Fine Tuning of PPAR Ligands for Type 2 Diabetes and Metabolic Syndrome

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Abstract: Type 2 diabetes mellitus (T2DM) is highly prevalent chronic disease. Recently, many biological targets are discovered for treatment of this disease. The identification of the nuclear hormone receptor peroxisome proliferator activated receptors (PPAR) and their subtypes α, γ and δ or β as targets for controlling lipid, glucose and energy homeostasis has proved to be exciting. As hyperlipidaemia, obesity and insulin resistance are independent risk factors for coronary heart disease and macrovascular complications of diabetes; new agents that increase insulin sensitivity as well as decrease hyperlipidaemia by distinct yet complementary mechanism are being studied as they may provide improved therapy for T2DM and related disorders. In this article, we review highly potent PPARγ agonists, PPARα/γ dual agonists, PPAR pan agonists, alternative PPAR ligands like partial agonists or selective PPAR modulators (SPPARMs) and antagonists from a chemist point of view.

Keywords: T2DM, PPAR, TZDs, dual agonist, pan agonist, partial agonist.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by high level of blood glucose, insulin resistance in liver and peripheral tissues accompanied by a defect in pancreatic β-cells. The risk of developing type 2 diabetes increases with age, obesity, family history of diabetes, cardiovascular disease (hypertension, dyslipidaemia) and a lack of physical activity [1-3]. Hyperglycemia has been shown to have only one component of a series of anomalies afflicting patients with type 2 diabetes. Concurrent maladies including insulin resistance, obesity, hypertension and dyslipidaemia; in combination constitute metabolic syndrome or syndrome X [4, 5]. According to world health organization the global burden of T2DM will exceed 300 million by the year 2030 [6].

Treatment of T2DM is currently performed with a combination of exercise and restrictions of calorie in take and/or drug therapy [7-9]. The identification of the nuclear hormone receptor, peroxisome proliferator activated receptors (PPAR) and their subtypes α, γ and δ or β as targets for controlling lipid, glucose and energy homeostasis has proved to be exciting [10-12]. PPARγ is molecular target for thiazolidinedione (TZD) class of insulin sensitizing antihyperglycemic agents [13-15]. As hyperlipidaemia, obesity and insulin resistance are independent risk factors for coronary heart disease and macrovascular complications of diabetes; new agents that increase insulin sensitivity as well as decrease hyperlipidaemia by distinct yet complementary mechanism are being studied as they may provide improved therapy for diabetes and related disorders.

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2. PPAR AGONISTS IN TREATMENT OF TYPE 2 DIABETES

While searching for novel and improved options for diabetic patients, the peroxisome proliferator activated receptor (PPAR) family still stands out as a potentially ideal target. These are included with nuclear receptor like retinoic acid receptors (RARs), thyroid hormone receptors (THRs) and steroid receptors. These modulate multiple aspects of lipid and carbohydrate metabolism and thus possess the propensity for addressing many features of the diabetic phenotype [16-18]. In this article, we review highly potent PPARγ agonists, PPARα/γ dual agonists, PPAR pan agonists, alternative PPAR ligands like partial agonists or selective PPAR modulators (SPPARMs) and antagonists.

PPARs are heterogenous and there are three subtypes. PPARα/δ/γ have great homology in their protein structures [19]. PPARα is expressed mainly in tissues involved in lipid oxidation such as liver, kidney, adrenal glands, cardiac muscle and skeletal muscles. PPARγ is expressed in adipose tissue, macrophages and vascular smooth muscles. PPARδ is unique as a result of its ubiquitous tissue distribution. Recent evidences suggest that like PPARα this subtype may play a prominent role in lipid catabolism [20].

These receptors have a protein domain structure common to other members of nuclear receptor gene family (Fig. **1**). This consists of a variable N-terminal region that has transcriptional activation function 1 domain (AF-1) responsible for phosphorylation of PPAR and DNA binding domain (DBD) which promote the binding of PPAR to PPRE in promoter region of target genes [21-23]. Ligand binding domain (LBD) within which lies a C–terminal region contains the transcriptional activation function 2 domain (AF-2). Ligand binding domain is responsible for ligand specificity and activation of PPAR binding to PPRE, which increases the expression of targeted genes.

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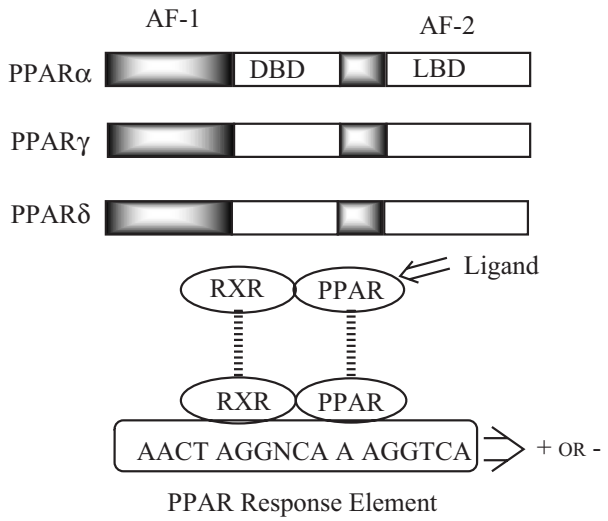


Fig. (1).

Recruitment of PPAR cofactors to assist the gene transcription processes is carried out by the ligand dependent activation function 2 (AF-2). PPARs form functionally active heterodimers with another nuclear receptor, 9-cis retinoic acid receptor (RXR), forming a complex that is able to bind to PPAR response elements, located in the promoter of PPAR target genes. The consensus sequence of PPRE is 5'-AACT AGGNCA A AGGTCA-3'. This interaction regulates the expression of target genes, many of which encode proteins involved in lipid metabolism and energy balance [24, 25].

PPAR ligands can be endogenous or exogenous like hypolipidemic, anti-inflammatory or insulin sensitizing drugs. Fatty acids have been discovered to bind to all three PPAR isotypes and cause gene expression. Several proteins also act as coactivators or corepressors that mediate the ability of nuclear receptors to initiate or suppress the transcription process [26, 27].

2.1. PPAR Agonists

The role of PPARγ and PPARα activation in ameliorating hyperglycemia and hyperlipidaemia associated with T2DM, originates with mainly two classes of compounds, thiazolidinediones and fibrates, which were empirically discovered *via* rodent pharmacology. The fibrates (clofibrate, fenofibrate and bezofibrate) are the drugs that effectively reduce triglycerides (TG), free fatty acids (FFA) and increases in high-density lipoproteins cholesterol in both rodents and man. Fibrates have also shown to improve glucose tolerance in type 2 diabetic patients, although this activity may not be attributable to activation of PPARα because some of these compounds also have appreciable PPARγ activity. Fibrates are well-tolerated drugs; however, they are associated with a number of side effects such as nausea, diarrhea and elevation in liver enzymes [28-30].

The thiazolidinediones (TZDs) represent a class of drugs that are insulin-sensitizing and are a major therapeutic advance in the treatment of type 2 diabetes. The ability of TZDs to improve the insulin sensitivity by showing that troglitazone was very effective in regulating plasma glucose, insulin, FFAs, TGs and ketone body level in several animal models of T2DM. The glucose lowering action of TZDs depends upon the presence of insulin. Insulin-deficient rats treated with TZDs have persistent hyperglycemia as long as insulin is absent, but respond better to exogenous insulin administration. Studies in different diabetic animal models have demonstrated that TZDs improve the stimulation of glucose disposal and inhibition of hepatic glucose production by insulin abolishing or preventing insulin resistance [31-34].

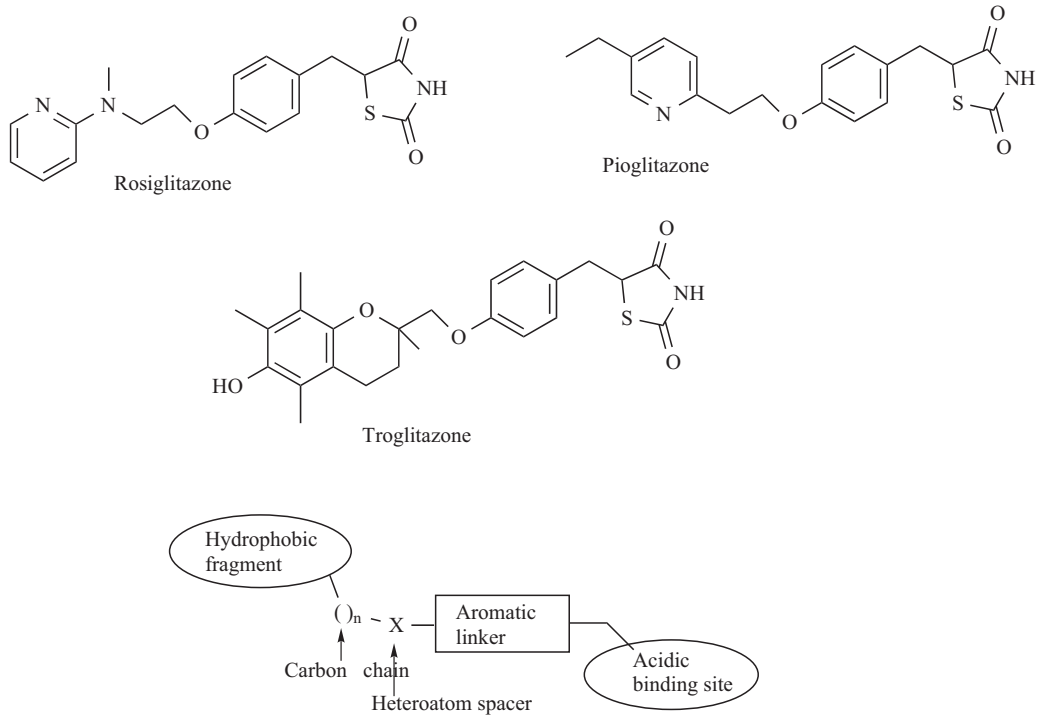


Fig. (2).

Troglitazone, (Fig. **2**) the first TZD to reach the market was completely withdrawn from clinical use in 2000 due to reports of severe, idiosyncratic hepatotoxicity. Today, two TZDs pioglitazone and rosiglitazone (Fig. **2**) are commercially available antidiabetic agents having similar clinical efficacy with improvements in insulin sensitivity and ability to lower fasting blood glucose by ~5-6 mg/ml relative to placebo. One potential area of distinction between these two TZDs is the greater impact of pioglitazone on diabetic dyslipidaemia [35, 36].

The discovery that the TZDs are potent, selective agonists of PPARγ provided important key link to understanding the molecular mechanism of these drugs. This provided the opportunity for target based approaches in effort to optimize selective PPARγ agonist as effective antihyperglycemic agents and selective PPARα agonist as antihyperlipidemic agents [37].

The thiazolidinedione ring is relevant to PPARγ activity whereas, substituted moieties modulate pharmacokinetic and pharmacodynamic properties. As a consequence of different side chains, TZDs differ in their pharmacological potencies. Their dose requirements for *in vitro* stimulation of glucose transport and their antihyperglycemic activity in *ob/ob* mice are consistent with the rank order binding affinities for PPARγ [38].

Molecular modeling and docking studies has given us further understanding that the PPARγ agonist essentially has three portions: acidic binding site, hydrophobic fragment and a linker unit (Fig. **2**). It turns out that the acidic binding portion could have groups like 2-ethoxy propionic acid or just an incipient acidic unit [39, 40]. Bioisosteric replacement of TZD was tried by various acidic groups like α-carbon substituted carboxylic acid, substituted oxazolidinedione, carbonated hydroxylurea, oxyiminoalkanoic acid, α-heteroatom substituted carboxylic acid, tetrazole, oxathiazole and tyrosine derivatives [41, 42].

The LBD is quite large for PPARγ and can accommodate a variety of structural units. This portion could be derivatives of mono, hetero-aromatic compounds, bicyclic aromatic or even tricyclic units. The linker unit is always a planar or aromatic ring with or without substitution. Among the aromatic groups studied are benzyl, naphthyl, pyridine and indole groups (Unpublished results) [42a].

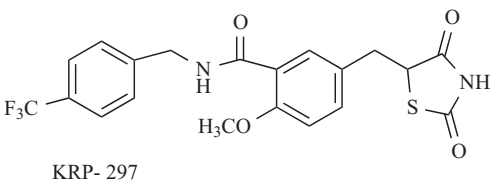
The most successful results reported are compounds with lipophilic unit of 2-phenyl-5-methyloxazole and two carbon chain linker with oxygen as hetero atom and benzyl group as middle planar ring with different acidic fragments.

2.2. PPARα/γ Dual Agonists

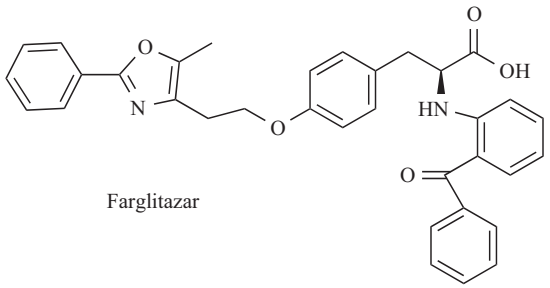
Generally, T2DM patients suffer from both hyperglycemia and dyslipidaemia. However, the major cause of mortality in T2DM patients is atherosclerotic macrovascular diseases. Such cardiovascular disease appears to result from diabetic dyslipidemia [43]. Considering the importance of glucose and lipid homeostasis, it is desirable to find ligands that can bind and activate both PPARα and PPARγ. In recent years, design of dual agonists PPARα/γ as well as PPARα/γ/δ (pan agonists) were taken up earnestly as they could provide beneficial metabolic effects that could reduce the extensive morbidity and mortality rate associated with T2DM [45].

First literature report of "balanced" PPARα/γ dual agonist was KRP-297 (MK-767) (Fig. **3**); a para-trifluoromethyl benzyl moiety containing TZD derivative that was reported to bind PPARα and PPARγ with an affinity of approximately 0.230 and 0.330 μM respectively, and cause transactivation of PPARα and PPARγ with potency of 1.0 and 0.8 μM respectively [46-48]. KRP-297 induced expression of acyl CoA oxidase mRNA (PPARα-regulated gene) in primary rat hepatocytes and in livers of obese rats and also induced the expression of AP2 mRNA (PPAR-regulated gene) in adipose tissue of obese rats. Treatment with KRP-297 resulted in significantly less weight gain relative to selective PPARγ agonists like pioglitazone and rosiglitazone in both fatty Zucker rats and db/db mice. KRP-297 was jointly developed by Kyorin pharmaceuticals and Merck & Co. but recently was terminated during phase III clinical trials for toxicological reasons [49]. It is unclear whether the toxicity observed is PPAR receptor mediated or compound mediated.

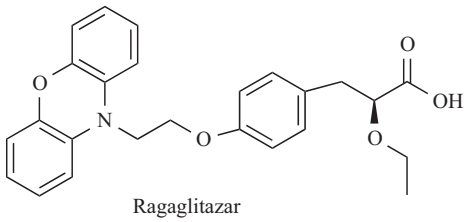
The alkyloxyphenylpropionic acid, ragaglitazar (Fig. **3**) (DRF 2725), lowered hyperglycemia, hypertrigly- ceridemia



KRP- 297



Farglitazar



Ragaglitazar

Fig. (3).

and hypercholesterolemia in diabetic rodents receive a high fat diet. In phase II clinical trials conducted with hypertriglyceridemic T2DM subjects, ragaglitazar reduced fasting plasma glucose hemoglobin, glycated hemoglobin (HbA1c), TG, FFA and total cholesterol levels and significantly elevates HDL-C. However, it had to be withdrawn at Phase II clinical trials due to tumor formation in rodent models [50, 51].

A huge array of molecules evaluated as PPARα/γ dual agonists have been tested *in vitro*, and *in vivo* on rodents models and some in obese insulin resistant rhesus monkey. Most results point that they are more efficacious in glucose or lipid control compared to single PPAR subtype selective agents supporting the presumption that PPARα/γ dual agonists might simultaneously improve pathological lipid profiles and hyperglycemia in T2DM patients [52].

However, many of the hopeful dual agonists had to be withdrawn at advanced stages of development due to various limitations and side effect. This has necessitated the regulatory authority to insist on these categories of compound to undergo extended two years carcinogenicity studies to address these concerns.

Recently, there is a distinct move to design ligands which show less potent PPARγ activity, specially having less adipogenecity, than PPARα activity. But the challenge is the identification of optimal ratios of PPARα and PPARγ agonist activity in a ligand. The idea is to selectively stimulate the genes affecting glucose and lipids without over stimulating them.

The study needs to effectively implemented in *in vivo* models and then again to cross to the actual human study is yet another quest.

Tesaglitazar (AZ-242) (Table **1**), a methylsulfonyl derivative is in phase III clinical trials. It has desirable preclinical efficacy in a rodent model of diabetes and dyslipidemia [53-57]. Muraglitazar (BMS 298585) an oxybenzylglycine derivative, is a potent and balanced PPARα/γ dual agonist, is also sufficiently attractive in animal models that it has advanced to Phase II trials [58-60] (Table **1**).

A collaborative effort between Eli Lilly and Ligand Pharmaceuticals has proposed a novel PPAR α/γ dual agonist exemplified by LY 510929, a thiophenyl substituted oxazole and an α-aryloxy β-aryl propionic acid. This molecule is equipotent at both α/γ receptor subtypes *in vitro* and has demonstrated very potent glucose lowering activity in ZDF rats, with an ED_{50} for glucose normalization of 0.004 mg/kg. Hybrid ligand of PPARα and PPARγ are also reported. These analogs contain the phenoxyisobutyric acid "head group" common to many fibrates attached to modified 2-phenyl-5-methyloxazole moiety common to several potent PPARγ ligands. Substitution at para position of the 2-phenyloxazole group provided a boost in potency at both receptor subtypes. An example from this series is biphenyl derivative LY 465608, which binds to PPARγ with an IC_{50} 0.548 μM and PPARα IC_{50} 0.174 μM. In addition to showing good antidiabetic and antihyperlipidemic efficacy in

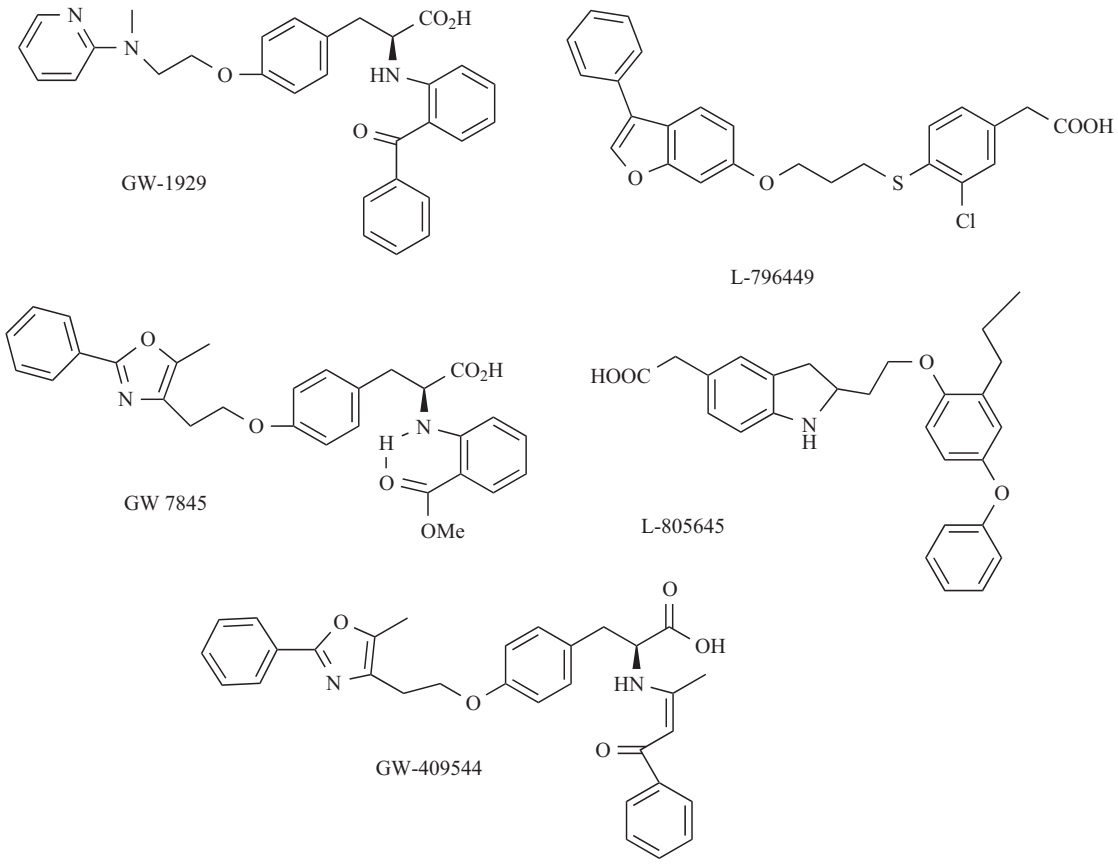


Fig. (4).

db/db mice and ZDF rats, LY 465608 also lowered the plasma TGs and raised the HDL-C in human apoA-I transgenic mice. However, this molecule also has considerable PPARδ agonist activity (EC_{50} 171 nm) and thus is more classified as pan agonist rather than PPARα/γ dual agonist as originally reported [61].

Glaxo Wellcome has described α-amino-β-phenyl propanoic acid derivative GW409544, a close structural analog of the selective a PPARγ against farglitazar. *In vitro* study of this compound places it as the most potent dual PPARα/γ agonist described to date, with a PPARα EC_{50} 0.002μM and PPARγ EC_{50} 0.0002μM [62-65].

Non-thiazolidinediones PPARγ agonists, which are comparable or superior to marketed TZDs in animal models are, GI 262570, GW 1929 and GW 7845 (Fig. **4**).Tyrosine based PPARγ agonists that were designed by replacing the TZD ring with a carboxylic acid and by introducing an amine function on alpha carbon while keeping the para-hydroxybenzyl moiety intact. In addition, a series of phenyl acetic acid derivatives, which showed potent activity at PPARγ is exemplified by L-796449; it is a potent agonist across all the three receptor subtypes at similar concentration. L-805645, which is a selective PPARγ agonist is also reported [66-69].

Thus, our understanding of the PPAR molecular mechanism of action has helped us in identifying antidiabetic compounds with improved efficacy and reduced side effects profile; weight gain and edema. Today many labs are utilizing a variety of technologies for rational PPAR design, including competitive binding assays, cellular transfection/ reporter gene assay and ligand activated cofactors recruitment assays. These methods have resulted in the identification of several PPAR categories and advancements of numerous compounds towards development pipeline.

2.3. PPAR δ and Pan Agonist

Because of the paucity of selective ligands, PPARδ was least understood in PPAR subtypes. Nevertheless, early PPARδ selective agonists were found to elevate HDL-C levels in diabetic mice, an important observation that indicated that PPARδ ligands might have beneficial effects on dyslipidemia. GW501516 was shown to be PPARδ agonist and increases HDL-C level while decreasing elevated TG and insulin levels in obese rhesus monkeys. GW501516 also attenuates weight gain and insulin resistance in high fat diet fed mice by increasing expression in skeletal muscle of genes that promote lipid catabolism and mitochondrial uncoupling, thereby increasing β-oxidation of fatty acids in skeletal muscle [70-72].

As the mechanism of PPARδ subtype was better understood, scientists like in Glaxo and Plexxikon started designing pan agonists (which binds not only alpha and gamma but also delta activity) with the idea of complementary improvement in lipid metabolism.

GSK 677954 is currently in Phase II testing and the compound had showed more than 30% reduction in blood glucose and insulin, greater than 20% reduction in LDL cholesterol and increases in HDL cholesterol, without weight gain or fluid retention.

Plexxikon's PLX204 has completed several preclinical studies in the Zucker diabetic fatty (ZDF) rat model of Type II diabetes. In that study, PLX204 lowered glucose and hemoglobin A1c (HbA1c) levels more than 50% compared to placebo, lowered triglycerides four times more than placebo and raised HDL cholesterol more than 25% compared to placebo without causing significant weight gain. Besides adding alpha and delta activity, company also indicated that PLX204 does not belong to the same chemical class as pioglitazone and rosiglitazone, which may account for some of differences in clinical profiles. The compound was discovered using Plexxikon's scaffold-based drug discovery technology, which starts by screening a core library of scaffolds against a family of targets and uses successive rounds of co-crystallization and chemistry to identify and optimize leads. It is also known that PLX204 is a partial agonist of PPAR gamma, which is believed to affect the compound's clinical profile more favorably compared to the full agonists [73].

2.4. PPAR Agonists and Antioxidants

Cellular reactive oxygen species (ROS, superoxide and H_2O_2), specially when chronically raised to high levels and associated with hyperglycemia, are known to have pathophysiological role in the vascular complications of diabetes as well as the progression of disease itself [74,75].

The possible sources of oxidative stress in diabetes include free radical generated by auto oxidation reaction of sugar and sugar adducts to protein.

Antioxidants are known to be interceptor of peroxy radical, singlet oxygen and hence inhibit lipid peroxidation, which is implicated in the alteration of glucose transport and microangiopathic complications in diabetes. Supplementation with an antioxidant is a promising complimentary treatment, which exerts beneficial effects in diabetes and provides support for complication of oxidative stress in β-cell dysfunction in diabetes. Moreover, antioxidants like probucol, vitamin E, glutathione (GSH), butylated hydroxyl toluene (BHT) and iron chelates desferrioxamine and α-lipoic acid have shown promising results in the treatment of diabetic neuropathy [75, 76]. Troglitazone, a PPARγ agonist which was introduced and latter withdrawn from market due to hepatotoxicity was designed to be an antioxidant by virtue of its chroman ring. Recently, we have reported a series of dual PPARα/γ agonists which also exhibit high antioxidant activity due to the presence of hydroxyl carvedilol moiety [77-79].

In vivo study done in db/db mice for compound 1 and 2 gave some very interesting results, while PG level was reduced by 1 when some given orally on 14th day about 70%, compound 2 did not show significant reduction similarly (Fig. **5**). Compound 1 could reduce TG level in db/db mice by 45% when given orally but 2 did not show any lowering effect. When 2 was tested in cholesterol fed SD rat orally, showed very good lowering in TC, TG, LDL and VLDL and increase in HDL [80].

Interestingly, the recently reported partial agonists which are in various stages of development by Merck had shown to possess the chroman ring unit of vitamin E at the DBD instead of being attached at the LBD as seen in troglitazone.

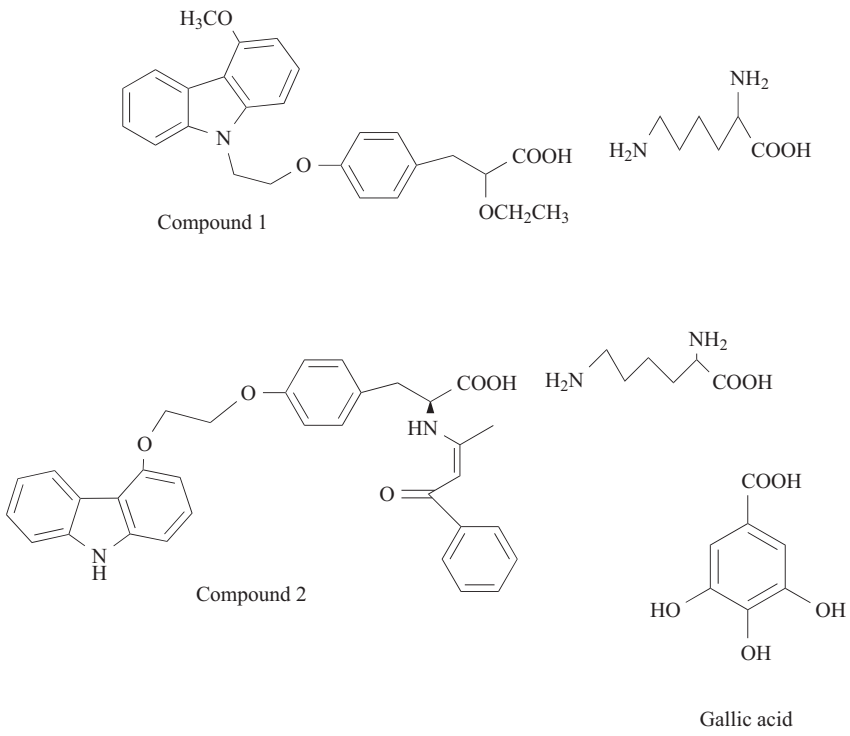


Fig. (5).

This has not been reported to cause hepatotoxicity; the group has not reported about their antioxidant activity.

Recently, Li's group has shown that the traditionally antidiabetic action of Punica *granatum* flower extract is through activation of PPARγ. The active component is believed to be gallic acid, which is also widely distributed in other herbal medicines showing antidiabetic and anti-inflammatory activity. Interestingly, gallic acid (Fig. **5**) is a polyphenol which is known to inhibit oxidation of lipids e.g. LDL, by scavenging ROS and delay the development of atherosclerosis lesions [81].

2.5. Partial Agonists and Antagonists

There has been a distinct shift from designing full agonists of PPARα/γ to partial agonists or selective PPARγ modulators. SPPARMs as detected through transcriptional assays have shown unique molecular and pharmacological properties while full agonists locating receptor into totally active modulators. Selectively activate or inactivate subjects of the gene regulated by PPAR and hopefully avoid the known side effects. They are also known to have altered backbones as compared to the full agonists on binding to the PPAR receptors [82-83].

The theory is reminiscent of the selective estrogen receptor modulators (SERMs) in which tamoxifen and raloxifene have been shown clearly to have therapeutic benefits over the native estrogen receptor agonist ligand estradiol.

Lot of work has been done on PPARγ partial agonist/SPPARMs especially on GW0072. *In vitro*, GW0072 was shown to be of high affinity, and partial agonist as defined relative to rosiglitazone. Furthermore, GW0072 has demonstrated a reduced ability to recruit specific cofactors and ability to competitively block rosiglitazone-mediated cofactor recruitment and transcriptional activity. *In vivo* GW0072 has demonstrated an ability to effectively improve insulin sensitivity in obese fa/fa rats [84].

Another compound FMOC-leucine (Fig. **6**) has been reported to induce a unique receptor conformation resulting in specific cofactor recruitment and target gene activation profiles. In preclinical pharmacology studies, FMOC-leucine improved insulin sensitivity in rodents models with essentially no associated weight gain. Although FMOC-leucine is unlikely to be developed as an antidiabetic therapy, the profile exhibited by this compound reinforces the potential benefit to partial activation /selective modulation [85, 86].

Yamanouchi pharmaceutical has disclosed YM-440 (Fig. **6**) a unique PPARγ modulator. In PPARγ binding studies, YM-440 demonstrated a Ki of 4 μM and yet appeared less potent in cell based activation assay with reported EC_{50} value of 30-100μM. *In vivo*, YM-440 displayed similar hypoglycemic activity to troglitazone and pioglitazone, but in contrast to the two TZDs it did not alter body weight gain in db/db mice [87].

Several of the TZD compounds also exhibit characteristics of partial agonists/ SPPARMs. Netoglitazone (Table **1**) currently in phase II trails has been described as a full agonist, partial agonist and even an antagonist based on its context specific activity.

Similarly, Troglitazone has been described as a PPARγ partial agonist. In humans, troglitazone effectively lowered blood glucose level and HbA1c, while improving insulin sensitivity and serum lipid profiles. Due to partial agonist/SPPARM profile, troglitazone clinically displayed a relatively low incidence of edema and weight gain.

In addition to partial agonist/SPPARMs, several PPAR antagonists appear capable of providing therapeutic benefit with potentially reduced side effects. Rieusaet *et al.* describes the phosphonophosphate SR-202 (Fig. **6**) as a synthetic PPARγ antagonist that inhibits both TZD-stimulated recruitment of the co-activator SRC-1 and TZDs induced transcriptional activity of the receptor in cell culture. SR-202 efficiently antagonizes hormone and TZD induced adipocyte differentiation. *In vivo*, SR-202 reduced both high fat diet induced adipocyte hypertrophy and insulin resistance. These effects were accompanied by smaller adipocyte and a reduction of TNF-α and leptin secretion. Treatment with SR-202 also improved insulin sensitivity in diabetic ob/ob mice [88].

Similarly, LG 100641 (Fig **6**) is described as a PPARγ antagonist with an ability to block TZD induced preadipocyte differentiation. However in 3T3-L1 adipocytes, LG 100641 induces insulin stimulated glucose uptake, suggesting that PPARγ mediated adipogenesis can be separated from the ability of the receptor to enhance insulin sensitive glucose transport. Besides, lists of compounds of various pharmaceutical companies, which are currently in pipeline at various stages of development are given in Table **1**.

3. CONCLUSION

At some point of time, TZDs were thought to be mainly PPARγ agonists. In order to be PPARα/γ dual agonist non-TZDs compounds like α-alkoxy propanoic acid and N-substituted tyrosine based derivatives were initially designed. But Merck group showed that even TZDs could be designed as dual agonists; these compounds were meta disubstituted (compound 3) at the linker unit instead of traditionally para position. Moreover, many of the compounds now in the pipeline have TZD unit as in Table **1**. [89-92].

At the LBD end, 2-phenyl-5-methyloxazole moiety or biaryl substituted oxazole are giving compounds good activity; besides, oxazoles, triazole units are also seen in compounds going into phase trials. On the DBD end, more compounds with free carboxylic acid group either as acetyl, glycyl, propanoic or isobutyric units is noticed in PPARα/γ dual predominantly PPARγ agonist.

There are several reports in literature of molecular modeling and docking studies along with binding studies of active compounds. However, these techniques at the moment are not able to predict the adverse biological effects and hence a plethora of pharmacological testing is required to

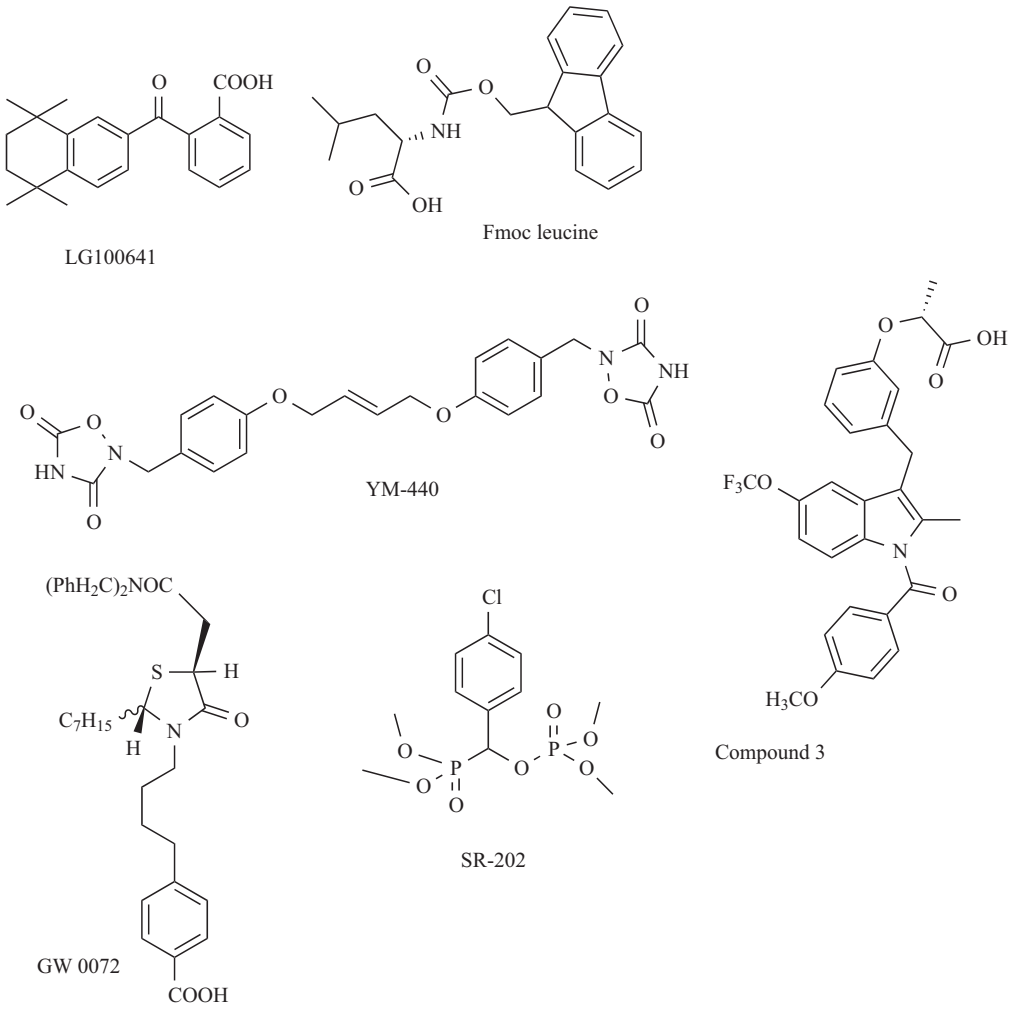
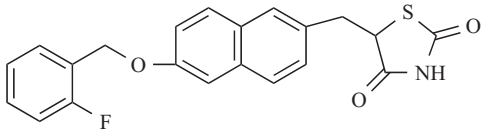
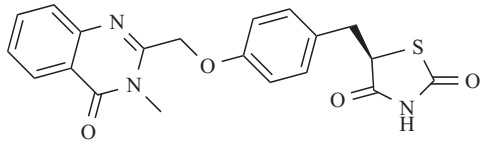
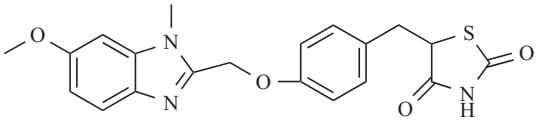
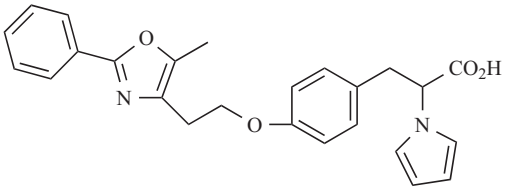
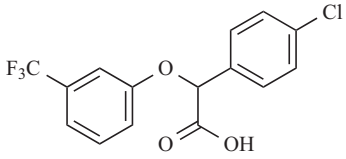
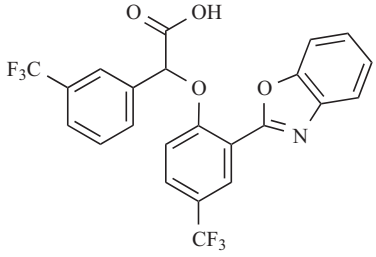
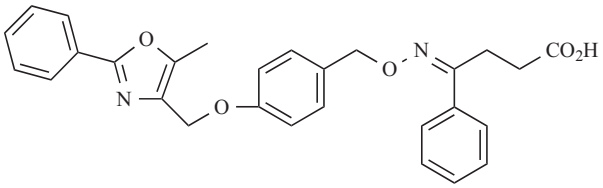
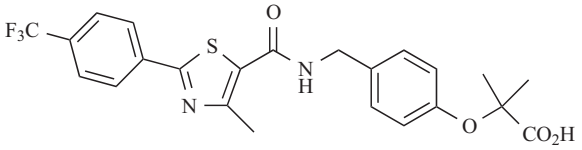
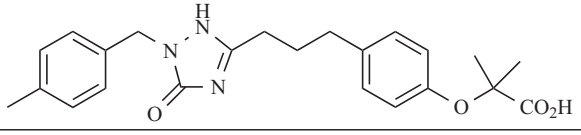
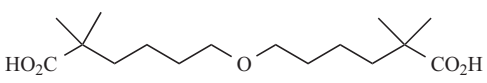
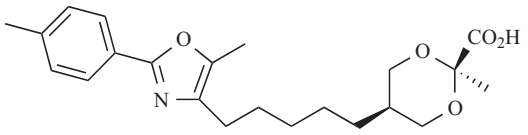
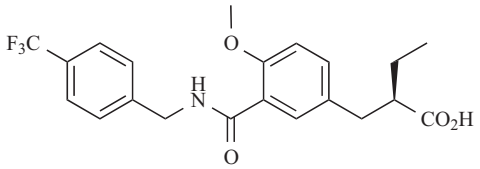
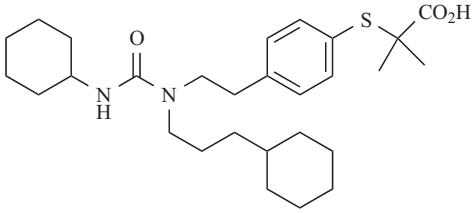
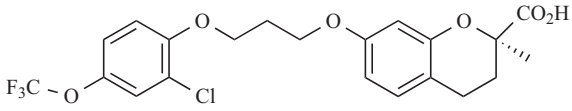
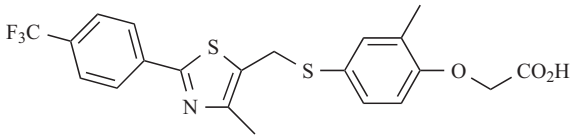
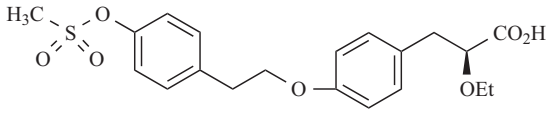
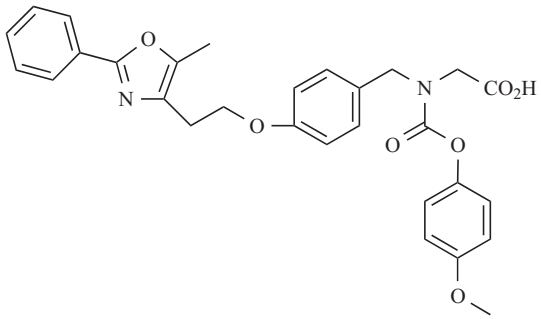
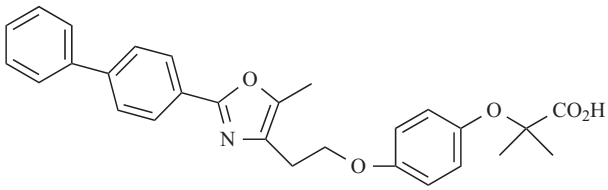
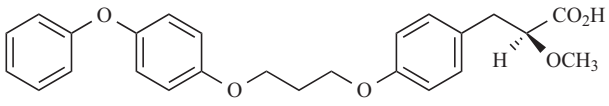


Fig. (6).

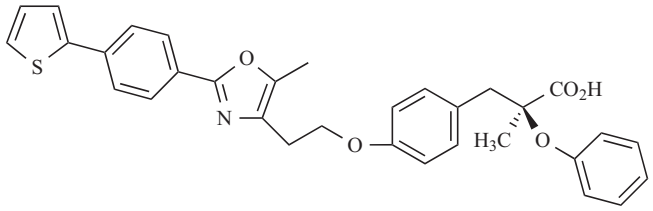
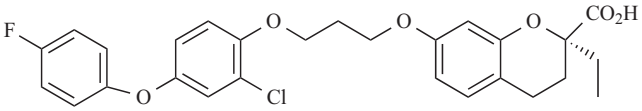
Table 1. List of Compounds in Different Phases of Clinical Trials

Serial	Compound No.	TA	Structure
1	Netoglitazone MCC-555 Phase-II	PPAR-γ agonist	
2	DRF-2593 Phase-II	PPAR-γ agonist	
3	CS-011 Phase-II	PPAR-γ agonist	
4	GW-7282 Preclinical	PPAR-γ agonist	
5	MBX-102 Metaglidasen Phase-II	PPAR-γ Partial agonist	
6	MBX-2044 Preclinical	PPAR-γ Partial agonist	
7	TAK-559 Phase-III	PPAR-γ Agonist Non-TZD	
8	GW-590735 Phase-II	PPAR-α predominant	 Most probable structure
9	LY-518674 Phase-II	PPAR-α predominant	
10	Gemcabene Phase-II	PPAR-α At high Conc.	

(Table 1) contd….

Serial	Compound No.	TA	Structure
11	NS-220 Phase-I	PPAR-α predominant	
12	KRP-101 Phase-I	PPAR-α agonist	
13	GW-7647 Preclinical	PPAR-α predominant	
14	Merck compound Preclinical	PPAR-α predominant	
15	GW-501516 Phase-II	PPAR-δ agonist	
16	Tesaglitazar AZ-242 Phase-III	PPAR-α and γ dual	
17	Muraglitazar Phase-III	PPAR-α and γ dual	
18	LY-465608 Phase-III	PPAR-α and γ dual	
19	Naveglitazar Phase-III	PPAR-α and γ dual	

(Table 1) contd….

Serial	Compound No.	TA	Structure
20	LY-929 Phase-II	PPAR-α and γ dual	
21	Merck compound Preclinical	PPAR-α and γ dual	

understand the complex SAR of these antidiabetic compounds.

In case of partial agonists and antagonists, not much structural generalization is possible. At the moment, lead compound generation is more or less empirical; more work needs to be done so that we understand the structural features of compounds showing improved pharmacological profile.

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