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Peroxisome proliferator-activated receptors as superior targets to treat diabetic disease, design strategies - review article

Diyabetik hastalığı tedavi etmek için üstün hedefler olarak peroksizom proliferatör ile aktive edilmiş reseptörler, tasarım stratejileri - inceleme makalesi

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Abstract
Thiazolidinedione (TZD), a class of drugs that are mainly used to control type II diabetes mellitus (T2DM), acts fundamentally as a ligand of peroxisome proliferator-activated receptors (PPARs). Besides activating pathways responsible for glycemic control via enhancing insulin sensitivity and lipid homeostasis, activating PPARs leads to exciting other pathways related to bone formation, inflammation, and cell proliferation. Unfortunately, this diverse effect via activating several pathways may show in some studies adverse health outcomes as osteological, hepatic, cardiovascular, and carcinogenic effects. Thus, an argent demand is present to find and develop new active and potent antiglycemic drugs for the treatment of T2DM. To achieve this goal, the structure of TZD for research is considered as a leading structure domain. This review would guide future research in the design of novel TZD derivatives through highlighting the general modifications conducted to the structure component of TZD scaffold affecting their potency, binding efficacy, and selectivity for the control of type II diabetes mellitus.
Keywords: Peroxisome proliferator-activated receptors, Thiazolidinediones, structure activity relationship, drug design, antidiabetic activity
Öz
Esas olarak tip II diabetes mellitus'u (T2DM) kontrol etmek için kullanılan bir ilaç sınıfı olan tiazolidinedion (TZD), temelde peroksizom proliferatör ile aktive edilen reseptörlerin (PPAR'lar)

bir ligandı olarak hareket eder. İnsülin duyarlılığını ve lipid homeostazını arttırarak glisemik kontrolden sorumlu yolları aktive etmenin yanı sıra, PPAR'ları aktive etmek kemik oluşumu, enflamasyon ve hücre proliferasyonu ile ilgili heyecan verici başka yollara yol açar. Ne yazık ki, birkaç yolu aktive ederek bu farklı etki, bazı çalışmalarda osteolojik, hepatik, kardiyovasküler ve kanserojen etkiler olarak olumsuz sağlık sonuçları gösterebilir. Bu nedenle, T2DM tedavisi için yeni aktif ve güçlü antiglisemik ilaçların bulunması ve geliştirilmesi için tartışmalı bir talep mevcuttur. Bu amaca ulaşmak için, araştırma için TZD'nin yapısı lider bir yapı alanı olarak kabul edilir. Bu inceleme, tip II diabetes mellitus kontrolü için TZD iskelesinin yapı bileşeninde gerçekleştirilen genel modifikasyonları, bunların potensini, bağlanma etkinliğini ve seçiciliğini vurgulayarak yeni TZD türevlerinin tasarımında gelecekteki araştırmalara rehberlik edecektir.
Anahtar Kelimeler: Peroksizom proliferatör ile aktive edilen reseptörler, Tiazolidindionlar, yapı aktivite ilişkisi, ilaç tasarımı, antidiyabetik aktivite.

1. Introduction

The group of metabolic diseases presents as a result of a defect in insulin action, insulin secretion, or both that finally leads to chronic hyperglycemia is called Diabetes Mellitus (DM). This proves the importance of insulin as an anabolic hormone in controlling lipid, carbohydrates, and proteins' metabolic abnormalities. These metabolic abnormalities are basically due to the low level of insulin secretion that leads to inadequate response or/and resistance of target tissues to insulin. The insulin resistance occurs at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes of skeletal muscles, mainly targeted tissue, adipose tissue, and to a lesser extent, liver.[1,2] The duration and type of diabetes are directly related to the severity of symptoms.[3] To distinguish between the DM disease symptoms and various hypoglycemic cases recorded, it has been assorted into different types. In 1997, the DM disease had been classified by the American Diabetes Association (ADA) into four types: type 1, type 2, other types, and gestational diabetes mellitus (GDM).[1] Until now, this classification adopted by ADA still the most accepted one.

Type 1 diabetes mellitus (T1DM), which is due to the destruction of pancreatic β cells. It is also known as the autoimmune type 1 diabetes due to the presence of autoantibodies, considered as a hallmark of type 1, that works against pancreatic β cells, although, it's role in the disease pathogenesis is not clear. Those autoantibodies are formed against glutamic acid decarboxylases (GADs), insulin, islet cell, transporter protein (ZnT8A), and protein tyrosine phosphatase. Before the onset of the disease by months or years, these pancreatic autoantibodies could be present and thus detected in the serum of type 1 diabetic patients. The destruction of pancreatic β cells is mainly through the humoral (B cell) response and insulitis (T-cell mediated inflammatory response). This type shows general symptoms that often develop suddenly such as lack of energy, polyuria, polydipsia, extreme tiredness, blurred vision, enuresis, slow-healing wounds, and sudden weight loss. Regarding adolescents and children, diabetic ketoacidosis and severe dehydration are developed. Type 1 DM accounts 5% -10% of diabetes cases, in general, and 80% - 90% of diabetes in adolescents and children. It's important to notice that, 78900 new diabetic cases are recorded per year by the IDF.[4] Regarding the adults and adolescence above 14 years of age, the type 1 shows a high prevalence, for example in 2010, the total accounts of type 1 in the United States was estimated to be 3 million[5] and, in 2019 was accounted to be 1.93 per 1000.[6]

On the other hand, type 2 diabetes mellitus (T2DM), characterized by a high blood glucose level due to insulin resistance besides a relatively low level of insulin, shows a higher global prevalence based on a 2019 report published by International Diabetes Federation (IDF) compared to type 1. The report mentioned that the global prevalence of T2DM in adults (20-79

years old) was 8.3% (382 million people), mainly intensify within 40-59 ages. The men show a higher prevalence than the woman with 14 million more (184 million women versus 198 million men). Additionally, during pregnancy, 21 million women are diagnosed with the diabetic disease. These accounts, by 2035, are predicted to exceed a 10.1% global prevalence with 592 million cases.[6-9] The IDF Diabetes Atlas, 9th edition 2019, showed the current and expected prevalence of diabetes in adults (20-79 years) for different regions worldwide (Figure 1). As shown, the highest accounts in 2019 were reported to western pacific region with 163 million and that expected to be increased to 212 million by 2045. Additionally, high concerns are directed to Middle East besides of Africa and North Africa regions that are expected to report an increase in the total diabetic cases by over 100%. 80 % of the total cases were counted for the low- and middle-income countries "where the epidemic is gathering pace at alarming rates".[10]
For diabetic patients, for insulin deficiency or resistance, many manifestations have been recognized besides of hyperglycemia, these include essential hypertension, nephropathy, obesity, dyslipidemia, non-alcoholic fatty liver disease, accumulation of lipoprotein, premature adrenarche, ovarian hyper and organism, systemic inflammation, polydipsia, polyphagia besides the aforementioned symptoms for type 1 like weight loss and blurred vision. If the diabetic is not controlled, stupor and coma are recognized, and finally, lead to death due to ketoacidosis. The severe dehydration besides of ketoacidosis recognized in some pediatric type 2 diabetic patients who are not recognized as obese generally lead to misclassification to type 1 diabetes.[11-13]
Because 90 % of diabetic patients around the world are counts to T2DM so considered as the predominant form, a group of drugs are developed and used to control T2DM such as Glitazones (Thiazolidinediones), Sulfonylureas, Glinides, Dipeptidyl Peptidase (DPP IV) Inhibitors, Gliflozins and Biguanides. Unfortunately, all the used drugs present uncontrolled side effects like obesity and hypoglycemia.[14] One of the most important classes of drugs used to treat T2DM is the TZD class which acts as antiglycemic agents via binding avidly to the gamma type of a nuclear receptor called peroxisome proliferator-activated receptor gamma (PPAR-γ).

The TZD class of drugs is orally administrated hypoglycemic agents used to treat T2DM alone or in combination with other orally or injectable hypoglycemic agents. This class includes a group of drugs that, in the late 1990s which is the time of their introduction, were dispensed as a first and a second line for the treatment of T2DM like Pioglitazone and Rosiglitazone (Figure 2).[15] Besides of glycemic control, TZDs show better outcomes and physiological effects than the other approved second line agents like Sulfonylurea and, in some cases, other 1st line hypoglycemic agents like Metformin. As a result, presenting another beneficial effect of TZDs, besides controlling hyperglycemia via enhancing insulin sensitivity, like anti-inflammatory effects, its use as antiglycemic agents was praised.[16]
As the PPAR receptors exist in different subtypes that differ in structure, effect, and region of distribution, the TZDs class of drugs mainly activates the gamma subtypes that exclusively present in adipose and epithelial tissues including urothelium.[17] However, the gamma subtype also presents in pancreatic β-cells, liver, immune cells, and bone tissues besides of other subtypes (α and β subtypes). As a result of activation of PPAR-γ receptors, numerous genes responsible for control glucose and lipid metabolism as well as genes regulate thrombotic function, vascular function, and the inflammatory response are expressed in a different pattern, as up-regulating or down-regulating pattern, and finally leads to both vascular and metabolic effects. Besides, to promote the metabolism of free fatty acids (FFA), TZDs increase the synthesis of triglyceride and non-oxidative glucose disposal, enhance lipid metabolism (raise the level of buoyant and large

LDL particles and HDL level) and lower the blood pressure besides of improving other common abnormalities related to T2DM like rheological abnormalities and vascular reactivity.[18,19] Unfortunately, TZDs are accompanied by a set of side effects such as a) edema and weight gain which is considered the most common one mainly demonstrated for diabetic patients who follow TZDs monotherapy or dual therapy in combination with other oral hypoglycemic agents or with insulin.[18] b) Hepatotoxic effects including liver failure were reported for the Troglitazone drug (in January 1997, the FDA in the USA approved it as the first marketed drug of TZDs class) and sometimes led to demonstrate death cases. c) Cardiovascular adverse effects like congestive heart failure (CHF) were also reported by the Framingham Heart Study in diabetic patients administrated TZDs. Also, it is well proved that cardiovascular disease is a prevalent complication of T2DM, and administrating TZDs led to elevate the risk of CHF in women diabetic patients to 5-fold and in men diabetic patients to 2.5-fold, this presents more highlights on the black side of TZDs.[15] d) Osteological adverse effects: some records reported that diabetic patients of T2DM were recognized with an increase in bone mineral density (BMD) and bone weight (BW). Finally, TZDs were recorded with, e) Carcinogenic effects: it has demonstrated that the risk for cancer is accreting for T2DM patients. Many types of cancer have been associated with T2DM such as liver, gastric, endometrial, pancreatic, renal, ovarian, breast, colon, bladder cancers. Here, several studies proved the increased rate of cancer mortality rate.[20] Given the above, to diminish the financial burden of T2DM patients and enhance the living equality, many attempts have been conducted by the medicinal chemists to find new antidiabetic agents with better activity and fewer side effects via modifying the existing drugs or discovering new natural leads. To achieve this goal, based on the approved beneficial outcomes of PPARs agonists agents like TZDs on management glucose and lipid metabolism, there is an indispensable need to understand the nature of binding interaction between PPARs and their agonist agents, as well as the chemical structure of PPAR. Additionally, to design new ligands with better specificity and binding affinity for PPAR-γ or dual as PPAR-α/γ agonists, more advanced techniques could be used like the quantitative structure-activity relationship (QSAR) and pharmacophore modeling and docking to get more in-depth knowledge about the TZDs besides of other agonist agents, especially regarding stereochemistry, binding groups, and topology are necessary.

Owing to the meaning of these pharmacological and chemical standpoints, this review will summarize the PPAR-α, β, and γ functions and chemical structures. As well, the existing chemical structures of TZDs will be discussed with respect to their agonist effects on PPAR-γ or PPAR-α/γ besides outlining the adverse outcomes pointed out in the literature. Additionally, we are going to delineate the pivotal TZD structures to lead the future attempts to develop the next generation PPAR-γ or PPAR-α/γ agonists as new aglitter antidiabetic agents.

Most plant and animal cells that undergo various metabolic functions like cholesterol metabolism, H_2O_2-based respiration, and β-oxidation of fatty acids (FAs) generally contain subcellular organelles called peroxisome proliferator-activated receptors (PPARs) proteins, firstly recognized in 1990, belong to the nuclear hormone receptor superfamily that includes 48 members.[21] From the structure point of view, there is a similarity between the thyroid or steroid hormone receptors and PPARs. As well, the similarity is extended their responses to small lipophilic ligands. As PPARs exist is three subtypes, each one responsible for mediating the physiological action of huge diverse fatty acids and fatty acids-derived molecules.

1.1 PPARs isoforms

PPARs belong to the nuclear receptor superfamily which is considered a wide diverse superfamily that constitutes a lot of members such as transcription factors, such as PPARs, glucocorticoid receptors, vitamin D, estrogen, retinoic acid, thyroid in addition to several other protein factors associated with xenobiotic metabolism. As heterodimers, PPARs with retinoid X receptor (RXR) act on DNA response elements. The lipid-derived elements considered the innate activating ligands of PPARs. The three subtypes of PPARs (α, β, and γ) present a fundamental role in energy metabolism; however, the activity spectrum and specificity of these subtypes are different. Regarding PPAR-γ, exists mainly in vascular smooth muscle and endothelial cells and works predominantly in regulating energy storage. PPAR-α presents mainly in the liver but, in the bone, heart, and muscle tissues expressed to a lesser extent. The last subtype (PPAR-β) plays a major role in regulating energy expenditure and displays a ubiquitous expression in the whole body.[22]

1.2 Mechanism of action of PPARs

Various genes are transrexpressed and transactivated as a result of binding peroxisome proliferator response elements (PPREs), which exists at the promoter of a target gene that consists of direct repeats of AGGTCA, with a heterodimers complex composed of PPARs and RXR. In the case of no ligands present, the gene transcription is blocked as a result of the co-repressor complex role associated with theses heterodimers. Balakumar *et al*., 2007 mentioned some agonist ligands act on PPARs.[23] RXR, like PPAR, presents as three subtypes: RXR-α, β, and γ. The 9-cis retinoic acid acts as an endogenous agonist to all districted isoforms.[24] With respect to these isoforms within the RXR-PPAR complex, no appointed actions have yet been confirmed. Whilst, antidiabetic action could be obtained through activating the heterodimers complex with rexinoids (synthetic RXR agonist), this action is comparable to the PPAR agonists effect recognized in mouse models of T2DM. The heterodimerization of RXR with PPARs is facilitated by the LBD and the eventual RXR-PPAR complex, with the recruitment of co-factors, subsequently binds to PPRE as briefly shown in Figure 3. [25]

The binding of DNA with RXR/PPAR complex is blocked in the absence of agonists/ligands by a group of co-repressor structures such as G-protein pathway suppressor 2 (GPS2), histone deacetylases (HDAC), and nuclear receptor co-repressors, high-affinity complexes are formed between the inert heterodimers of RXR-PPAR and these co-repressors. In order to initiate the transcription process, various transcriptional co-activators/co-factors such as steroid receptor coactivator (SRC)-1, CREB binding protein (CBP), histone acetyltransferase p300, and PPAR coactivator (PGC-1) are recruited.[26]

1.3 PPAR structure

Figure 4 represents the structure of PPARs as one dimension shape. Many advanced techniques have been incorporated to study the PPARs structure extensively like solvent mapping techniques, molecular modeling, and X-ray crystallography with respect to main structural domains including ligand-binding domain (LBD), co-activator binding site (Co-FBD), and DNA binding domain/region (DBD). This finally led to provide insight into the binding mode. PPAR-γ is comprehensively studded in-depth, other than other subtypes, including interactions and structure. Additionally, it is examined in different cases such as presence or absence of the ligands, co-activator peptides in a DNA bound or unbound state, and as heterodimers with RXR-α or as homodimers. It was proved that the N-terminal (5'), involved in the phosphorylation of PPAR, contains the DNA binding domain (DBD) but the C-terminal (3') contains the ligand-binding domain (LBD) as demonstrated in the 3-D structure of PPARs.[27] The 5ˡ-AF-1 domain

associated with a region that is independent of A/B domain which is responsible for phosphorylation of PPAR.
In the promoter region of the target gene, the peroxisome proliferation response element (PPRE) binds to DNA. The co-FBD/D domain especially binds to co-factors. The binding of specific small molecules with LBD or E/F domain leads to sequential gene expression as a result of receptor activating. The E/F domain contains a ligand-dependent region called the AF-2 region which facilitates the gene transcription process.[28]

1.3.1 Structure of DNA binding domain of PPARs

The A/B domain of PPARs plays a substantial role in protein phosphorylation, works as a functional activator of the transcriptional process, or interacts directly with other regulatory proteins or receptor domains. Additionally, it is believed that this region does not possess a significative binding side due to the absence of conserved amino acid sequence or residues of high hydrophobic character as a consequence of its high mobility. PPAR-γ ligands were recorded with no action on the region of A/B. In the highly conserved and central DNA binding domain, two binding sites of zinc are recognized. As well, architectural elements are present with the ability for sequence-specific binding to DNA.[29,30] Beyond short carboxy terminals extensions (CTE), The DBD structure of nuclear receptors was not visualized. Examining the RTX/PPAR-γ complex in depth has demonstrated that, the polarity in PPAR-γ is mainly based on CTE. The structure of DBD showed a close vicinity to the LBD structure after investigating the structures of PPAR-γ in-depth.

1.3.2 Structure of ligand binding domain of PPARs

Various endogenous ligands like fatty acids including their metabolites considered agonist ligands to PPARs isoforms (α, β, and γ).[31] Examining the LBD structure of these three isoforms using the X-ray crystallographic technique showed similar structures. As shown in Figure 5-A**,** the LBD of PPARs structurally consists of thirteen α-helices, H1–H12, and H2' helices, besides small four-stranded β-sheets, S1–S4, folded into a single region/domain. The LBD with respect to the secondary structure shows a sandwich-like structure of three layers of antiparallel α-helices. The three long helices (H3, H7, and H10/H11) made up the two outer layers of the sandwich. The helices that made up the middle layer (H4, H5, H8, and H9) are absent from the bottom half of the domain while building the top half. Thus, for ligand binding function, this middle layer exists a large binding cavity (~1400A˚) that displays a Y shape with three arms. This distinct structure of binding site plays a major role in facilitating the interaction/binding with diverse structure ligands like presenting various conformations with different functional groups or ligands with single/branched chains.[32-34]
In and out Y shape cavity, ten meaningful binding sites (P1- P4. E1, E2, C1, C2, B, and F) have been reported and characterized using solvent mapping techniques on the RXR/PPAR-γ heterodimers as shown in Figure 5-B. Only the four binding sites (P1-P4) exist inside the Y-shape binding cavity of the LBD while, the other six binding sites present in the outside region. The binding sites E1 and E2 present in the entrance region unlike B and F binding sites, which present in the surface of the Y-shape binding region. Regarding C1 and C2 binding sites, they are present in the co-activator binding region.
With respect to P1 and P2 binding sites, they constitute a significant hydrophobic pocket that functions as an excellent binding target for all agonists that interact with H12. Examples that could interact with the residues in this binding region are the polar nucleus and carboxyl head group of TZDs and Ragaglitazar (a partial agonist ligand), respectively. Comparing to P1 and P2

binding sites that are located at arm-I, the P3 and P4 binding sites present at arm-II and made up a larger hydrophobic pocket. The E2 binding site, the main ligand entrance site, also exhibits a hydrophobic behavior that located at arm-III. The actions including interaction with co-activators and dimerization with RXR are related to the other binding sites located outside the Y-shape cavity.[34]

1.3.3 Structural variations between LBD of PPAR-α and γ

The PPAR-α isoform, as well as PPAR-γ isoform, constitute of 34 amino acid residues with respect to the Y-shaped binding region of LBD. A high percent of similarity, around eighty percent, regarding the size of the binding cavity and that amino acid constituent has been recognized in both isoforms. The ligand specificity of PPARs is as a result of the minor differences in the topology, arm-I presents two minor differences in amino acid residues. As the binding sites present in this arm interact mainly with the polar head groups of ligands, these differences in amino acid residues (even these changes are minor) lead to a significant influence on the ligand specificity. The amino acid residues His323 and Phe363 located at the arm-I of PPAR-γ are replaced by Tyr314 and Ile354 for PPAR-α, respectively. With respect to arm-II, the Gly284 amino acid residue of PPAR-γ is replaced by a bulky lipophilic Cys275 residue in PPAR-α. The ligand entrance site, located at arm-III, presents a remarkable difference represented by the replacement of Arg288 residue of PPAR-γ by Tr279 in PPAR-α.[27]

2. Structure-Activity Relationship (SAR) Studies on TZDs

The medicinal chemistry has an integral mission in relating the molecular structure to its pharmacological effect. To improve molecular pharmacodynamic and pharmacokinetic properties of a leading drug including decreasing adverse effects, improving potency and selectivity and enhancing bioavailability, assessing the mode and nature of binding as well as figuring out the pharmacophores becomes indispensable. For pharmacophore identification, trying to screen, recognize, and synthesize prototype analogues is a usual method to get reliable results. However, this approach is time-consuming and is considered as an old approach. Currently, a wide range of sophisticated advanced computer programs are employed extensively in the drug modification, design, and discovery application.

As a result, to develop new synthetic PPAR-γ agonists, the TZDs have been suggested to be stereotype molecules for developing. With respect to literature, as shown in Figure 6, a simplified topology of a typical synthetic TZD is identified. As shown, the topology structure exhibits a "U" shaped geometry. Head is a thiazolidinedione functional group which exhibits polar and acidic character. The Linker-1 (L1) should not exceed three carbon atoms in length whilst, linker-2 (L2) could be extended up to four carbon/hetero atoms. **Ar** symbol represents a central heteroaromatic/aromatic ring. The tail position should be represented by a bulky lipophilic group like heteroaromatic/aromatic rings.[35]

2.1 Significance of Thiazolidinedione structure and its binding interactions

The linker-1 is directly connected to the position 5 of a ring nucleus, thiazolidine-2,4-dione ring, in TZDs (Glitazones). With respect to a series of Glitazones hypoglycemic agents, Rosiglitazone **(1)** and Pioglitazone (**2**) (Figure 7) are taken as the lead molecules.[36] To control T2DM, an interesting area of research like structural modifications has been directed to these two antidiabetic agents to develop and design new drugs with better profiles. The PPAR-γ, in general, considered as a specific, agonist, and strong targets for TZD derivatives via two styles: the van

der Waals and hydrophobic interactions are employed to bind with lipophilic ligands and, H-bonds are employed to bind with polar acidic ligands.[36] Thus TZDs have a lipophilic acid behavior, of which the lipophilic binding sites in arm-II and arm-III interact with lipophilic tail residues of TZDs while the hydrophilic binding site (P1) exists in arm-I interacts with the acidic head group of TZDs. The aliphatic linkers have a significant role in achieving an efficient binding through acting as spacers, thus the functional groups of TZDs (lipophilic tail and head group) could be positioned properly with the corresponding binding sites of the receptor. Further hydrophobic interaction is obtained by the central phenyl ring. The binding interactions of LBD of PPAR-γ with Rosiglitazone antidiabetic drug are sorted out in Figure 8. As shown, Rosiglitazone forms a U-shaped conformation through interacting with helix-12.[37,38]
The residues associated with forming H-bond with the acidic head group of TZDs are the Tyr473 of helix-12, His449 of helix-11, and His323 of Helix-4. Additionally, through acting as both H-bond donors and acceptors, the oxygen and nitrogen atoms of the nucleus ring could form H-bond with Ser289 (located at helix-3). The β strand besides α-helix 3, 5, 6, and 7, located at arm-II and arm-III of LBD, mainly participate in interacting with the hydrophobic tail moiety of Rosiglitazone, which accounts for the potency and efficiency of binding profile. The helix-3 shows additional hydrophobic interaction with the central phenyl ring.[39]
The ligands binding and co-activators, not the only factors that control the transcriptional activity of PPAR-γ, the state of phosphorylation plays a major role as well. For example, many studies reported that the phosphorylation of Ser273 residue of PPAR-γ led to obesity development. In the case of the Rosiglitazone diabetic drug, this phosphorylation is suppressed.[40]
A lot of research attempts have been conducted to find new TZD derivatives with better therapeutic profiles via improving insulin sensitivity, anti-inflammatory, and anti-cancer effects, as well as decreasing their adverse effects.[41,42] The thiazolidine-2,4-dione ring (nucleus ring of TZDs) have never been subjected to modification, indicating the significance of this moiety. However, a range of heteroaryl, aryl, or lipophilic chain substituents could be linked to the nucleus ring to develop new antidiabetic agents with better pharmacodynamic and pharmacokinetic profiles.[43]

2.2 Modifications on linker-1 (L1)

The linker methylene carbon atom located between the central phenyl ring and the nucleus ring of TZDs is displayed in Rosiglitazone and Pioglitazone (Figure 7). Besides the beneficial effects of Rosiglitazone via enhancing insulin sensitivity, it displayed a protective effect on the myocardium. The previous studies demonstrated that to retain the antidiabetic activity of Glitazones, a maximum three carbon atom length of the straight alkyl chain is essential. Branching in the structure has been shown if the linker-1 exceeds the length of three carbon atoms. The unsaturated bulky alkyl linker in compound (3), Figure 7, provides additional hydrophobic interaction, which led to improving molecular binding efficiency.[44] Thus, the length and nature of the alkyl linker should be retained, so this space created presents an excellent fitting between functional groups of ligands and the binding cavities of the LBD. The polar residues located at the binding site corresponding to L1 do not exhibit any electrostatic interaction. Hence, the linkers are usually represented as aliphatic/hydrocarbon chains without an electronegative atom.

2.3 Modifications on central phenyl ring

The aromatic group center plays a major role in the overall ligand activity via introducing hydrophobic interactions with LBD of PPAR-γ, especially with helix 3. With respect to all classical series of Glitazones, except Englitazone (4) and Netoglitazone (5), shown in Figure 7,

the aromatic group center is represented by a phenyl ring. With respect to Englitazone ligand (acts as a strong agonist for PPAR-γ), the central aromatic ring is represented by benzdihydropyran whilst, naphthyl moiety is used to occupy the central position for Netoglitazone (agonist ligand for PPAR-α and γ). This dual-action of Netoglitazone may have a role in minimizing the ligand effect on body weight, so control obesity, as a result of creating partial adipogenesis.[45,46] Thus, it's considered a potential candidate for T2DM patients who are accompanied by high cardiovascular risk and obesity.[47] This expects that the binding mode of Glitazones is mainly influenced by modifying the central ring structure, so the ability to modify agonist properties including potency and selectivity, as well as minimizing adverse effects.

2.4 Modifications on linker-2 (L2)

L2 exists between the hydrophobic tail and the central aromatic ring. With respect to Rosiglitazone (1) as displayed in Figure 7**,** the L2 is represented by ethylene with two terminal heteroatoms, oxygen, and nitrogen that have a methyl branch. As shown, among all the Glitazones, it follows the SAR guide via displaying the maximum number of atoms (four carbon/hetero atoms length). Whilst, the L2 in Pioglitazone is represented by ethylene group connected to just one terminal oxygen atom. The "U" geometry of binding conformation displayed in Figure 8 for Rosiglitazone indicates the vital role of L2. This linker should provide sufficient flexibility to achieve this ideal "U" shape binding conformation. Thus, the binding efficacy would be mainly influenced by chain length besides the nature of heteroatoms that exists in the chain.

A group of conventional Glitazones with diverse linkers are shown in Figure 9. This change leads to get different ligands with different binding modes and outcomes. A very short L2 is introduced for Ciglitazone (6) that is considered a prototype for Glitazones. Compared to Rosiglitazone, Ciglitazone presents Oxymethylene linker (–O-CH_2–) and due to its high toxicity, it has been withdrawn from the market. Similar to Ciglitazone, L2 is also represented by Oxymethylene linker in Troglitazone (7) and Rivoglitazone (8). Their high adverse effects led to stop using them.[48]

Troglitazone structure was modified into various analogues and their activities were assessed against glucose and triglyceride plasma levels. With keeping the nature of L2 link (–O-CH_2–) in Troglitazone, the L1 and the central aromatic ring was modified to an unsaturated branched linker and to a naphthyl spacer, respectively. As a result, analogue 9 (Figure 9) was designed and synthesized. This analogue displayed a hypoglycemic effect via decreasing glucose level but the triglyceride level did not change.[49]

Modifying L2 and the hydrophobic tail to an amido-methylene group and trifluoromethyl phenyl ring, respectively, led to getting compound 10**,** called KRP-297. Unfortunately, this drug displayed a carcinogenic effect and was withdrawn from therapeutic use in spite of acting as a dual agonist ligand for PPAR-α/γ.[50] Extending L2 to constitute six-carbon/hetero-atoms chain led to producing compound 11. This compound revealed good antihyperglycemic, antihyperlipidemic, and anti-obesity properties. The oxime function group exists in the L2 linker, through boosting the hydrophobic interactions with the receptor, plays an important role in binding.[51] Attempts to insert unusual moieties like sulfonyl groups to L2 linker led to finding new antidiabetic agents related to Glitazones. A moderate antidiabetic agent (compound 12) was produced by introducing a benzothiazole group as a high lipophilic tail and a sulfonyl moiety to L2. This led to finding a series of Glitazone derivatives bearing sulfonyl L2 that could be administrated orally like compound 13. The sulfonyl moiety as the weakest acceptor is suggested to form short H-bonds with the polar residues at the entrance of LBD.[52]

2.5 Modifications on lipophilic tail

Regarding the ligand-receptor interaction, in general, extending the hydrophobic area that takes part in the reaction with the receptor moieties leads to enhance binding efficiency and hence, improves binding affinity.[53] However, the binding affinity here is highly influenced by the desolvation phenomenon presented by the lipophilic moieties of both ligand and receptor, during the binding process.[44,54] Thus, to decrease the desolvation effect and hence enhancing binding energy, the lipophilic binding cavities of the receptor should be matched properly with lipophilic binding groups of the ligand. Moreover, the hydration status of the receptor as an apo-form (unbound state) should be verified. These two hints are considered the key factors in docking the ligands with the receptors.[55,56] As a result of proving that filling 55% percent of the targeted protein volume represents the optimal binding state, the size of the lipophilic moieties is critical.[57] The binding sites P3 and P4 exist in the LBD of PPAR-γ exhibit large lipophilic cavities.

It's interesting to mention that the strong agonist antidiabetic agent Rosiglitazone (1) makes lipophilic interaction only with the P3 binding site. However, the lipophilic tail group is represented by a large size pyridine ring, the molecular structure considered small and this large ring is unable to reach the P4 binding site. In contrast, as shown in Figure 9, the lipophilic tail group regarding Balaglitazone (14) is represented by a bulky moiety of benzopyrimidinone that makes a contact with both binding sites P3 and P4. This action at both lipophilic sites has a good correlation with it's a partial agonist action on PPAR-γ. Representing the hydrophobic tail moiety with a fused heterocyclic or polynuclear aromatic rings would provide additional lipophilic interaction and extend the volume occupied at the binding cavity and hence, the mechanism of action, binding efficacy would be changed. Balaglitazone, developed by Dr. Reddy's labs, completed a phase III trial in Denmark, Finland and Sweden. However of exhibiting a superior action compared to Pioglitazone such as more potent, minor cardiac arrest, minor risk of fluid retention, and no adverse effects on bone, the clinical studies discontinued due to not demonstrating the competitive potential effect compared to similar products already marketed for type 2 diabetes.[58]

Thus, due to the beneficial therapeutic actions associated with the absence of usual adverse effects, the PPAR-γ partial agonists currently attract a lot of interest. Studies have reported that the binding interactions finally change the transcriptional outcomes as a result of inducing specific conformational variations. To enhance the therapeutic profiles of antidiabetic drugs like Pioglitazone and Rosiglitazone via diminishing their side effects but with retaining the antidiabetic and antihyperlipidemic action, the co-regulators are considered key factors that could be slightly modulated to fine-turn the final pharmacological action. Subjecting the present Glitazones drugs for structural modifications could be a reliable strategy to achieve that specific modulation of the transcriptional activity.[59,60]

Various ring structures diverse in hydrophobicity and size could be used to identify the topology structure of Glitazones. With respect to the nature of the lipophilic tail and the topology structure, the TZD analogues are classified into two main types: conventional and Non-conventional TZD. The conventional class fits into the topology of synthetic PPAR-γ and, based on the nature of the lipophilic tail, it further sub-classified into a) Pyridyl and Pyrimidyl analogues that present large size rings as hydrophobic tail groups. b) Naphthyl, Styryl, Diphenyloxy, and Pyridyl-Pyrrolidinyl analogues, the hydrophobic tails here are represented by bulky groups. And c) miscellaneous like Indolyl, Pthalazinyl, Quinazolinyl, Quinoxalinyl, and Benzpyryl (chroman) analogues. Regarding the non-conventional TZDs, that do not fit into the topology of synthetic PPAR-γ, is also sub-

classified into: TZDs without characteristic lipophilic tail and TZDs without characteristic linkers subclasses.

2.5.1 Conventional TZDs

2.5.1.1 Pyridyl and Pyrimidyl analogues

Figure 10 shows two pyridyl analogues (compound 15 and 16) and one pyrimidyl analogue (compound 17). At micromolar concentrations, the agonistic activity of the pyridyl TZD analogues was reported with enhanced potency. With respect to pyridyl TZDs, L1 and L2 are represented by simple methylene groups attached to a central phenyl ring. Despite the high structural similarity, compound 15 revealed a higher agonistic activity than compound 16. These results could be related to the stereochemistry of the pyridine ring, locating at a more favorable position in compound 15 leads to better fitting in the lipophilic cavity.[61,62]
On the other hand, compound 17, a pyrimidyl TZD analogue, displayed a superior clinical profile compared to the antidiabetic drugs; Pioglitazone and Rosiglitazone. It exhibited higher transcriptional and agonistic activity for PPAR-γ, lesser side effects, and better oral absorption.[63] It's suggested that bulky lipophilic tail for compound 17, pyrimidine ring-substituted alkyl groups plays a significant role in that superior effects. This bulky tail is expected to obey the 55% rule of the volume occupied, thus presenting a better affinity.

2.5.1.2 Naphthyl, Styryl, Diphenyloxy, and Pyridyl-Pyrrolidinyl analogues

These analogues are characterized by the presence of bulky hydrophobic tails, some examples are shown in Figure 10. Compound 18, a tetrahydronaphthalene analogue reported with a moderate hypoglycemic effect, consists of a bulky naphthyl lipophilic tail connected directly to a central phenyl ring, L1 is an unsaturated linker.[64] As a result of the absence of L2 and the short length of L1, the ability of this compound to interact properly with the binding sites P3 and P4 is very minimal. The compound 19, a Styryl analogue, exhibited a comparable PPAR-γ agonistic action associated with a better anti-diabetic effect.[65] A considerable effect on insulin sensitivity besides exhibiting a dual agonistic action on PPAR-α/γ was reported for compound 20, which contains a bulky diphenyloxy lipophilic tail and an extended L2 chain of five atoms.[66] The hydrophobic tail moiety and L1 linker in compound 21 is represented by a pyrrolidine ring directly attached to the pyridine ring and an unsaturated linker, respectively. This compound displayed a better antidiabetic and antihyperlipidemic effect compared to the Troglitazone drug.[67]

2.5.1.3 Miscellaneous

Figure 10 displays the structures of compounds 22 and 23 that represent indole and imidazopyridyl derivatives, respectively. Compound 22 exhibited an excellent profile with better insulin sensitivity if compared to the Rosiglitazone drug. Also, it exhibited a superior antihyperlipidemic effect compared to Troglitazone and Rosiglitazone drugs via improving the HDL cholesterol levels.[68] The imidazopyridyl derivative (23) also revealed promising outcomes as a hypoglycemic agent but with lesser adverse effects often associated with Rosiglitazone, like cardiovascular diseases.[69] Indole and imidazopyridyl rings have behaved as the best lipophilic moieties to represent the lipophilic tail fraction to minimize the side effects besides improving the agonist activity for PPAR-γ. This proposes that the lipophilic indole and imidazopyridyl residues have the ability to interact and fill the lipophilic binding cavities properly, thus the transcriptional activity is specially modulated that usually leads ultimately to reduce adverse effects.
Compounds 24, 25, and 26, as shown in Figure 10, represent the pthalazinyl, quinazolinyl, and quinoxalinyl analogues, respectively. The compound 26 displayed a higher PPAR-γ agonistic

effect compared to compound 24 (pthalazinyl derivative). Additionally, it's approved that the presence of activating groups like methyl at positions 6 and 7 on quinoxalinyl ring, compared to analogues containing deactivating groups like phenyl ring, behaved excellent hypoglycemic and antihyperlipidemic activity. Regarding quinoxalinyl analogues, a significant antihyperlipidemic effect has been reported with the analogues containing shorter L2 lengths.

To achieve an ideal PPAR-γ agonistic activity, the length of L2 should be represented by a maximum of three atoms. Due to the steric effect, as suggested, the pthalazinyl and quinazolinyl analogues revealed lesser PPAR-γ agonistic activity compared to quinoxalinyl analogues. This steric effect gives rise to improper contact within the lipophilic binding cavity.[70,71]

Assessing the hypoglycemic and antihyperlipidemic effects of molecule 27, a benzoxazolyl analogue, and molecule 28 proved some activities (Figure 10). Representing the L2, in both derivatives, with n-propyl substituent led to getting the extreme effect.[72,73] Regarding compound 29, a benzoxazinyl analogue, was reported with a dual PPAR-α/γ agonistic activity indicating that, in designing, the ring expansion strategy could be favorable to target both receptors, PPAR-α and γ (Figure 10).

Analyzing these three series analogues from the structural point of view demonstrated that, the molecules reported with an optimum agonistic activity hold short linkers like two to three atoms. This optimal activity turned to a full PPAR-γ agonist if these short linkers were extended to 4 atoms length. TZD Analogues with a bulky lipophilic tail like benzoxazine moiety connected to ideal L2 (three atoms) and L1 lengths would result in a potential dual agonistic activity besides lacking adverse effects.[74]

Compound 30, a benzpyryl derivative, exhibited a mild activity on elevated lipid and glucose levels. As shown in Figure 10, compound 18 lacks L2 and has a substituent on the nitrogen N-3 of the TZD ring.[75] Also Figure 10 shows the chemical structure of compound 31in which, the lipophilic tail is represented by a bulky dibenzpyryl ring whilst, L2 as an unsaturated chain of three atoms. This molecule exhibited an agonistic activity for all receptor isoforms, PPAR-α, -β, and –γ.[76]

2.5.2 Non-conventional TZDs

This class of TZDs represents, as mentioned before, the analogues which do not follow the classical topology of synthetic PPAR-γ. A series of non-conventional thiazolidinedione based amide analogues were designed and synthesized besides monitoring their blood glucose-lowering action and adverse effects. As shown in Figure 10, this group lacks L2, the lipophilic tail group is represented by a simple phenyl ring, and L1 moiety is an unsaturated link of one carbon atom. A moiety of pyrazole ring connected directly to an aromatic ring applied as the central phenyl ring in which, the nature of this aromatic ring is the only difference within these analogues.

Based on the recorded data in Table 1, when the aromatic ring is a phenyl ring (32a) or 4-fluorophenyl (32b), a moderate hypoglycemic effect is obtained. Replacing the fluorine with a chlorine atom led to get compound 32c that displayed the most promising results compared to other analogues (highest hypoglycemic effect). The results obtained by molecular docking of compound 32c against PPAR-γ, showed excellent H-bond interactions with ILE-281 and SER-342 amino acids, with LYS-367 via halogen interaction, and with ARG-288 via π-π interaction and these findings could explain that superior action of 32c. Also, this molecule elevated the gene expression of PPAR-γ by 2.1 fold accompanied by transactivation effects equals to 53.65%, which is comparable to Pioglitazone and Rosiglitazone with 62.21% and 86.4% transactivation respectively. Furthermore, the molecule did not display any noticeable hepatotoxic effect or significant change in body weight. Furthermore, compounds 32i and 32l, similar to 32a and 32b,

displayed moderate effects whilst, 32n and 32m showed significant blood glucose-lowering effects when compared to reference drugs.
Evaluating the hepatic protectivity of the most advantageous compounds 32c, 32e and 32m, showed an excellent hepatoprotective effect via returning ALP, ALT, and AST enzyme levels to normal ranges. Compound 32n displayed excellent hypoglycemic action but unfortunately, reported with mild liver. The other analogues did not display any favorable hypoglycemic effect.[15]
Additionally, Figure 10 displays two non-conventional analogues that contain neither specific bulky hydrophobic tails nor characteristic linkers. Compound 33 elicited moderate hypoglycemic effect whilst, antihyperglycemic activity was reported for compound 34.[35,77]

2.6 Hybrid TZD analogues

Base on the fact that: if two agents present independent pharmacological activity are linked covalently, a synergistic activity could be achieved. This is the concept of Pharmacophore merging or hybridization. Very diverse compounds could be subjected in this strategy including polypeptides, amino acids, small organic and inorganic molecules, natural ligands, and nucleic acids. Through the rational approach, using compound libraries or computational techniques in drug design, the molecules to be subjected are identified.[78] Figure 11 shows two examples of hybrid TZD analogues. As a result of hybridizing a classical TZDs structure contains L2, central phenyl ring, and L1 with a potent antioxidant α-lipoic acid to represent the hydrophobic tail (compound 35). This hybrid analogue behaved an outstanding pharmacological profile exemplified via presenting a potent PPAR-γ agonistic activity accompanied by an extreme reduction in triglyceride levels.[79] Compound 36 represents a novel hybrid analogue of TZD in which, a phenylalanine amino acid is substituted on the ring nitrogen of thiazolidinedione. The polar residues exist at the head of phenylalanine create additional hydrogen bond interactions, this participates mainly in enhancing its binding efficiency. This analogue was reported with a synergistic activity at nanomolar levels.[80]
The hybrid molecules, besides applying in T2DM, were also effective to control the skin inflammatory conditions, vascular restenosis, and obesity. Additionally, anti-inflammatory and anti-malignant activities have been reported for several other hybrid agents. Thus, for significant antidiabetic effects along with minimum cardiovascular complications, hybrid molecules are currently considered as a novel class of PPAR-γ agonists.[81]

3. Free Fatty Acid Receptor 1 (FFAR1) as emerging target for Thiazolidinediones

A lot of favorable research attempts have been recently focused on treating DM via regulating insulin secretion using free fatty acids. It's recently proved that the medium to long-chain fatty acids induces insulin release via stimulating FFAR1, also termed as G-protein coupled receptor 40 (GPR 40). This stimulation will ultimately improve glucose-dependent secretion of insulin from pancreatic β-cells via affecting the protein kinase-C pathway besides other several signaling pathways.[82] A short to medium carbon chain length presents ten carbon atoms minimum, contains a potential free carbonyl group and unsaturated or saturated carbon is considered the proposed pharmacophore to stimulate these targets.[83]
Lately, FFAR1 attracts attention because they have been proved to be stimulated positively by TZDs hypoglycemic agents, however, the mechanism of activation.[84] Hence targeting the FFAR1 to treat T2DM currently presents a vast scope for the development of TZDs as agonists/antagonists ligands. The compounds 37 and 38, shown in Figure 12, represent new TZD analogues that were reported with a dual FFAR1 and PPAR-γ agonistic activity at micromolar

levels. They led to boost both insulin sensitivity and release. As shown, these analogues follow the conventional topology of the synthetic agonists in which, the biphenyl and benzimidazole bulky groups used to represent the lipophilic tail of compounds 36 and 37, respectively.[85]
The activation of FFAR1 by the TZD analogue Rosiglitazone, as demonstrated by a study, led to improving PPAR-γ efficiency via regulating signals transductions.[86] Hence this regulating effect of these dual agonistic ligands is expected to play a vital role in glucose homeostasis. This new-found concept regarding the advantageous effects of dual agonistic agents has unveiled reliable novel strategies to dominate the T2DM disease.

4. Conclusion

Studying SAR of TZDs led to discover plentiful diverse derivatives which mean that, TZDs could tolerate the presence of diverse hydrophobic tails, central aromatic rings, and linkers that finally resulted in modifying their pharmacodynamic properties via enhancing selectivity and potency along with decreasing adverse effects. As well, some modifications led to improve their pharmacokinetic properties such as upgrading oral bioavailability. Often, TZDs present a bulky structure that is considered substantial to create proper contact with the large lipophilic and polar cavities of the LBD of the target. Based on the previous studies, the main headlines that could summarize the SAR of TZDs as promising ligands to treat T2DM are: the methylene group (one carbon atom) is suggested as the best choice to represent the L1 moiety to connect the TZD acidic ring with the central phenyl ring. Any advantageous effects had not been achieved in case of the insertion of a heteroatom in this linker. Regarding the central phenyl ring, it is commonly occupied by a simple phenyl ring. A dual agonistic effect could be obtained if the phenyl ring is expanded or replaced by a naphthyl ring. Insertion of electron-withdrawing groups (Cl, F, NO_2) to central aromatic moieties were more profound in regulating glucose level toward normal range and maximizing gene expression compared to moieties accommodate electron-withdrawing groups (CH_3, OH, OCH_3). Substituting the para position with electron releasing groups showed a more potent hypoglycemic effect than meta position. Increasing the number of electron releasing substituents led to better performance. With respect to L2, the carbon chain between central phenyl ring and the lipophilic tail should be at least of two atoms length. To output optimum agonistic activity, the L2 chain should be represented by a maximum four atoms chain that accommodates at least one heteroatom. As regards to the lipophilic tail group, the size plays a significant role in determining the efficacy of binding. In conclusion, TZDs with big lipophilic tail and short/lengthy connectors act as potent PPAR-γ agonists. Whilst, a dual PPAR-α/γ or PPAR-γ /FFAR1 agonistic activity could be achieved using a bulky hydrophobic tail and short linkers. These agonist ligands exhibit different binding modes.
Because of the structural requirements to achieve a dual PPAR-α/γ agonistic effects are still not completely identified, TZD analogues exhibiting that dual activity are still rare. Further in-depth studies regarding structure and action mechanisms of dual agonists of PPAR/FFAR1 or PPAR are required. This could be accomplished through applying advanced molecular modeling techniques.

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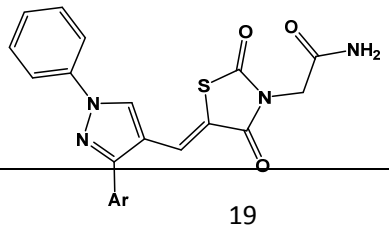
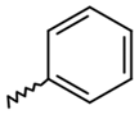
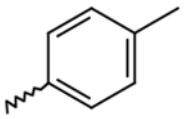
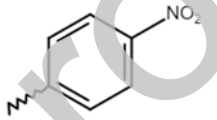
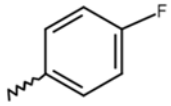
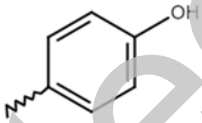
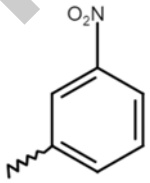
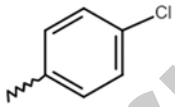
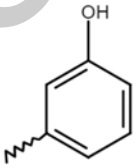
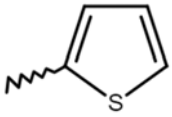
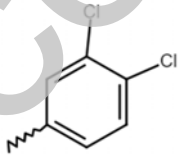
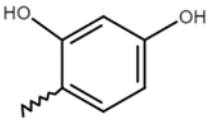
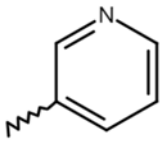
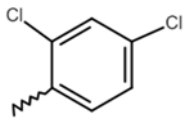
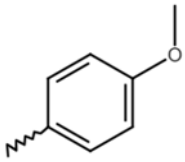
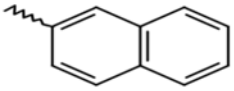
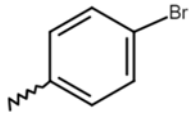
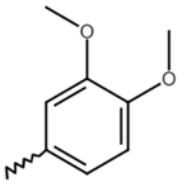
Table 1: Amide based thiazolidinedione analogues.[15]



32 a-q

Comp.	Ar	Comp.	Ar	Comp.	Ar
32a	Phenyl 	32g	4-methylphenyl 	32m	4-nitrophenyl 
32b	4-fluorophenyl 	32h	4-hydroxyphenyl 	32n	3-nitrophenyl 
32c	4-clorophenyl 	32i	3-hydroxyphenyl 	32o	Thiphene-2-yl 
32d	3,4-diclorophenyl 	32j	3,4-dihydroxyphenyl 	32p	Pyridine-3-yl 
	2,4-diclorophenyl		4-methoxyphenyl		2-naftyl

32e		32k		32q	
32f	4-bromophenyl 	32l	3,4-dimethoxyphenyl 		

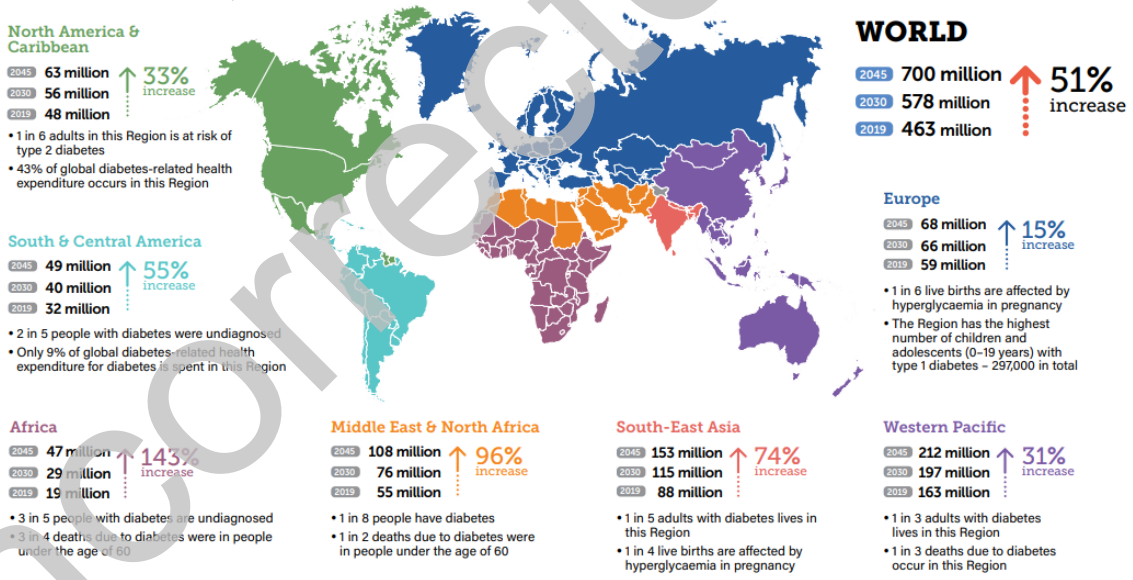


Figure 1: Prevalence of diabetes in adults (20-79 years) in various regions.[10]

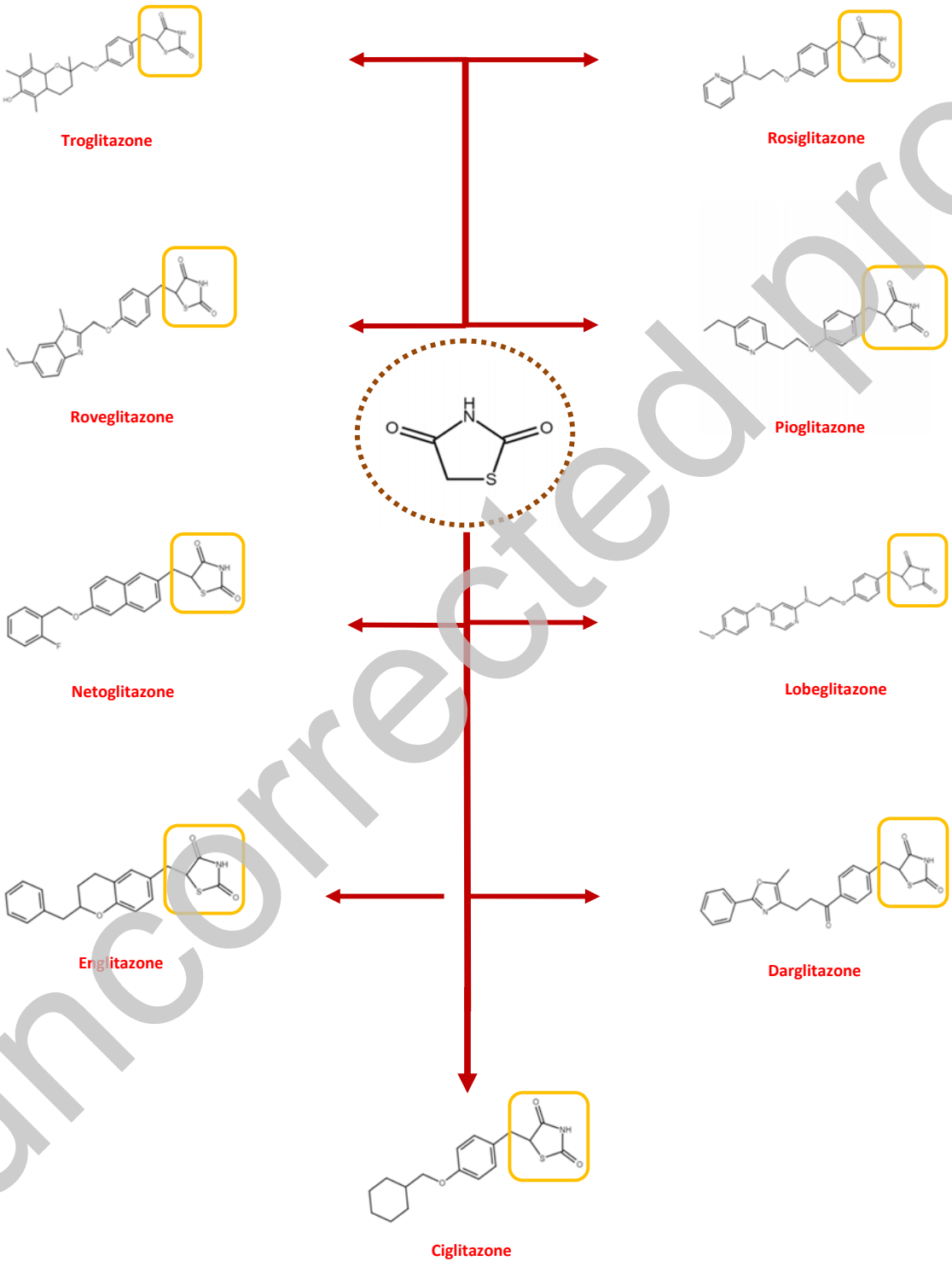


Figure 2: Current approved anti-diabetic drugs that follow thiazolidinediones class.[15]

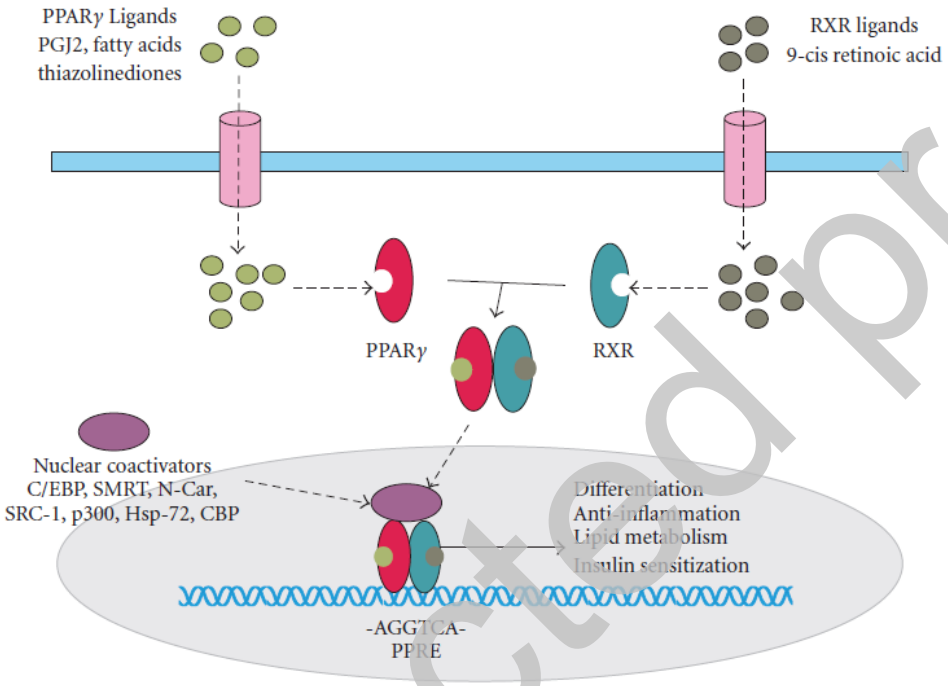


Figure 3: Current mode of action for PPAR-γ. PPAR-γ and RXR form a heterodimer, which is activated by the respective ligands. The activated PPAR-γ/RXR heterodimer will be translocated into nucleus and regulates downstream target genes in concert with nuclear receptor coactivators.[25]

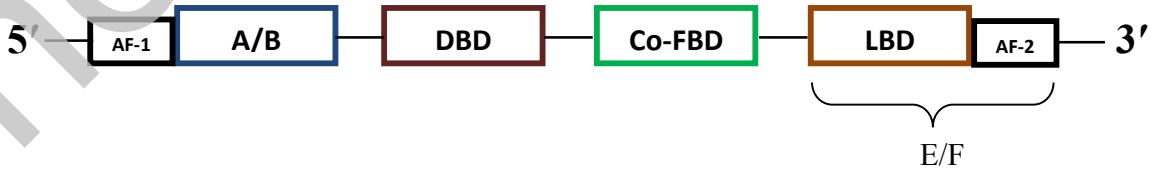


Figure 4: One-dimensional structure of the di□erent binding domains of PPARs.[28]

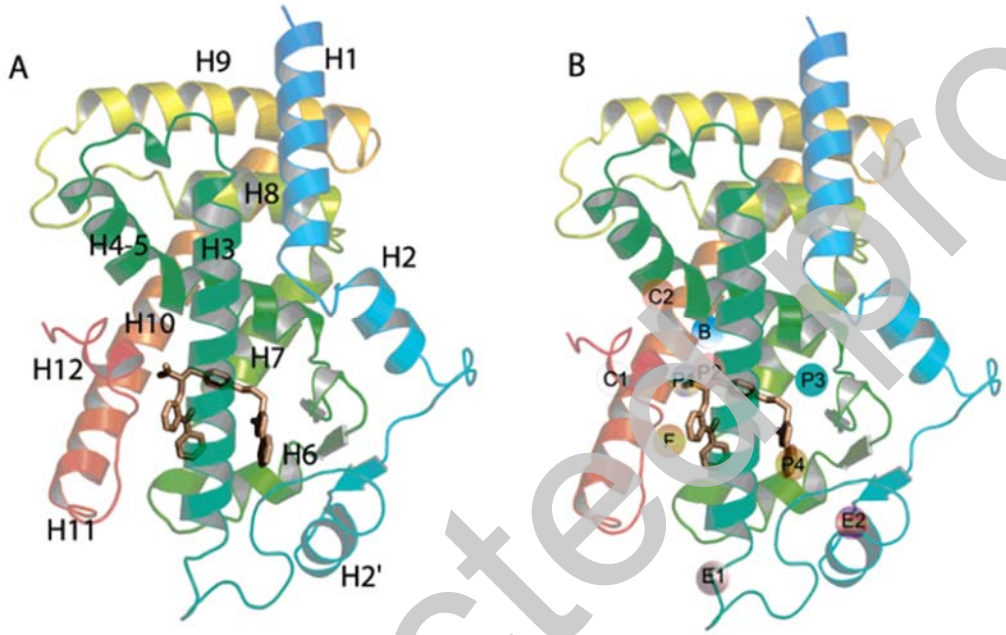


Figure 5: Structure of the PPARγ LBD. (A) Polypeptide backbone is shown as a cartoon, indicating the 12 R helices that comprise the domain.[34]

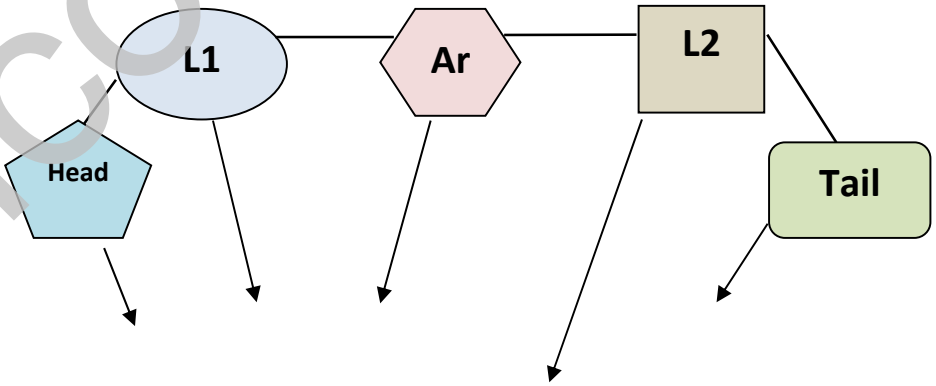
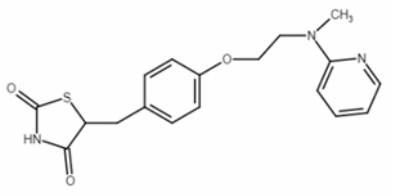
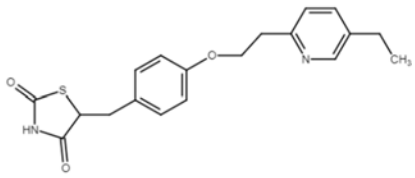


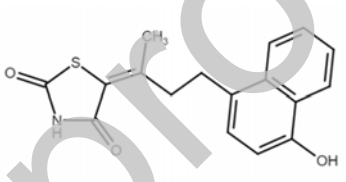
Figure 6: Simplified topology of a typical synthetic thiazolidinedione (Pioglitazone).[35]



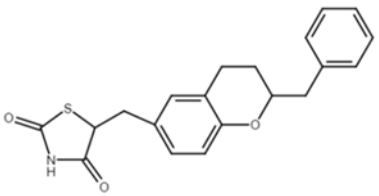
Compound 1



Compound 2



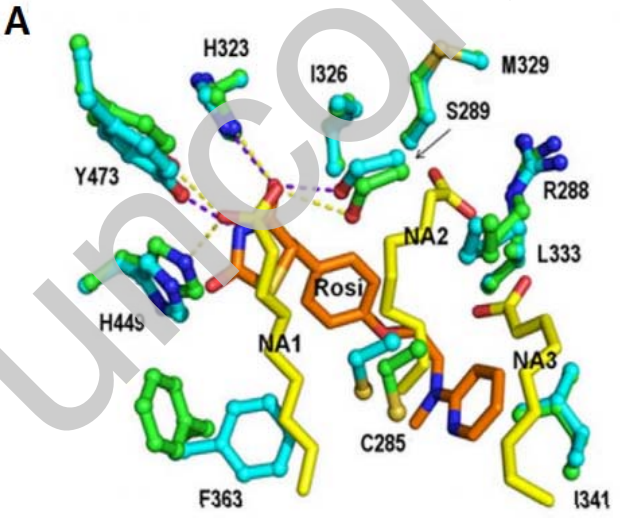
Compound 3



Compound 4

Compound 5

Figure 7: SAR of some TZDs.[36,44-46]



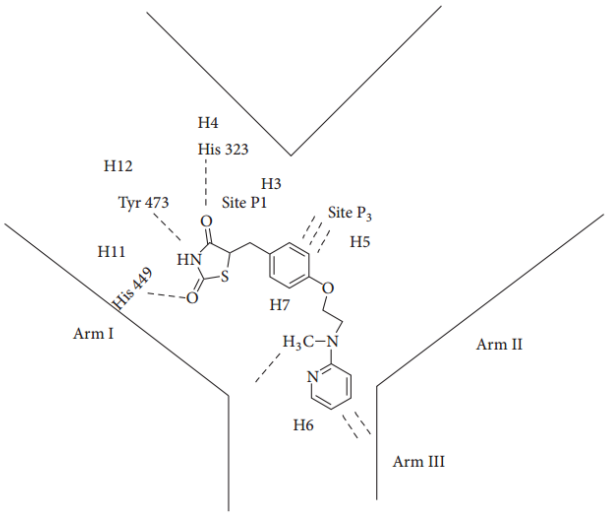


Figure 8: A) Rosiglitazone binding mode with PPARγ (PPARγ blue, ligand transparent pink) in the presence of NA (nonanoic acid) (PPARγ green, ligand yellow). B) Binding interactions of Rosiglitazone with PPAR-γ revealing the three binding arms within the ligand binding domain.[35,38]

Compound 6 Compound 7 Compound 8

Compound 9 Compound 10 Compound 11

Compound 12 Compound 13 Compound 14

Figure 9: Compound 6, 7 and 8 with short linker, L2. Compound 9 represents Troglitazone analogue. Compound 10, 11, 12 and 13 are TZDs with modifications on L2. Compound 14 is Balaglitazone.[48-52,58]

Compound 15 Compound 16 Compound 17