENCES

[1]. Gale, E. A. (2006). Troglitazone: the lesson that nobody learned?. Diabetologia, 49(1), 1-6.

[2]. Niknahad, H., Heidari, R., Alzuhairi, A. M., & Najibi, A. (2014). Mitochondrial dysfunction as a mechanism for pioglitazone-induced injury toward HepG2 cell line. Pharmaceutical Sciences, 20(4), 169-174.

[3]. Berthelot-Garcias, E. (2008). Long-term risk of cardiovascular events with Rosiglitazone. mt cardio, 4(1), 40-43.

[4]. Shah, P., & Mudaliar, S. (2010). Pioglitazone: side effect and safety profile. Expert opinion on drug safety, 9(2), 347-354.

[5]. Home, P. D., Pocock, S. J., Beck-Nielsen, H., Curtis, P. S., Gomis, R., Hanefeld, M., ... & McMurray, J. J. (2009). Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. The Lancet, 373(9681), 2125-2135.

[6]. Monami, M., Dicembrini, I., & Mannucci, E. (2014). Thiazolidinediones and cancer: results of a meta-analysis of randomized clinical trials. Acta diabetologica, 51, 91-101.

[7]. Hu, D., Wu, C. Q., Li, Z. J., Liu, Y., Fan, X., Wang, Q. J., & Ding, R. G. (2015). Characterizing the mechanism of thiazolidinedione-induced hepatotoxicity: An in vitro model in mitochondria. Toxicology and applied pharmacology, 284(2), 134-141.

[8]. Kwon, M. J., Lee, Y. J., Jung, H. S., Shin, H. M., Kim, T. N., Lee, S. H., ... & Park, J. H. (2019). The direct effect of lobeglitazone, a new thiazolidinedione, on pancreatic beta cells: a comparison with other thiazolidinediones. Diabetes research and clinical practice, 151, 209-223.

[9]. Kim, M. K., Chae, Y. N., Choi, S. H., Moon, H. S., Son, M. H., Bae, M. H., ... & Shin, C. Y. (2011). PAM-1616, a selective peroxisome proliferator-activated receptor γ modulator with preserved anti-diabetic efficacy and reduced adverse effects. European journal of pharmacology, 650(2-3), 673-681.

[10]. Koffarnus, R. L., Wargo, K. A., & Phillippe, H. M. (2013). Rivoglitazone: a new thiazolidinedione for the treatment of type 2 diabetes mellitus. Annals of Pharmacotherapy, 47(6), 877-885.

[11]. Li, M., Pan, L. C., Simmons, H. A., Li, Y., Healy, D. R., Robinson, B. S., ... & Brown, T. A. (2006). Surface-specific effects of a PPARγ agonist, darglitazone, on bone in mice. Bone, 39(4), 796-806.

[12]. Li, M., Pan, L. C., Simmons, H. A., Li, Y., Healy, D. R., Robinson, B. S., ... & Brown, T. A. (2006). Surface-specific effects of a PPARγ agonist, darglitazone, on bone in mice. Bone, 39(4), 796-806.

[13]. Lazarenko, O. P., Rzonca, S. O., Hogue, W. R., Swain, F. L., Suva, L. J., & Lecka-Czernik, B. (2007). Rosiglitazone induces decreases in bone mass and strength that are reminiscent of aged bone. Endocrinology, 148(6), 2669-2680.

[14]. Murphy, C. E., & Rodgers, P. T. (2007). Effects of thiazolidinediones on bone loss and fracture. Annals of Pharmacotherapy, 41(12), 2014-2018.

[15]. Chaturvedi, R. N., Pendem, K., Patel, V. P., Sharma, M., & Malhotra, S. (2018, August 9). Design, synthesis, molecular docking, and in vitro antidiabetic activity of novel PPARγ agonist. Monatshefte Für Chemie - Chemical Monthly, 149(11), 2069–2084.

[16]. Hu, D., Wu, C. Q., Li, Z. J., Liu, Y., Fan, X., Wang, Q. J., & Ding, R. G. (2015). Characterizing the mechanism of thiazolidinedione-induced hepatotoxicity: An in vitro model in mitochondria. Toxicology and applied pharmacology, 284(2), 134-141.

[17]. Singh, S., Loke, Y. K., & Furberg, C. D. (2011, February 15). Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systematic review and meta-analysis. Thorax, 66(5), 383–388.

[18]. Divakaruni, A. S., Wiley, S. E., Rogers, G. W., Andreyev, A. Y., Petrosyan, S., Loviscach, M., Wall, E. A., Yadava, N., Heuck, A. P., Ferrick, D. A., Henry, R. R., McDonald, W. G., Colca, J. R., Simon, M.

I., Ciaraldi, T. P., & Murphy, A. N. (2013, March

[19]. Blagg, J. (2010, September 15). Structural Alerts for Toxicity. Burger's Medicinal Chemistry and Drug Discovery, 301–334.

[20]. Yen, C. J., Beamer, B. A., Negri, C., Silver, K., Brown, K. A., Yarnall, D. P., Burns, D. K., Roth, J., & Shuldiner, A. R. (1997, December). Molecular Scanning of the Human Peroxisome Proliferator Activated Receptor γ (hPPARγ) Gene in Diabetic Caucasians: Identification of a Pro12Ala PPARγ2 Missense Mutation. Biochemical and Biophysical Research Communications, 241(2), 270–274.

[21]. Zhang, F., Lavan, B. E., & Gregoire, F. M. (2007). Selective Modulators of PPAR-γActivity: Molecular Aspects Related to Obesity and Side-Effects. PPAR Research, 2007, 1–7.

[22]. Dunn, F. L., Higgins, L. S., Fredrickson, J., & DePaoli, A. M. (2011, May). Selective modulation of PPARγ activity can lower plasma glucose without typical thiazolidinedione side-effects in patients with Type 2 diabetes. Journal of Diabetes and Its Complications, 25(3), 151–158.

[23]. Agrawal, R., Jain, P., & N. Dikshit, S. (2012, February 1). Balaglitazone: A Second Generation Peroxisome Proliferator-Activated Receptor (PPAR) Gamma (γ) Agonist. Mini-Reviews in Medicinal Chemistry, 12(2), 87–97.

[24]. Amato, A. A., Rajagopalan, S., Lin, J. Z., Carvalho, B. M., Figueira, A. C., Lu, J., Ayers, S. D., Mottin, M., Silveira, R. L., Souza, P. C., Mourão, R. H., Saad, M. J., Togashi, M., Simeoni, L. A., Abdalla, D. S., Skaf, M. S., Polikparpov, I., Lima, M. C., Galdino, S. L., . . . Neves, F. A. (2012, August). GQ-16, a Novel Peroxisome Proliferator-activated Receptor γ (PPARγ) Ligand, Promotes Insulin Sensitization without Weight Gain. Journal of Biological Chemistry, 287(33), 28169–28179.

[25]. Kim, M. K., Chae, Y. N., Kim, H. S., Choi, S. H., Son, M. H., Kim, S. H., Kim, J. K., Moon, H. S., Park, S. K., Shin, Y. A., Kim, J. G., Lee, C. H., Lim, J. I., & Shin, C. Y. (2009, May). PAR-1622 is a selective peroxisome proliferator-activated receptor γ partial activator with preserved antidiabetic efficacy and broader safety profile for fluid retention. Archives of Pharmacal Research, 32(5), 721–727.

[26]. Li, Y., Wang, Z., Furukawa, N., Escaron, P., Weiszmann, J., Lee, G., Lindstrom, M., Liu, J., Liu, X., Xu, H., Plotnikova, O., Prasad, V., Walker, N., Learned, R. M., & Chen, J. L. (2008, April). T2384, a Novel Antidiabetic Agent with Unique Peroxisome Proliferator-activated Receptor γ Binding Properties. Journal of Biological Chemistry, 283(14), 9168–9176

[27]. van Marrewijk, L. M., Polyak, S. W., Hijnen, M., Kuruvilla, D., Chang, M. R., Shin, Y., Kamenecka, T. M., Griffin, P. R., & Bruning, J. B. (2015, December 3). SR2067 Reveals a Unique Kinetic and Structural Signature for PPARγ Partial Agonism. ACS Chemical Biology, 11(1), 273–283.

[28]. Bansal, G., Thanikachalam, P. V., Maurya, R. K., Chawla, P., & Ramamurthy, S. (2020, May). An overview on medicinal perspective of thiazolidine-2,4-dione: A remarkable scaffold in the treatment of type 2 diabetes. Journal of Advanced Research, 23, 163–205.

[29]. Norisada, N., Masuzaki, H., Fujimoto, M., Inoue, G., Hosoda, K., Hayashi, T., Watanabe, M., Muraoka, S., Yoneda, F., & Nakao, K. (2004, December). Antidiabetic and adipogenic properties in a newly synthesized thiazolidine derivative, FPFS-410. Metabolism, 53(12), 1532–1537.

[30]. Gregoire, F. M., Zhang, F., Clarke, H. J., Gustafson, T. A., Sears, D. D., Favelyukis, S., Lenhard, J., Rentzeperis, D., Clemens, L. E., Mu, Y., & Lavan, B. E. (2009, July 1). MBX-102/JNJ39659100, a Novel Peroxisome Proliferator-Activated Receptor-Ligand with Weak Transactivation Activity Retains Antidiabetic Properties in the Absence of Weight Gain and Edema. Molecular Endocrinology, 23(7), 975–988.

[31]. Xie, X., Zhou, X., Chen, W., Long, L., Li, W., Yang, X., Li, S., & Wang, L. (2015, January). L312, a novel PPARγ ligand with potent anti-diabetic activity by selective regulation. Biochimica Et Biophysica Acta (BBA) - General Subjects, 1850(1), 62–72

[32]. Wu, G., Yi, J., Liu, L., Wang, P., Zhang, Z., & Li, Z. (2013). Pseudoginsenoside F11, a Novel Partial PPARγAgonist, Promotes Adiponectin Oligomerization and Secretion in 3T3-L1 Adipocytes. PPAR Research, 2013,

[33]. Lazarenko, O. P., Rzonca, S. O., Suva, L. J., & Lecka-Czernik, B. (2006, January). Netoglitazone is a PPAR-gamma ligand with selective effects on bone and fat. Bone, 38(1), 74–84.

[34]. Kim, M. K., Chae, Y. N., Choi, S. H., Moon, H. S., Son, M. H., Bae, M. H., Choi, H. H., Hur, Y., Kim, E., Park, Y. H., Park, C. S., Kim, J. G., Lim, J. I., & Shin, C. Y. (2011, January). PAM-1616, a selective peroxisome proliferator-activated receptor γ modulator with preserved anti-diabetic efficacy and reduced adverse effects. European Journal of Pharmacology, 650(2–3), 673–681.

[35]. Nakles, R. E., Kallakury, B. V., & Furth, P. A. (2013, June). The PPARγ Agonist Efatutazone Increases the Spectrum of Well-Differentiated Mammary Cancer Subtypes Initiated by Loss of Full-Length BRCA1 in Association with TP53 Haploinsufficiency. The American Journal of Pathology, 182(6), 1976–1985

[36]. Schupp, M., Clemenz, M., Gineste, R., Witt, H., Janke, J., Helleboid, S., Hennuyer, N., Ruiz, P., Unger, T., Staels, B., & Kintscher, U. (2005, December 1). Molecular Characterization of New Selective Peroxisome Proliferator–Activated Receptor γ Modulators With Angiotensin Receptor Blocking Activity. Diabetes, 54(12), 3442–3452.

[37]. Sengupta, P., Das, A., Ibrahim, F., Mandal, U. K., Chatterjee, B., Mahmood, S., Das, S. K., & Kifayatullah, M. (2016, November). Safety profiling of pioglitazone and telmisartan combination by sub-chronic toxicity study in rat. Regulatory Toxicology and Pharmacology, 81, 155–161.

[38]. Ohashi, M., Oyama, T., Putranto, E. W., Waku, T., Nobusada, H., Kataoka, K., Matsuno, K., Yashiro, M., Morikawa, K., Huh, N. H., & Miyachi, H. (2013, April). Design and synthesis of a series of α-benzyl phenylpropanoic acid-type peroxisome proliferator-activated receptor (PPAR) gamma partial agonists with improved aqueous solubility. Bioorganic & Medicinal Chemistry, 21(8), 2319–2332.

[39]. Saha, S., Chan, D. S. Z., Lee, C. Y., Wong, W., New, L. S., Chui, W. K., Yap, C. W., Chan, E. C. Y., & Ho, H. K. (2012, December). Pyrrolidinediones reduce the toxicity of thiazolidinediones and modify their anti-diabetic and anti-cancer properties. European Journal of Pharmacology, 697(1–3), 13–23.

[40]. Kumar, R., Mittal, A., & Ramachandran, U. (2007, August). Design and synthesis of 6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid derivatives as PPARγ activators. Bioorganic & Medicinal Chemistry Letters, 17(16), 4613–4618.

[41]. Sharon, A., Pratap, R., Tiwari, P., Srivastava, A., Maulik, P., & Ram, V. J. (2005, April). Synthesis and in vivo antihyperglycemic activity of 5-(1H-pyrazol-3-yl)methyl-1H-tetrazoles. Bioorganic & Medicinal Chemistry Letters, 15(8), 2115–2117

[42]. Jadhav, R., Gupta-Rajoria, R., Pal, T., & Chelakara Subramanian, R. (2012, November 1). Design, Synthesis and In-vivo Hypoglycemic Evaluation of Novel Non - TZD'S in a Type - 2 Diabetic Model. Medicinal Chemistry, 9(1), 104–111.

[43]. Wang, R., Li, W., Liu, M., & Xu, W. (2009, February). Synthesis and Biological Activity Evaluation of Novel Imidazolidinedione Derivatives, as Potent Antidiabetic Agent. Journal of the Chinese Chemical Society, 56(1), 34–39.

[44]. Reetu, R., Garg, A., Roy, K. K., Roy, A., Gupta, S., & Malakar, C. C. (2022, January 1). In-silico studies for targeting PPARγ for the Type II Diabetes Mellitus.

[45]. Desai, R. C., Gratale, D. F., Han, W., Koyama, H., Metzger, E., Lombardo, V. K., MacNaul, K. L., Doebber, T. W., Berger, J. P., Leung, K., Franklin, R., Moller, D. E., Heck, J. V., & Sahoo, S. P. (2003, October). Aryloxazolidinediones: identification of potent orally active PPAR dual α/γ agonists. Bioorganic & Medicinal Chemistry Letters, 13(20), 3541–3544.

[46]. Al Neyadi, S. S., Adem, A., Amir, N., Ghattas, M. A., Abdou, I. M., & Salem, A. A. (2024, January 25). Novel

Thiazolidinedione and Rhodanine Derivatives Regulate Glucose Metabolism, Improve Insulin Sensitivity, and Activate the Peroxisome Proliferator-Activated γ Receptor. ACS Omega, 9(5), 5463–5484.

[47]. Joshi, H., Marulkar, K., Gota, V., & S Ramaa, C. (2017). Hydroxy Cinnamic Acid Derivatives as Partial PPAR γ Agonists: In silico Studies, Synthesis and Biological Characterization Against Chronic Myeloid Leukemia Cell Line (K562). Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 17(4), 524-541.