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Review

Type II diabetes mellitus and obesity: Common links, existing therapeutics and future developments

Subhadeep Banerjee[1]*, Indrani Talukdar[2], Arnab Banerjee[2], Arnav Gupta[2], Advait Balaji[2] and Raviprasad Aduri[2]*

[1]*Department of Chemistry, BITS Pilani, K K Birla Goa Campus, Zuarinagar 403 726, Goa, India*

[2]*Department of Biological Sciences, BITS Pilani, K K Birla Goa Campus, Zuarinagar 403 726, Goa, India*

**Corresponding authors (Emails, subhadeepb@goa.bits-pilani.ac.in; aduri@goa.bits-pilani.ac.in)*

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Type II diabetes mellitus (T2DM) and obesity are two common pathophysiological conditions of metabolic syndrome (MetS), a collection of similar metabolic dysfunctions due to sedentary lifestyle and overnutrition. Obesity arises from improper adipogenesis which otherwise has a crucial role in maintaining proper metabolic functions. Downstream events arising from obesity have been linked to T2DM. The nuclear receptor peroxisome proliferator activator gamma (PPAR-γ), responsible for maintaining lipid and glucose homeostasis, is down-regulated under obesity leading to a weakened insulin sensitivity of the human body. In course of our review we will outline details of the down-regulation mechanism, provide an overview of the current clinical therapeutics and their shortcomings. Toxicity studies on the seminal drug troglitazone, belonging to the most effective glitazone anti-diabetic category, is also discussed. This will lead to an overview about structural adaptations on the existing glitazones to alleviate their side effects and toxicity. Finally, we forward a concept of novel therapeutics mimicking the glitazone framework, based on some design concepts and preliminary *in silico* studies. These could be later developed into dual acting drugs towards alleviating the deleterious effects of obesity on normal glucose metabolism, and address obesity in itself.

Keywords. T2DM; obesity; PPAR-γ; TNF-α; SPPARγMs; glitazones

Abbreviations: GLUT, glucose transporter; NFκB, nuclear factor kappa B; JUNK, c-Jun N-terminal kinase; IKKβ, inhibitor of nuclear factor kappa-B kinase subunit beta; MAPK, mitogen activated protein kinase; FAS, fatty acid synthase; PEPCK, phosphoenolpyruvate carboxykinase; ACS, acetyl-CoA synthase; LPL, lipoprotein lipase; PKCθ, protein kinase C theta; ERK, extracellular signal-regulated kinase

1. Introduction

At present, one of the major health issues escalating into life-threatening condition is the metabolic syndrome (MetS), attributed to sedentary lifestyle and surplus energy intake. MetS is identified as a clustering of abdominal obesity, high blood pressure, high blood sugar, high serum triglycerides and low high-density lipoprotein (HDL) levels (Saklayen 2018). The occurrence of MetS is a global problem and is also rapidly increasing in developing countries like India and other South Asian countries, leading to increased mortality and morbidity (Pandit *et al.* 2012). MetS is often associated with cardiovascular disease, obesity and type II diabetes mellitus (T2DM). Incidentally, in the context of MetS, the Indian subcontinent has the largest number of diabetics globally, earning the dubious distinction of being the 'diabetes capital of the world' (Joshi and Parikh 2007). T2DM is the most prevalent form of the disease and is a chronic condition where despite high insulin levels there is also high blood glucose concentration. Obesity arising from improper adipogenesis itself constitutes a serious health concern and a major characteristic of MetS having a strong relationship with insulin resistance (Unnikrishnan *et al*. 2012). Traditionally adipose tissue was considered to be an energy storage organ. Now it is appreciated that it has a key role in the integration of systemic metabolism by secreting a large group of cytokines, known as adipokines, and plays an important role in glucose homeostasis (Kwon *et al.* 2013).

In this review, we will delineate the common links between the two main MetS conditions, T2DM and obesity, discuss their common molecular pathophysiology, current therapeutics, and possible novel interventions that specifically and simultaneously target these two conditions. We have divided the review into three major sections. In the first section, we discuss the

roles of the nuclear receptor PPAR-γ and its most crucial regulator TNF-α in maintaining glucose and lipid homeostasis and the correlation between their regulation under diabetic and obese conditions. In the next section, we focus on the insulin resistance in the context of molecular therapeutic approaches. Here we discuss the drugs either currently available in the market or undergoing active research for amelioration of T2DM and obesity related conditions. In the last section, we propose a novel class of small molecules based on certain general design principles and *in silico* modelling studies as the potential next generation anti-diabetic and anti-obesity therapeutics related to the regulation of PPAR-γ and TNF-α.

2. Discussion: molecular events in T2DM and obesity

2.1 *Role of free fatty acids (FFAs) and PPAR-γ*

Metabolic dysfunctions such as T2DM and obesity involve common molecules in their pathophysiology. Elevated levels of free fatty acids (FFAs) in the circulation play the most significant role in T2DM and obesity, as shown by *in vitro* and *in vivo* experiments (Boden 1997). Adipocytes in adipose tissue manage the levels of FFAs in the circulatory system by storing them as triacylglycerols (TAG). The nuclear receptor peroxisome proliferator activated receptor (PPAR-γ) plays a crucial role in this process both in adipose tissues and skeletal muscles (Nakamura *et al.* 2014). Being a transcription factor, PPAR-γ controls the levels of TAG by transcriptionally controlling various metabolic enzymes, viz. PEPCK, FAS, ACS, LPL, and other factors such as GLUT4 (Wu *et al.* 1998). Up regulation of GLUT4 mediates the entry of glucose, which is to be converted to glycerol phosphate to provide the backbone of TAG, into adipose tissues and skeletal muscle. Other direct targets of PPAR-γ, the TAG metabolism enzymes, for example PEPCK, FAS, ACS, perilipin, etc. help to synthesize or protect TAG from hydrolysis at various steps (Guilherme *et al.* 2008). Finally, lipo-protein lipase (LPL) is also regulated by PPAR-γ, which hydrolyses TAG in chylomicron remnants and VLDL (very low density lipoprotein) to produce FFAs in order to be taken up as FA-esters by the adipocytes (Gervois *et al.* 2000). Once inside, these FA-esters in combination with the glycerol phosphate backbone are converted into TAG once again. Therefore, we see that the main role played by PPAR-γ in glucose homeostasis is through moderation of cellular FFA levels. In the next section, we delineate the role of PPAR-γ in normal adipogenesis, which is also a key event for maintenance of cellular insulin sensitivity leading to normal glucose levels in circulation.

2.2 *Adipocytes and PPAR-γ*

PPAR-γ also plays a role in differentiation of pre-adipocytes into mature insulin-sensitive adipocytes, which produce normal adipokine profile (Leonardini *et al.* 2009). PPAR-γ as a transcription factor (TF) regulates expression of the CCAAT/enhancer binding proteins (C/EBPs), another TF which plays a role in differentiation (Rosen *et al.* 2002). PPAR-γ also recruits additional TFs to help the normal differentiation of the pre-adipocytes (Wu *et al.* 1999). It was shown that mice with adipose tissue–specific loss of PPAR-γ display decreased fat pad size and enhanced insulin resistance in adipose tissue and liver (He *et al*. 2003). Adipose tissue releases fatty acids on one hand and on the other it releases chemokines like adiponectin, visfatin, resistin, tumor necrosis factor (TNF-α) and interleukin 6, etc (Rosen and Spiegelman 2006). Most adipokines lead to metabolic dysfunction due to excess adipose tissue mass, causing increased pro-inflammatory adipokine levels like leptin, TNF-α, etc. Resistin, an adipokine, induced insulin resistance in mice, and mice lacking resistin had low blood glucose levels post fasting owing to low hepatic glucose production (Banerjee *et al.* 2004). Interestingly, another adipokine, which is anti-inflammatory in nature, adiponectin, showed an opposite trend where it protected against several metabolic dysfunctions and ameliorates insulin resistance and glucose tolerance (Maeda *et al.* 1996). The normal functioning of PPAR-γ for participation in glucose homeostasis and adipogenesis can only occur by ligand mediated activation of the receptor. Thus, we now need to summarize the type and nature of ligands that are essential for this purpose.

2.3 *Natural ligands for PPAR-γ*

Derivatives of long-chain polyunsaturated fatty acids are the known ligands of PPAR-γ. PPAR-γ can be activated by metabolites of arachidonic acid obtained from the cyclooxygenase and lipooxygenase pathways (Sun *et al.* 2015) and by fatty acid derived components released from oxidized low density lipoproteins (Nagy *et al.* 1998). Further, PPAR-γ activation has beneficial roles in adipogenesis by activating the expression of adiponectin, an insulin sensitizer in liver and muscle (Nawrocki *et al.* 2006). Also ligand bound PPAR-γ antagonizes the function of pro-inflammatory transcription factors such as TNF-α, nuclear factor-κB (NF-κB), thereby decreasing the expression of pro-inflammatory cytokines and diminishing the inflamed state in the adipose tissue (Pascual *et al.* 2005).

2.4 *Role of TNF-α in promoting T2DM*

TNF-α plays a major role in the development of T2DM, primarily in obese individuals. While role of other microenvironment such as high glucose accumulation, high free fatty acids in the circulation and impairment of insulin signal transduction also contribute to this disease, all these aspects could be linked primarily to the over secretion of the pro-

inflammatory cytokine TNF-α. The biologically active soluble form of TNF-α exerts its effects *via* type I (p55) and II (p75) TNF-α receptors (Pandey *et al.* 2003). The type II receptor is more associated to the TNF-α expression whereas the type I receptor is more present in the omental than subcutaneous adipocytes. The expression levels of both the receptors are altered in fat and muscle cells of diabetic and obese rats, while insulin-sensitizers and food restriction restore their expression (Hofmann *et al.* 1994). In obese conditions, excess calorie intake leads to metabolic overload which causes increased triglyceride (TG) input, and adipocyte enlargement. On further overloading with TG, hypertrophy of adipocytes occurs, followed by increased secretion of macrophage chemo-attractants (for example monocyte chemo-attractant protein-1, MCP-1) which recruits additional macrophages. Infiltrating macrophages in enlarged adipocytes in turn secrete large amounts of TNF-α resulting in a chronic inflammatory state with impaired TG deposition, enhancement of free fatty acids (FFAs) level and increased lipolysis (Kanda 2006). TNF-α is a regulator of several signaling cascades, causing activation of various Ser/Thr kinases (for example IKKβ, JNK, PKCθ, p38 MAPK, etc.,) (Hirosumi *et al.* 2002; Griffin *et al.* 1999; Um *et al.* 2004; Yuan *et al.* 2001). Activation of these kinases interferes with insulin signaling pathway causing impairment of GLUT receptors translocation to the membrane for glucose uptake. This results in inhibition of insulin sensitivity and increase in blood glucose level (Dresner *et al.* 1999).

2.5 *Role of TNF-α in obesity*

TNF-α not only increases the level of FFAs by down-regulating PPAR-γ by different mechanisms but also shows a direct effect on insulin resistance. Various reports have shown that increased levels of TNF-α directly up regulates the inhibitor kappa kinase (IKK-β) and various stress induced mitogen activated protein (MAP) kinases (JNK, p38) which in turn prevent insulin sensitivity, by phosphorylating serine residues of IRS proteins as mentioned earlier. Involvement of p38 MAPK, up regulated either by TNF-α or FFA, has been reported to regulate lipogenic gene expression (Talukdar *et al.* 2005). Activation of IKK-β and JNK also up regulate transcription factors NFκβ and AP1, which in turn regulate transcription of various regulatory genes involved in lipogenesis (Ruan *et al.* 2002). TNF-α also induces the level of hormone sensitive lipase, (HSL), via activating the generation of cAMP (by down-regulation of inhibitory G-protein-coupled receptor) in inflammatory adipocytes. HSL breaks down TAG to generate FFA (Arner 2005). On the other hand, TNF-α inhibits LPL (Hube and Hauner 1999), which prevents the entry of esterified FA into adipocytes for storage. TNF-α is shown to inhibit the production of GLUT 4 (Gustafson *et al.* 2009), directly attributing to insulin resistance. TNF-α also down-regulates the function and expression of perilipin (Zhang *et al.* 2002) and other lipid droplet involved in packaging of fat droplets and lipolysis. Down-regulation of these proteins (perilipin for example), removes the protective shield covering the lipid droplets exposing the later to various hydrolyzing enzymes (HSL for example) leading to generation of FFAs (figure 1).

2.6 *Common pathophysiology between TNF-α and PPAR-γ in regulating obesity and T2DM*

PPAR-γ maintains desired FFA levels in circulatory system in lean and healthy individuals. However, in obese individuals, PPAR-γ is counteracted by TNF-α. Elevated levels of TNF-α in adipose tissue leads to its dysfunction (Hotamisligil *et al.* 1995). TNF-α down-regulates PPAR-γ by various mechanisms (both at transcriptional and post-transcriptional levels) leading to increased levels of FFAs in the circulation (Ye 2008). The excess amount of FFAs once taken up by skeletal muscle causes insulin resistance and impaired glucose uptake. Though FFA-mediated insulin resistance could be achieved by different pathways, knockdown and inhibitor-studies have confirmed that the high fat mediated activation of various Ser/Thr kinases (for example, IKKβ, JNK, PKCθ, Erk, p38 MAPK, etc.) plays the most critical role (Kraegen *et al.* 2001; Hirosumi *et al.* 2002; Griffin *et al.* 1999; Kim *et al.* 2004; Um *et al.* 2004; Yuan *et al.* 2001; Aguirre *et al.* 2004). Activation of these kinases down-regulates the insulin signaling transduction pathway mainly by phosphorylating insulin receptor substrate (IRS) proteins at serine residues (Gao *et al.* 2002). Serine phosphorylation of IRS proteins has been shown to inhibit their activation caused by insulin, which results in the down-regulation of the phosphatidyl-insitol-3-kinase (PI3K)-Akt cascade (Yu *et al.* 2002). Thus, we see that the interplay of both PPAR-γ and TNFα results in down-regulation of the former in promoting T2DM particularly in obese individuals and this crosstalk is a common feature that could be targeted by the next generation therapeutic drugs aimed at alleviating obesity induced T2DM (figure 1). However, before focusing on development of newer drugs with well-defined operational window, it would be appropriate to outline briefly the existing therapies available for T2DM.

3. Current molecular therapeutics for T2DM

There are several methodologies in clinical practice to alleviate T2DM. Among the different categories of drugs in use against T2DM, metformin (table 1) belonging to the category of biguanides is the first line medication. This molecule works by reducing liver glucose production, promoting glucose uptake by skeletal muscles and also enhancing insulin sensitivity of cells. Even though it is the most widely used oral medication, this drug suffers from prominent side effects such as gastrointestinal irritation, diarrhea, cramps,

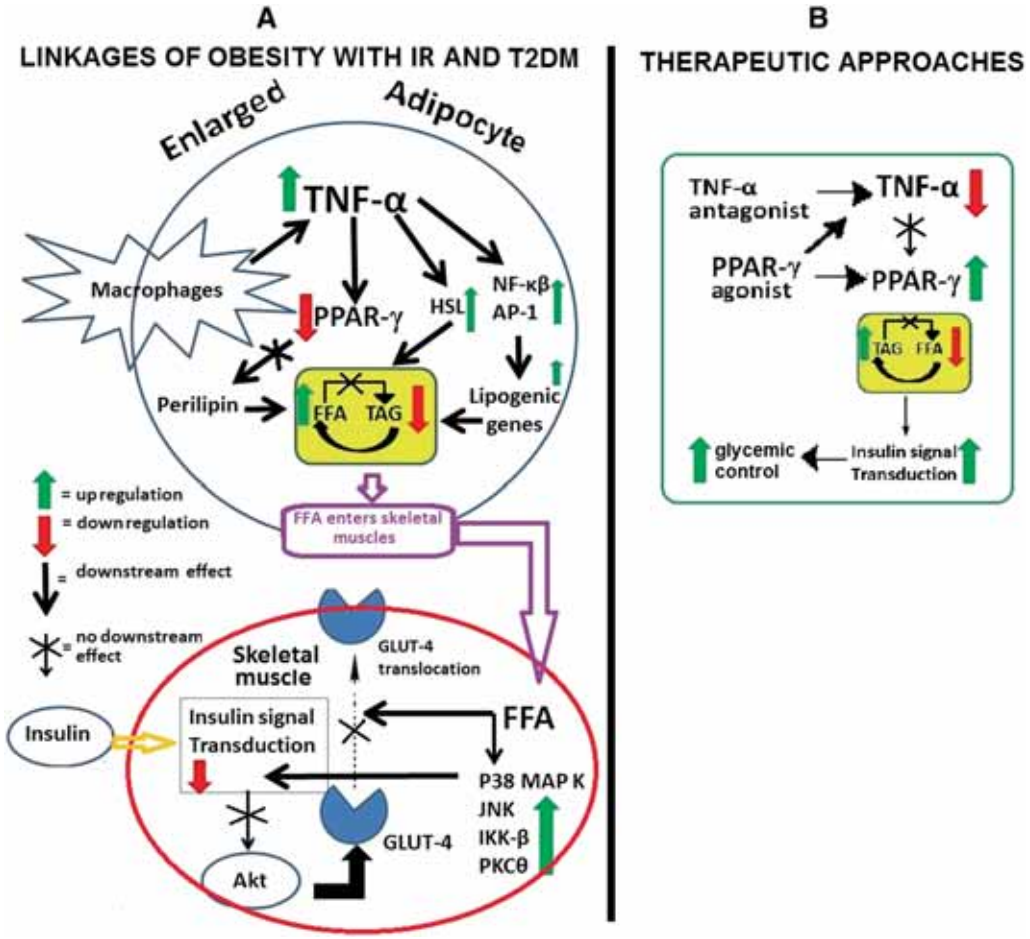


Figure 1. Schematic diagram of regulation of PPAR-γ by TNF-α leading to insulin resistance (IR) under obese condition (**A**) and different therapeutic interventions (**B**).

nausea, vomiting, and increased flatulence (Maruthur *et al.* 2016). However, the most serious adverse effect of metformin use is lactic acidosis and hence it is contraindicated in people (about 9 in 100,000) with any possibility for occurrence of the same (Bolen *et al.* 2007). Glimepiride (table 1) belongs to the sulfonylurea category and is also an important anti-diabetic drug classified as an insulin secretagogue, which enhances the release of insulin by pancreatic beta cells and by increasing the activity of intracellular insulin receptors. This promotes the uptake of blood glucose by cells, thereby reducing blood sugar levels. The main side effects in case of glimepiride are gastrointestinal tract problems, occasional allergic reactions, and chance of hypoglycemia when the drug is first introduced (Davis 2004). Voglibose (table 1) represents an example of the alpha-glucosidase inhibitor class of drugs which reduces the amount of available blood glucose by preventing the digestion of complex carbohydrates after a meal. Since this is a competitive inhibitor, it must be taken at the start of a meal for best action. However, the side effects arise from presence of undigested carbohydrates in the intestines and subsequent bacterial digestion in the colon could result in flatulence and diarrhea. In case of accidental hypoglycemia, the patient would require direct feeding of glucose and not higher carbohydrates sugar, since the enzyme involved in the hydrolysis of complex carbohydrates into glucose is inhibited by the drug (Dabhi *et al.* 2013). Sitagliptin (table 1) represents an example of a drug belonging to the category of dipeptidyl peptidase-4 inhibitor. The incretins (GLP-1 and GIP) are metabolic hormones which stimulate the release of insulin from pancreatic beta cells in response to a meal. Dipeptidyl peptidase-4 enzyme acts as inhibitor for the incretins and lowers the plasma insulin levels. Hence sitagliptin, by acting as inhibitors of this very enzyme, restores incretin activity and thus helps to raise insulin levels after a meal. The main side effects include headache, nausea, hypersensitivity, skin reactions, and small risk of heart failure (Herman *et al.* 2006). This drug when used in combination therapy with sulfonylureas may increase the risk of hypoglycemic attacks (Olansky 2010a, b; FDA. 2015-08-28). Another class of anti-diabetic drugs is the Gliflozin category. These molecules are inhibitors of the sodium glucose transport protein (SGLT), whose role is to ensure re-absorption of glucose from the kidneys during glomerular filtration and thereby

Table 1. List of current anti-diabetic medications including the ones in advanced stages of research

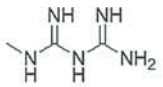
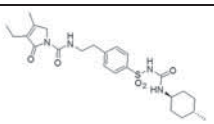
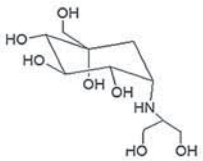
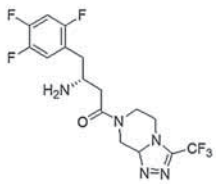
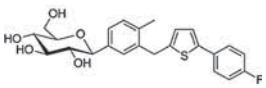
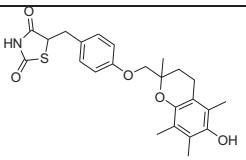
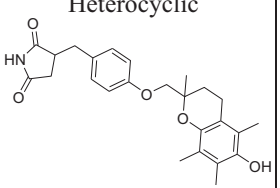
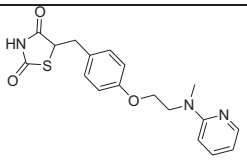
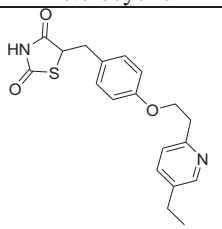
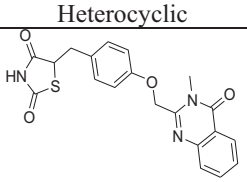
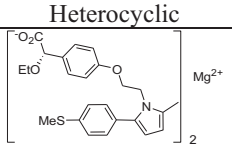
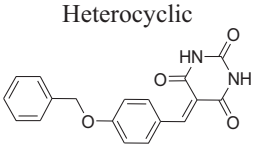
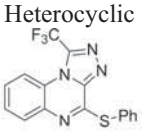
Sl #	Generic name	Brand Name(s)	Classification	Chemical structure and class	Benefits/side effects	Reference
1	Metformin	Glycomet, Glucophage	Insulin sensitizer	 biguanid	Benefits: increase in insulin sensitivity Side effects: gastrointestinal irritation, diarrhea, cramps, nausea, vomiting, flatulence, lactic acidosis	Maruthur *et al.* 2016
2	Glimepiride	Amaryl, Gemer	Insulin secretagogue	 sulfonyl urea	Benefits: enhanced tissue insulin levels Side effects: hypoglycemia	Davis 2004
3	Voglibose	Voglib	α-glucosidase inhibitor	 carbohydrate based	Benefits: prevents high blood sugar levels post meals Side effects: hypoglycemia	Dabhi *et al.* 2013
4	Sitagliptin	Januvia	DPP4 inhibitor	Hetero cyclic 	Benefits: prevents high blood sugar levels post meal Side effects: headache, nausea, hypersensitivity, skin reactions	Herman *et al.* 2006
5	Canagliflozin	Invokana, Sulisent	SGLT inhibitor	carbohydrateand hetrocylic based 	Benefits: prevents urinary loss of systemic glucose Side effects: ketoacidosis, urinary tract infections	Scheen 2014
6	Troglitazone	Resulin	PPAR-γ agonist	 Heterocyclic	Benefits: more tissue insulin sensitivity Side effects: hepatic toxicity	Gale EAM. 2006
7	Trosuccinimide	___	_____	Heterocyclic 	Benefits: no hepatic toxicity as in entry (6) Side effects: not studied	Saha *et al.* 2010

Table 1. continued

8	Rosiglitazone	Avandia	PPAR-γ agonist	 Heterocyclic	Benefits: more tissue insulin sensitivity Side effects: weight gain, edema	Chen *et al.* 2012 Tuccori *et al.* 2016
9	Pioglitazone	Actos	PPAR-γ agonist	 Heterocyclic	Benefits: more tissue insulin sensitivity Side effects: weight gain, edema	Chen *et al.* 2012 Tuccori *et al.* 2016
10	Balaglitazone	___	PPAR-γ partial agonist	 Heterocyclic	Benefits: more tissue insulin sensitivity Side effects: reduced edema and weight gain	Agrawal *et al.* 2012
11	Saroglitazar	___	PPAR-a/γ agonist	 Heterocyclic	Benefits: more tissue insulin sensitivity and better lipid level management Side effects: No adverse effects reported	Sosale, *et al.* 2015
12	Barbaturic acid derivative (BA)	____	PPAR-γ pan agonist	Heterocyclic 	Benefits: PPARgamma activators Side effects: No adverse effects reported	Dixit *et al.* 2016
13	Triazolo-quinoxaline 1	___	TNFα-R1 antagonist	Heterocyclic 	Benefits: anti-inflammatory Side effects: No adverse effects reported	Gururaja *et al.* 2007
16	Triazolo-quinoxaline 2	___	TNFα inhibitor	Heterocyclic 	Benefits: anti-inflammatory Side effects: No adverse effects reported	Guirado *et al.* 2012

prevent loss of plasma glucose through kidneys. However, in T2DM the gliflozins by acting as SGLT inhibitors, allow the loss of blood glucose through kidneys leading to optimum levels in circulation. The main side effects of these molecules are ketoacidosis, urinary tract infections, and chances of hypoglycemia (Scheen 2014).

Thiazolidinediones (TZDs) are agonists of PPAR-γ who restore its FFA lowering function and rescue insulin signal transduction cascade, in T2DM. They feature a sulfur-containing TZD ring which is mainly responsible for its bioactivity (table 1) through specific binding inside the PPAR-γ active site (Jain *et al.* 2013). The first approved

TZD for T2DM was troglitazone (table 1). The drug was approved by the Food and Drug Administration of the United States of America in January 1997. However, acute liver failures started being reported for its use including the death of a patient at an NIH controlled anti-diabetic health study in 1998. Troglitazone was withdrawn from the market in March 2000 (Gale 2006). Chan's group at NUS, Singapore, carried out synthesis and comparative toxicological studies in THLE-2 cell lines of a non-sulfur containing troglitazone analogue (table 1; trosuccinimide) bearing a pyrrolidine head group. They established that troglitazone was significantly more toxic than trosuccinimide (EC_{50} for troglitazone = 27.2 μM, EC_{50} for trosuccinimide = 138.5 μM; MTT assay). The sulfur atom in TZD created toxic reactive metabolites (RMs), as a result of reaction between itself and the hepatic glutathione thiol group. Similar RM formation was not observed for trosuccinimide. Hence, the sulfur containing TZD ring in proved to be susceptible to bio-conjugative toxic adducts formation (Saha *et al.* 2010). The two approved and available TZD drugs rosiglitazone and pioglitazone (table 1) have been under the scanner of government agencies globally, account of their potential hepatotoxicity attributed to the sulfur moiety and possibility of bladder cancer for pioglitazone (Chen *et al.* 2012; Tuccori *et al.* 2016). They are contraindicated for patients with cardiac ailments. One major side effect of all TZDs is weight gain accompanied by water retention, leading to edema in patients (Nesto *et al.* 2003). However it is noteworthy that with the exception of TZDs and metformin all other drugs work to enhance the blood insulin levels to induce lower blood glucose levels, or reduce the overall availability of blood glucose. Since at the heart of T2DM lies impaired insulin signaling pathway, the mode of action of TZDs presents a more targeted approach towards better disease management. The focus of the next generation drug discovery research is to retain the anti-diabetic action of TZDs while exhibiting reduced side-effects related to weight gain, obesity, and edema. If it could be possible to only ensure the insulin sensitizing functions of PPAR-γ while not promoting those co-factors which exhibit the related side effects that would be most desirable.

Recent research has proven that through selective agonism of PPAR-γ, the insulin sensitizing functions can be uncoupled from the co-factors inducing the weight gain and edema related side effects. A selective partial agonist of PPAR-γ, termed as selective peroxisome proliferator activated receptor gamma modulator (SPPARγM), is capable of binding inside the same active site of PPAR-γ as a full agonist (Zhang *et al.* 2007). However, the mode of binding of the partial agonist is very different. In case of rosiglitazone a full agonist, its sulfur containing head group forms an H-bond with tyrosine residue 473 of helix 12 inside the active site (figure 2, red ribbon) (Nolte *et al.* 1998). This tight binding interaction alters the protein structure in such a way to simultaneously recruit the insulin sensitizing factors as well as the side-effect inducing factors. However, the partial agonist stays away from the tyrosine 473 residue of helix 12 of the active site and mostly stays wrapped around helix 3 (figure 2). As a result, the structure of PPAR-γ is modified in a subtle way that only those transcription factors related to cellular insulin sensitization are activated (Kroker and Bruning 2015). SPPARγMs include the molecule balaglitazone (table 1) which is being developed by Dr. Reddy's as a SPPARγM for application in T2DM. Clinical studies were performed with 409 subjects of randomized, double blind, parallel-group placebo and active comparator-controlled subject categories to understand the usefulness and safety of balaglitazone. This trial met its primary objective of significantly reducing HbA1c and postprandial glucose as compared to the marketed drug pioglitazone (Agrawal *et al.* 2012). It showed better safety profile and fewer reports of severe adverse effects like heart failure, peripheral edema, and myocardial infarction. Balaglitazone shows less fluid retention, less heart enlargement and no reduction of bone formation as compared to PPAR-γ full agonists in preclinical studies. Also, a number of structures without the TZD headgroup could act as partial agonists. These include the PA082, INT131 (currently in pre-clinical trial stage) and SR2067 (figure 2) (Burgermeister *et al.* 2006; Taygerly *et al.* 2013; van Marrewijk *et al.* 2016). A look at the crystal structure of INT131 inside PPAR-γ and its comparison with rosiglitazone establishes the differences in binding patterns (figure 2). Unlike rosiglitazone, for INT131 its sulfonamide linker and *meta*-dichlorobenzene head group is away from helix 12. The entire molecule wraps around helix 3 with the terminal quinoline moiety occupying the same hydrophobic pocket between helix H6, H3, and H2a as that of the terminal pyridine ring in rosiglitazone. In INT131 and SR2067, a hydrophobic interaction between the terminal quinoline (for INT131) / napthalene (for SR2067) moiety and the alkyl side chain of isoleucine residue number 341 of the β-sheet was observed. This anchored the molecules away from tyrosine 473 of helix 12 and differentiates it from exhibiting a full agonist behavior. Also, the IC50 values of rosiglitazone and INT131 towards PPAR-γ binding obtained from a ligand displacement assay (0.20 uM versus 0.017 uM respectively), depict the easier displacement of bound INT131, which incidentally is only 40% efficient as compared to rosiglitazone in PPAR-γ transactivation assay (Taygerly *et al.* 2013).

In addition to partial agonism, dual agonism of different closely related PPAR receptor subtypes is also a new strategy being applied for better glycemic control in T2DM as well as achieving some additional benefits. T2DM patients are also afflicted by atherogenic lipid abnormalities which further worsens MetS. In contrast to the insulin sensitizing action of PPAR-γ, PPAR-α (another related receptor subtype of PPAR-γ found in abundance in hepatocytes) is crucial for uptake and oxidation of fatty acids and in metabolism of lipoprotein. Hence, it is crucial to develop molecules which could act as dual activating ligands both for PPAR-α and PPAR-γ in order to manage symptoms of dislipidemia and T2DM. The success of such dual acting drugs depended

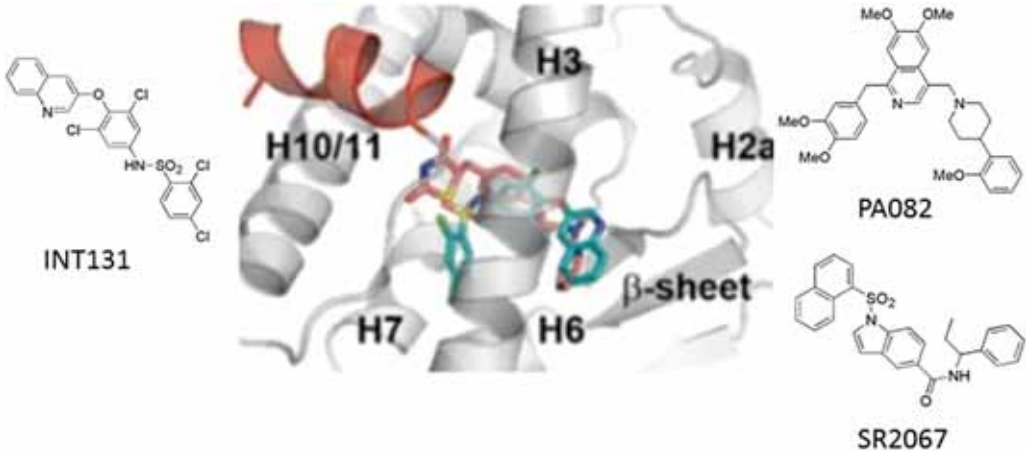


Figure 2. Different examples of SPPARγMs and the comparative binding of one of them (INT131, in blue) with rosiglitazone inside the PPAR-γ active site. Center image adapted from ref. 59b. Rosiglitazone is indicated by red color wireframe and Helix 12 by the red ribbon.

upon a difference in the binding and activity of the ligand towards each receptor subtype. It was found that for certain novel α-aryloxyphenylacetic acid derivatives the most optimum and balanced action occurs when the molecule behaves as a full agonist of PPAR-α and only a partial agonist of PPAR-γ, which helps reduce the side effects associated with full agonists of PPAR-γ (Shi *et al* 2005). This molecule presents a good case study for comparison of partial as well as dual agonism. In the crystal structure of this ligand with PPAR-γ, the carboxylic acid group binds to the crucial Y473 residue of helix 12, but does not exhibit a 'full residue match' with that of full agonist rosiglitazone. It merely wraps around helix 3 and hence exhibits typical partial agonist behavior for PPAR-γ (Shi *et al* 2005; figure 1). The structural mechanism of binding of the same molecule with PPAR-α was not available, but the authors believed that α-aryloxyphenylacetic acid derivatives were bound to the PPAR-α pocket atypical to that of a full agonist due to the compact molecular structure.

There exists a good example of dual agonism in the virtual screening and X-ray crystallography studies of Capelli *et al.* (2016), whereby they identify the same dual agonist molecule exhibiting different binding characteristics between the binding pockets of PPAR-α and PPAR-γ. In the first case the molecule (bearing a carboxylic acid head, a short aromatic linker and a hydrophobic tail) binds analogous to a partial agonist away from helix 12 remaining somewhat parallel to helix 3 (Capelli *et al.* 2016; figure 3). In contrast, in the PPAR-α binding pocket it remains close to helix 12 and forms a strong H-bonding interaction with tyrosine 464 and histidine 440 residues which are essential for full agonist behavior. The ligand binding assays also record this dual agonism behavior of the molecule with lower EC50 values for PPAR-α than PPAR-γ (0.31 uM against 5.3 uM).

An example of a successful PPAR-α/γ dual agonist is the drug Saroglitazar (table 1) in treatment of T2DM and dyslipidemia (Sosale *et al.* 2015). It is approved for use by the Drug Controller General of India. Saroglitazar is used in the

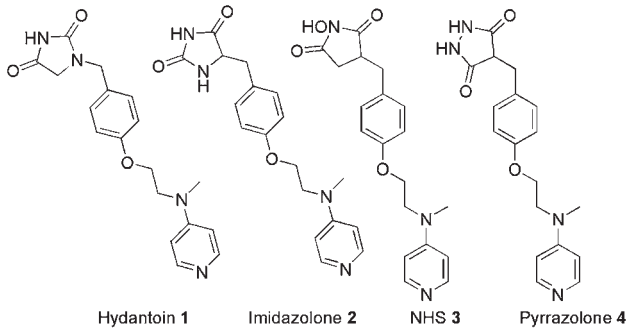


Figure 3. Novel proposed TZD mimics with sulfur free headgroups.

treatment of diabetic dyslipidemia and hypertriglyceridemia. In clinical studies, saroglitazar exhibited reduction of triglycerides (TG), LDL cholesterol, VLDL cholesterol, non-HDL cholesterol, and an increase in HDL cholesterol – a characteristic feature of atherogenic diabetic dyslipidemia (ADD). It is extremely useful in reducing the fasting plasma glucose and HBA1c in T2DM patients. Also in addition to small molecular therapeutics, herbal formulations play an important role in the management of T2DM and its related symptoms. A number of medicinal plants with proven anti-diabetic effects are in use. These include *Allium sativum*, *Eugenia jambolana*, *Momordica charantia*, *Ocimum sanctum*, *Phyllanthus amarus*, *Pterocarpus marsupium*, *Tinospora cordifolia*, and *Withania somnifera*. In addition to having insulin sensitizing actions, these plants also exhibit anti-oxidative properties which are crucial to an overall well-being in diabetic conditions (Modak *et al.* 2007).

We here would also like to highlight some progress made in T2DM drug discovery using *in silico* techniques. Since the PPAR-γ receptor binding site has a Y-shaped cavity, molecular docking towards discovery of novel Y-shaped ligands capable of fitting inside the PPAR-γ site completely have been carried out. Barbituric acid (BA) derivatives (table 1) were designed, evaluated for ligand binding and

finally synthesized for PPAR-γ activation (Dixit *et al.* 2016). Time-resolved fluorescence resonance energy transfer (FRET) studies were utilized to understand the nature of binding of the synthesized molecules with the PPAR-γ receptor and the IC_{50} values were measured. The significant outcome of this study was that the BA derivatives bearing a six membered head group exhibited the desired moderate level of PPAR-γ binding affinities. Research work was also carried out for *in silico* drug discovery and lead identification as ligands for PPAR-γ using the HipHop program. Attempts were made to generate a common pharmacophore for pan PPAR agonists (acting on all three subtypes – α, γ, δ). Presence of hydrogen bond acceptor (HBA) units on one terminus of the molecules was essential, as was presence of one hydrophobic tail group (HTG) possessing other side chain moieties. These features when combined with the unique 3D arrangement of other moieties on the HTG are the signatures of a PAN agonist that could enter active sites of all three PPAR subtypes. The chemical features in the top scoring proposed structure(s) matched with the known interactions of the pan agonists in the PPAR-γ active site. Five molecules exhibited similar or better scores than the reference molecule. Important H-bonding interactions with His323, Tyr473, Ser289 and His449 as in case of various PPAR-γ agonists were also observed. This *in silico* pharmacophore mapping exercise therefore established the importance and role of the different chemical moieties present in the pan PPAR agonists, a useful discovery for future research work (Sundriyal and Bharatam 2009). In the next section, we will examine utility of TNF-α as a drug target for posible T2DM.amelioration.

4. TNF-α as the drug target for obesity

As TNF-α has been identified as a key component in obesity-linked insulin resistance, it is thus a target for management of insulin resistance condition and obesity. There are studies stating about novel approaches like using anti-TNF-α antibodies, such as infliximab, for targeting the soluble receptor complex to reduce TNF-α levels and manage obesity and diabetes. Anti-TNF-α therapies have mostly concentrated on reducing its production levels or aimed towards leading to a lowering of its physiological effects. There are however, very few studies of observing the effects of lowering the TNF-α levels and/or its physiological action in connection to relieving T2DM. Recently a new class of TNF-α receptor inhibitors has been developed by Rigel Pharmaceuticals Inc, USA. 1,2,4-triazoloquinoxalines (TQ) (table 1) were reported to inhibit complexation of TNF-αRI receptor with its associated death domain protein and receptor interacting protein 1 (Gururaja *et al.* 2007). This is normally the initial intracellular signaling event following TNF-α stimulation of its receptor leading to internalization of the receptor-protein complex. This molecular mechanism would in general set off a number of TNF-α induced pathways (such as NFκβ activation) that may be undesirable in the given context for the cell. Therefore, by interfering with the aforementioned complex formation process set off by TNF-α stimulation, this particular TQ molecule is able to protect the liver epithelial cells subject to the experiment from the harmful effects of TNF-α induction. A separate series of the triazoloquinoxaline class of molecules (table 1, category II) also exhibited inhibition of TNF-α activity with very low toxicity (Guirado *et al.* 2012). These were proposed as potential anti-inflammatory agents. These molecules were administered *in vitro* to HL-60 cell lines induced with lipopolysaccharide (LPS) for pro-inflammatory cytokine production and ELISA monitoring for TNF-α levels. A number of these types of triazoloquinoxalines proved capable of inhibition of TNF-α in low (~ 10 μM) concentrations. These findings about anti-TNF-α therapies are encouraging signals for further research and development. It would be worth exploring whether the advantages of alleviation of TNF-α induced cellular toxicity and inflammatory responses, could be extended to restoring the normal PPAR-γ activity and improving insulin sensitivity of the cells. Expectedly, the research findings would be better utilized towards restoring glucose homeostasis in T2DM and reduction of obese condition in affected individuals.

5. A new proposal for design of next generation anti-diabetics based on our *in silico* findings

A brief outline of the various therapeutic options available for treatment of T2DM as listed above (table 1) proves the general superiority of the glitazone family of drugs over everyone else. This is due to the fact that they attempt to address the main symptom of the disease which is lack of tissue insulin sensitivity. Hence, among the various approaches towards preparation of better and safer medications as the next generation anti-diabetic drugs, the thiazolidinedione containing glitazones offer a good starting point. As discussed in an earlier section, the current state of the art towards newer drugs involves preparation of partial agonists of the nuclear receptor PPAR-γ entitled the SPPARγMs. This is due to the fact that partial agonists were best suited for selectively promoting only the insulin sensitizing functions, while minimizing the side effects known for glitazones. We propose the following structures as shown in figure 3 as alternatives to the known TZD glitazone drugs (table 1) as examples of possible TZD molecules with a similar headgroup, but devoid of the sulfur atom.

The idea was based on replacement of the TZD head group by similar non-sulfur containing 5-membered rings of similar polarities without much alteration in the side chain residues. We set out to design a new category of SPPARγMs based on the glitazone motif itself. As shown earlier in figure 3, the current SPPARγMs in various stages of research, except balaglitazone, deviate much from the

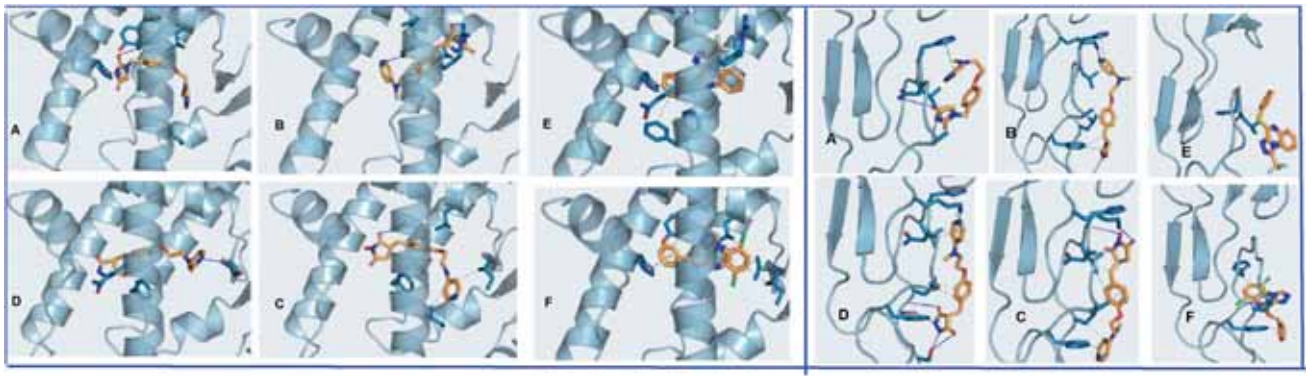


Figure 4. (**Left panel**) Lowest energy conformers of non-sulfurated TZD mimics: (**A**) hydantoin, (**B**) imidazalone, (**C**) N-hydroxy succinimide (NHS), and (**D**) pyrrazolone bound to PPAR-γ and TQ analogues: (**E**) TQ1 and (**F**) TQ2 bound to PPAR-γ. (**Right panel**) Lowest energy conformers of non-sulfurated TZD mimics: (**A**) hydantoin, (**B**) Imidazalone, (**C**) NHS, and (**D**) Pyrrazolone bound to TNF-αR1 and TQ analogues: (**E**) TQ1 and (**F**) TQ2 bound to TNF-αR1. Refer to the main text for the interaction profile of the bound ligands.

glitazone framework. While balaglitazone did show SPPARγM like characteristics and also possessed the glitazone architecture, unfortunately, it did also bear the sulfur atom in its TZD ring. Since the troglitazone toxicity implicated the presence of the sulfur atom of the TZD ring, we therefore came up with this idea of preserving the overall glitazone-like structures but removing the sulfur from the TZD ring. We are interested to see if the binding mode of the new non-TZD head groups would be different from that of the TZDs and if so, particularly would the H-bonding between the tyrosine 473 residue of helix 12 would be weaker, stronger or the same? Would the non-TZD head groups occupy the exact same active site space as in rosiglitazone? Would the non-TZD show tight binding like full agonists or a wrap-around binding of helix 3 like partial agonists? The three dimensional structure of PPAR-γ was elucidated using X-ray crystallography and the structures are available both for PPAR-γ and PPAR-γ bound with rosiglitazone. We have used both these structures to explore the binding capabilities of the designed non-TZD based glitazones given in figure 3. To the X-ray structure of PPAR-γ, we have docked the newly proposed structures **1-4** using AutoDock (Morris *et al.* 2009). Since the co-crystal structure of rosiglitazone with PPAR-γ is available, we have chosen a grid box encompassing 8 A radius of the binding pocket of the rosiglitazone. The partial charges and hydrogens were added using the default parameters of Autodock. The binding energies of the best poses of each of the ligands are in the range of 8.2 to 8.9 Kcal/mol. These initial docking studies were done by considering the protein rigid and allowing the ligand to be flexible. When the entire protein was targeted instead of the pocket around the rosiglitazone, we have observed that binding of the ligand to the same binding pocket. This further gave the confidence to perform all the docking studies with a defined search grid box around the rosiglitazone binding pocket. Shown in figure 4 are the best docked models (highest binding affinity) of each of these four compounds to PPAR-γ. Lack of sulfur does not inhibit their binding to the active site of PPAR-γ. However, as seen for all the proposed new molecules (figure 3), and unlike the full agonist rosiglitazone (figure 2), the hydantoin head group of **1** is displaced away from helix 12. Hence there is no scope of H-bonding with the tyrosine 473 of helix 12. The measured distance between the NH of TZD ring and the OH of tyrosine 473 is 2.6 A in rosiglitazone and 3.6 A in Hydantoin (see appendix 1). All of the molecules, exhibit a conformation wrapped-around Helix 3. They exhibit an ability to bind inside the active site of PPAR-γ; but not in a similar manner to the full agonist rosiglitazone. In every case, the polar non-TZD head group is pointed away from the helix 12. In **2** the imidazalone head group is pointed in the opposite direction to the helix 12. Since the ability to stay away from helix 12 is a desirable characteristic for a molecule to behave as a partial agonist of PPAR-γ, these proposed structures show promising results. We have also explored the ability of the newly proposed sulfur lacking TZD mimics to bind the TNF-α receptor 1. Recently crystallized TNF-αR1 receptor with a potential small molecule ligand is used for the docking studies (Carter *et al.* 2001). As can be seen from figure 3, the proposed TZD mimics bind to TNF-αR1 with similar affinities as the proposed ligand and often in a similar orientation, albeit the TZD mimics tend to have more interactions than the proposed ligand. TQ analogs, which are known antagonists of TNF-αR1 receptor, are also probed for potential dual target nature. Herein, we have carried out docking studies of TQ analogs (table 1) with both PPAR-γ and TNFα-R1 receptor. Once again, our preliminary docking studies implicate these analogues to bind to both the targets albeit with different binding conformations (figure 4). Thus, based on our preliminary docking studies and the comparative analysis of the existing drugs to treat obesity mediated T2DM, it is quite encouraging to speculate the possibility of the novel dual target TZDms and TQ mimics to overcome the MetS. One

pertaining concern in the proposed dual role of these drugs is target location. TNFα-R1 resides both on the cell surface as well as in the soluble form (sTNFαR1) whereas PPAR-γ is cytosolic. Since this novel class of molecules is inspired from the TZD, targeting the PPAR-γ by these drugs would be achievable in similar fashion. It has been shown that the insulin resistance is associated with alternative shedding of TNF alpha receptors in T2DM (Fernandez-Real *et al.* 2002). As far as targeting the TNFα-R1, we envision this to be concentration dependent targeting, *i.e.* when the concentration of these receptors is high, as can be seen in the case of T2DM, the drug will target these receptors. That is how we envision these drugs achieving their dual-target activity.

6. Conclusions

The links between two most important MetS conditions T2DM and obesity having been well established and understood; it is therefore important to explore new avenues of research into their alleviation. Since both these diseases are of much public health concern, a serious effort is required to find a lasting and reliable therapeutic methodology. Here, we have highlighted the role of maintaining proper insulin signaling in body as well as need to fight against conditions that could interfere with the same. We have identified the role of obese condition in promoting insulin resistance and outlined that a possible solution to managing T2DM is clearly linked with fighting obesity and inflammatory responses of the body. We have therefore proposed that investigations should be carried out to study the effects of anti-inflammatory therapeutics as to whether they can restore cellular insulin signaling pathways in addition to reducing inflammatory responses. We have also proposed the rational design of new sulfur free TZD glitazone type molecules as potential partial agonists of nuclear receptor PPAR-γ while retaining most of the other structural features of the TZD drugs. To substantiate our proposed sulfur-free TZD mimics, we have carried out *in silico* docking studies of these types of ligands for PPAR-γ. Our results have encouraged us to believe that sulfur free non-TZD glitazone molecules could in fact possess the desired partial agonist behavior. In this way, the exclusively insulin sensitizing functions of these molecules could be studied devoid of the undesirable side effects of normal sulfurated glitazones. Also, since in obese diabetic patients the chemokine factor TNF-α causes further degradation of receptor PPAR-γ, it would also be important to study the effects of blocking of the TNF-α receptor with novel synthetic molecular antagonists and see if that induced activation of the PPAR-γ receptor. We hope that such a dual drug discovery approach could be best suited to re-sensitize a diabetic pathophysiology, towards insulin mediated glucose uptake, while preventing downstream effects of the obese condition to interfere with the same.

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Corresponding editor: Ullas Kolthur-Seetharam