INTRODUCTION

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1 Introduction

1.1 Metabolic disorder

Metabolic disorder is a generic term that describes a wide range of diseases those affect normal body metabolism and is quite common in industrialized countries. Approximately 20-30% of the population suffers from this disorder and the increase in the prevalence of metabolic disorder is closely linked to type II diabetes, hypertension and obesity [1,2]. In other words metabolic disorder is defined as a cluster of disorders in the metabolism of carbohydrates and lipids which includes obesity, hyperglycemia, dyslipidemia and hypertension.

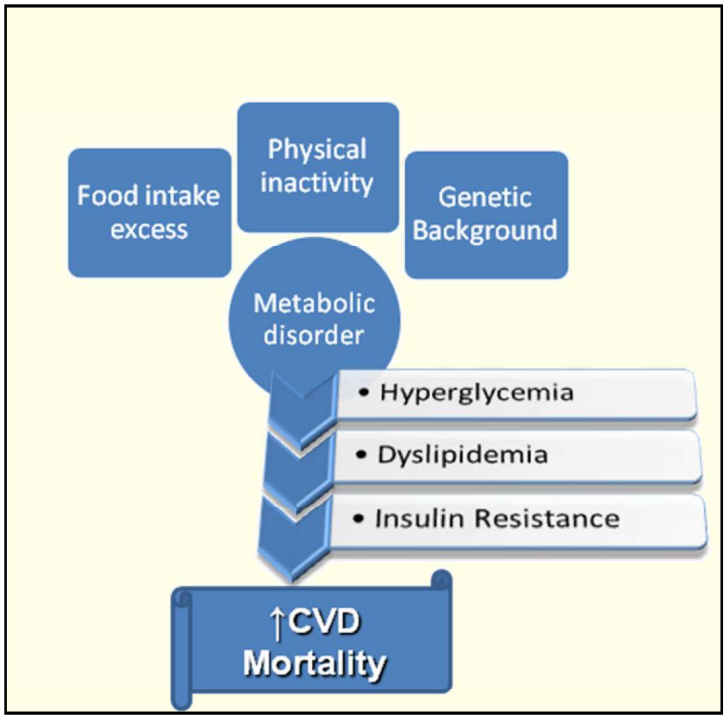


Figure 1 : Metabolic disorder and CVD

An association between certain metabolic disorders and cardiovascular disease has been known since 1940s. Earlier to that in 1920s hypertension, hyperglycemia and hyperuricaemia were considered in the description of metabolic disorders. Later in the 1940s obesity as a component was also

reported [3]. Further in 1980s it was more clearly defined and the term metabolic syndrome (also known as syndrome X) was coined to designate a cluster of metabolic risk factors like diabetes and cardiovascular disease that come together in a single individual [4]. In more current times, the term metabolic syndrome is found throughout medical literature and in the lay press as well. There are slight differences in the criteria of diagnosis depending on which authority is quoted. Regardless, the concept of a clustering of risks factors leading to cardiovascular disease is well accepted.

Metabolic disorders affect the production of energy within individual human cells. In the process of metabolism, digestive food is broken down by several enzymes into amino acids, fatty acids, carbohydrates, and glucose and blood transports them to the cells. After they enter in to cells, enzymes through chemical reactions metabolize these compounds and during these processes, the energy from these compounds is released to be use by the body or it is stored in body tissues. Metabolic disorders are caused by defects or any alterations in the complicated process of metabolism which results in wide range of diseases including obesity, hyperglycemia, dyslipidemia and hypertension (discussed further below). These abnormalities either alone or in combination dramatically increase the risk of the development of potentially life-threatening disease are considered as major manifestations of the syndrome and it can lead to a high risk of developing type 2 diabetes and cardiovascular disease [5-7]. The major classes of metabolic disorders are given below.

- Disorders of carbohydrate metabolism

- Disorders of amino acid metabolism
- Disorders of organic acid metabolism
- Disorders of fatty acid oxidation and mitochondrial metabolism
- Disorders of porphyrin metabolism
- Disorders of purine or pyrimidine metabolism
- Disorders of steroid metabolism
- Disorders of mitochondrial function
- Disorders of peroxisomal function
- Lysosomal storage disorders

As mentioned, the main features of metabolic disorder include dyslipidemia, diabetes, insulin resistance, hypertension (high blood pressure), cholesterol abnormalities, and an increased risk of atherosclerosis. Patients are most often overweight or obese [8,9].

1.1.1 Prevalence of metabolic disorder

The prevalence rates of metabolic disorder were 35.8-39.5% among Urban Asian Indians. The most common abnormality found among females was central obesity and elevated blood pressure among males. Risk factors associated with metabolic disorder are increasing age, female gender, sedentary lifestyle and diabetes in parents [10]. Excess weight contributes to about 90% cases of type 2 diabetes. Because of obesity and the associated metabolic disorder nearly 197 million people worldwide have impaired glucose tolerance as most common effect. This number is expected to increase to 420 million by 2025

[11]. Metabolic disorder drug market is expected to increase nearly $13 Billion by 2013.

1.1.2 Dyslipidemia

The lipoproteins are made up of lipids and protein molecules. Lipoproteins are classified on the basis of their densities (**Table 1**).

Table 1 : Classification of lipoproteins

Class	Density (g/mL)	Protein	Cholesterol	PL	TG
HDL	>1.063	33%	30%	29%	4%
LDL	1.019–1.063	25%	50%	21%	8%
IDL	1.006–1.019	18%	29%	22%	31%
VLDL	0.95–1.006	10%	22%	18%	50%
Chylomicron	<0.95	<2%	8%	7%	84%

VLDL- Very Low Density Lipoproteins; IDL-Intermediate Density Lipoproteins; LDL-Low Density Lipoproteins; HDL-High Density Lipoproteins; TG-Triglyceride; PL-Phospholipid. (Note - The remaining composition is made up of apoproteins)

Cholesterol and triglycerides are main components of membrane of living cells. In addition to their role in cell structure, cholesterol serves as a source of energy. Dyslipidemia is characterized by the elevated levels of lipids (cholesterol and/or triglycerides) or a low HDL (high density lipoprotein) level in the blood. There are different types of cholesterols and the alterations in the level of cholesterols and triglycerides in the bloodstream results in the condition called dyslipidemia. The most common types of dyslipidemia are due to high levels of LDL (low density lipoprotein) cholesterol, low levels of HDL (high density lipoprotein) cholesterol or high levels of triglycerides. Dyslipidemia has been recognized as the major risk

factor in causing cardiovascular diseases. When the levels of LDL cholesterol which is also considered as "bad" cholesterol are elevated, fatty deposits (plaques) build up in the arteries. Over time, plaques narrow the arteries, producing atherosclerosis (hardening of the arteries). This inturn causes heart disease, heart attack, peripheral artery disease (reduced blood flow in the limbs, usually the legs), or stroke.

National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) recommends target levels for both LDL cholesterol and HDL cholesterol to evaluate risk for CVD. In the 3rd report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults, previous and new NCEP guidelines were compared (**Table 2**).

Table 2 : NCEP recommended target levels LDL and HDL

Lipoprotein	Blood Lipid Level	Previous Guidelines	New Guidelines
LDL	optimal	< 130 mg/dL	< 100 mg/dL
	above optimal	n/a	100-129 mg/dL
	borderline high	130-159 mg/dL	130-159 mg/dL
HDL	high	160 mg/dL	160-189 mg/dL
	very high	n/a	> 190 mg/dL
	minimum	> 35 mg/dL	> 40 mg/dL

In addition to this total cholesterol (TC)/ HDL and LDL/HDL cholesterol ratio has become recognized as a stronger risk predictor for assessing risk of CVD than each lipid parameter [12-14]. The existing focus on monitoring levels of LDL-C, Total cholesterol (TC) and HDL is slowly shifting towards monitoring ratio of TC/HDL and LDL/HDL. The ratio reflects the amount of cholesterol is being stored in cells, how much is being utilized and removed [15]. The cut-off and

target lipoprotein ratio for men and women provide information on risk factors (**Table 3**) [16].

Table 3 : Risk categories and target levels for total cholesterol/HDL-C, LDL-C/HDL-C ratio

	Risk		Target	
Ratio	**Men**	**Women**	**Men**	**Women**
TC/HDL	> 5	> 4.5	< 4.5	< 4.0
LDL/HDL	> 3.5	> 3.0	<3.0	<2.5

Quality of life of large population in the world is affected by atherosclerosis a peripheral vascular diseases affect. Low levels of HDL and high levels of triglycerides can also increase fat build-up in the arteries. Whereas high levels of HDL cholesterol protect the heart by helping to remove the build-up of LDL from the arteries. There are studies illustrate protective effects of HDL against progression of atherosclerosis. Thus, HDL is a crucial factor for the treatment of patients having high levels of cholesterol [17-19]. The pathogenesis of atherosclerosis and coronary artery diseases is discussed by Ross and Glomset [20,21]. The most common lipid disorder is hypercholesteromia caused by high levels of cholesterol in blood. Central obesity or insulin resistance (a condition in which the body doesn't use insulin properly) either alone or in combination are risk factors for dyslipidemia are commonly found in patients with endocrine disorders such as diabetes, hypothyroidism (low levels of thyroid hormone) and polycystic ovary syndrome (PCOS).

1.1.3 Obesity

Worldwide, health of human being is progressively threatened by an imbalance between increased dietary intake and decreased energy expenditure

through physical activity, resulting in obesity, a serious and chronic disease [22]. According to WHO definition overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. The body mass index (BMI) calculation is also used to define obesity .Overweight is defined by a body mass index (BMI) that is equal or more than 25 kg/m^2 but less than 30 kg/m^2, and obesity implies a BMI equal or more than 30 kg/m^2. Obesity has increased at a striking rate over the three decades. The projection of the WHO by the year 2015 is that approximately 2.3 billion adults will be overweight and more than 700 million will be obese [23]. However, more efficient therapies to treat this abnormality is essential, as obesity is closely associated with several diseases such as coronary heart disease, stroke, diabetes, gout, osteoarthritis, hyperlipidaemia and reduced fertility. Possibility of social and psychological consequences because of obesity cannot be ignored [24].

1.1.4 Diabetes

Large portion of global population is affected by diabetes and its associated complications. Diabetes is chronic disease in which levels of blood glucose are higher than normal. Insulin, a hormone produced by the pancreas, helps glucose transport from the bloodstream into cells where it is used for energy. Diabetes occurs when the pancreas doesn't produce enough insulin or when the effectiveness of insulin in transporting glucose into cells is diminished, or a combination of both. As a result glucose doesn't enter the cells and levels in blood are high. Over time high levels of glucose in the blood can lead to increased plaque deposits on the inner walls of the blood vessel.

Since people with diabetes are at high risk for cardiovascular disease, keeping blood glucose levels to normal is essential for prevention of diabetes and related complications. Regulating blood pressure and lipid levels is equally important to manage cardiovascular disease risk. The most distinct lipid profile in diabetic patients consists of elevated LDL and triglyceride levels, low HDL levels which ultimately lead to atherosclerosis. This lipid pattern is closely related to central obesity and insulin resistance. Because type 2 diabetes plays central role in the metabolic syndrome, there is a need for a safe and an effective drug, to treat insulin resistance, diabetes and hyperlipidemia [25].

1.2 Currently marketed drugs for the treatment of metabolic disorder

At present following are existing treatments available for the treatment of this life threatening disease.

Table 4 : Currently marketed drugs for the treatment of metabolic disorder

Indication	Currently available therapy
Dislipidemia	Statins
	Niacin
	Fibrates
Hyperglycemia & Insulin resistance	Sulfonylureas
	Meglitinides
	Alpha-glucosidase inhibitors
	Dipeptidyl peptidase-4 (DPP-4) inhibitors
	GLP agonists
	Glitazones
	Biguanides

1.3 Diagnosis and potential targets for the treatment of metabolic disorder.

Metabolic disorder denote a cluster of metabolic risk factors, described above. There are few criteria for diagnosing the metabolic disorder (**Table 5**). According to the third report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) presence of three or more components are diagnosed with metabolic syndrome [26].

Table 5 : Criteria for diagnosing the metabolic disorder

Criteria	Limit
Elevated waist circumference	Men: equal to or greater than 40 inches Women: equal to or greater than 35 inches
Reduced HDL cholesterol	Men: less than 40 mg/dL, or currently taking medication to increase HDL Women: less than 50 mg/dL, or currently taking medication to increase HDL
Elevated triglycerides	Equal to or greater than 150 mg/dL, or currently taking medication to lower triglycerides
Elevated blood pressure	Equal to or greater than 135/85 mm Hg, or currently taking medication to reduce BP
High blood glucose	Fasting glucose equal to or greater than 100 mg/dL, or currently taking medication to lower glucose levels

Most people who have the metabolic disorder feel healthy and may not have symptoms. The cluster of diseases does take place following specific

molecular mechanisms, therefore it is difficult to find out therapeutic solution for the treatment of such disease. Lifestyle modification is considered as the first line therapy. Weight reduction usually requires a specifically tailored multifaceted program that includes diet and exercise. Only lifestyle modifications do not result in normalization of body weight, cannot improve reduce lipid levels and thus reduce CVD risk. Individuals having high levels of cholesterol, triglycerides along with obesity cannot be cured until they are put on intense therapy. In such scenario of high unmet clinical need, novel therapies are necessary to reduce the further consequences of the disease. As science has progressed, number of approaches have been explored by virtue of the enormous interest amongst academia and pharmaceutical industry scientists. There has been remarkable advancement happened during last few decades to find a way to treat such disease. Many newer genes, proteins have been identified in genomics and proteomics area, several ways have been tried to deliver a drugs through formulation techniques, likewise many new targets are identified to treat metabolic disorder. The potential biological targets to treat the metabolic disorder are discussed below.

1.3.1 Potential targets for the treatment of dyslipidemia

1.3.1.1 Targets for HDL raising drugs

- Cholesteryl ester transfer protein (CETP) inhibitors
- ATP-binding cassette transporter A1
- Liver X receptors
- Nuclear retinoid X receptor

1.3.1.2 Targets for LDL lowering drugs

- HMG-CoA reductase inhibitors
- TR-Beta agonists
- ACAT inhibitors

1.3.1.3 Targets for triglyceride lowering drugs

- Microsomal triglyceride transfer protein
- Stearoyl-CoA desaturase-1
- **Dual PPARα/γ agonist**

1.3.1.4 Other selected lipid modulators in development

- Ileal bile acid transport inhibitors
- Acyl-coenzyme A-cholesterol acyltransferase inhibitors

1.3.2 Potential targets for the treatment of type 2 diabetes

1.3.2.1 Targeting liver

- Hepatic enzyme inhibitors
- **PPARα**
- Glukokinase
- Glucagon antagonists

1.3.2.2 Targeting beta cell/brain

- GLP-1

1.3.2.3 Targeting muscle/fat

- PPARδ
- Protein tyrosine phosphatase-1b (PTP-1b)

- **PPARγ**
- AMPK
- 11bHSD1
- Hormone sensitive lipase
- Adiponectin

1.3.2.4 Targeting the Gut

- DPP-IV inhibitors

Several drugs with different mechanisms of action are at various stages of development. Some of the above mentioned biological targets yielded in fruitful results. Some of the targets confronted issues mainly related to safety of a molecule or target itself. For several targets the successful attempts delivered molecules which was developed, marketed and still they are drug of choice e.g. Atorvastatien (HMG-CoA reductase inhibitor), Glibenclamide (Sulfonylureas), Xenical (lipase inhibitor), Vildagliptin, Sitagliptin (DPP-IV inhibitor). Failure, on the other hand, where molecules could reach up to clinical trial stage but safety concerns were flagged and hence they were discontinued e.g. Muraglitazar, Tesaglitazar (PPARα/γ agonists), Rimonabent (CB1 Antagonist), Torcetrapib (CETP inhibitor). However, in some cases molecule has gone up to market and at later stage it was withdrawn due to toxicity findings. e.g. Rosiglitazone.

Process of drug discovery is too complex and regular upgradation is required. In this context some of the potential targets related to metabolic disorder are briefly described below.

1.4 Dyslipidemia targets

1.4.1 Cholesteryl ester transfer protein (CETP) inhibitors

Inhibition of cholesteryl ester transfer protein (CETP), a key protein involved in reverse cholesterol transport, can lead to increases in high-density lipoprotein cholesterol (HDL-C) levels and thus, is under evaluation as an antiatherogenic strategy. Various CETP inhibitors currently under development are Anacetrapib, Dalcetrapib [27].

But the unsuccessful story of Torcetrapib (CP-529,414, Pfizer) which was developed by Pfizer has put question mark on this target. This is because its development was halted in 2006 when phase III studies showed excessive all cause mortality in the treatment group receiving a combination of Atorvastatin and the study drug [28].

1.4.2 Microsomal triglyceride transfer protein inhibitors (MTP inhibitors)

MTP has distinct function in liver as well as in intestine. In liver assembly of triglyceride and Apo-B-100 is mediated by MTP. Similarly in intestine MTP is responsible for the assembly of triglyceride and Apo-B-48. Altogather MTP plays crucial role for the generation of triglyceride rich chylomicrones in liver and for VLDL in intestine [29]. Therefore MTP inhibitor can cause reduction in plasma triglyceride and cholesterol. Till date many compounds have progressed to clinical trials stage and fatty liver was the main side effect observed [30,31]. To overcome this side effect, enterocyte specific inhibitors of MTP (also known as IInd generation MTP inhibitors) are developed [32].

1.4.3 HMG-CoA reductase inhibitors

Since the discovery of statins these compounds are considered as first-line therapy for the treatment of hypercholesterolemia. HMG-CoA reductase inhibitors are a class of drug used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase involved in the rate limiting step of cholesterol synthesis, and ultimately plays a central role in the production of cholesterol in the liver [33]. Statins mainly reduces LDL-C. On the top of statins several other drugs are being used as combination therapy. Rhabdomyolysis, elevation of liver enzymes, creatine kinase etc are some of the common side effects of the statins [34,35]. Increased cholesterol levels are closely associated with cardiovascular diseases (CVD), and statins are used in the prevention of these diseases. Atorvastatin, the most successful drug belongs to this class.

1.5 Diabetes targets

1.5.1 Glucokinase (GK) Activators

The metabolism of dietary glucose has been extensively studied and taught. The primary cellular pathway for deriving energy from glucose is glycolysis in which glucose itself is the initial substrate for the first enzyme of this pathway, glucokinase (GK). GK is actually one of several enzymes of the glycolytic pathway that converts glucose to glucose-6-phosphate. Although all tissues have a hexose kinase for this purpose, GK is expressed in neuronal/neuroendocrine cells, hepatocytes, and pancreatic β-cells and GK is the rate-limiting step in liver and β-cells [36]. Mutations of GK results in severe diabetic syndromes on the other hand gain of function mutations produce

hypoglycemia and hyperinsulinemia [37,38]. Therefore it can be assessed that GK acts as a glucose sensor, upregulating insulin (from pancreas) and promoting glucose storage as glycogen to liver under diabetic conditions [39]. Several small molecule activators of GK (GKA) activity have been discovered and characterized that increases glucose-stimulated insulin secretion (GSIS) [40].

1.5.2 GLP-1 receptor (GLP-1R) agonist

Gastrointestinal hormones called incretins are insulin secretagogues. The Glucagon-like peptide-1 (GLP-1) and Gastric inhibitory peptide (glucose-dependent insulinotropic peptide or GIP) are two main incretin molecules. Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4) [41]. GLP agonists (e.g. Exendin/Exenatide) bind to a membrane GLP receptor. As a result insulin release from the pancreatic beta cells is increased. Exenatide is a polypeptide that was originally isolated from the venom of gila monsters and exhibits 53% identity with GLP-1 [42]. However it is 10 to 100 fold more potent than endogenous GLP-1 owing to its resistance to degradation by dipeptidyl peptidase-IV (DPP-IV) which typically completely degrades incretins within a few minutes of their secretion [43]. Exenatide is administered via subcutaneous injection twice a day and produces significant reduction in HbA1c, fasting plasma glucose (FPG), and postprandial glucose levels. Exenatide achieved HbA1c levels <7% (average decline of 0.8%) in 46% of patients that failed metformin with a mean weight loss of 2.8 kg [44]. The most common side effect is nausea and occasional hypoglycemia. Decrease in gastric motility is mainly responsible for nausea. Exenatide is indicated as adjunctive therapy to

improve glycemic control in DM-II (diabetes mellitus type II) patients who are taking Metformin, a sulfonylurea, a TZD, or a combination thereof, but have not achieved adequate glycemic control [45].

1.5.3 DPP-IV inhibitors

The incretin effect is limited by the action of the serine protease DPP-IV which rapidly cleaves GLP-1 and GIP. This hypothesis was supported by the observation in DPP-IV knockout mice in which GIP and GLP-1 levels were increased and demonstrated enhanced insulin secretion after oral glucose challenge [41]. Theoretical advantage of DPP-IV inhibitors is that they would also potentiate the effects of GIP and other incretins. Sitagliptin was the first DPP-IV inhibitor approved in 2006. Sitagliptin significantly lowers blood glucose and HbA1c when used as monotherapy but these effects were not as potent as Metformin [46].

1.6 Why PPARs ?

Since cardiovascular disease (CVD) and diabetes are the main risk factors of metabolic disorder, synchronized therapies, which concurrently control diabetes and inhibit progression of CV complications will be an attractive therapeutic option in the treatment of metabolic disorder. It is difficult to find out the exact cause and it is equally difficult task to chase any specific molecular mechanisms. In order to develop such new therapeutic agents working on pathway which addresses multiple risk factors would be the effective treatment of metabolic disorder. PPAR has a crucial role to play in lipid metabolism, control glucose homeostasis and also is known to improve insulin sensitivity.

Collectively, the PPARs regulate expression of a diverse set of target genes involved in the control of the above mentioned processes. Considering this effects where therapeutic intervention via PPAR mediated processes may be beneficial, PPARs can be thrilling target to develop a drug for the treatment of metabolic disorder.

1.6.1 PPAR agonists

Type II diabetes begins with resistance to insulin. In such condition higher levels of insulin are needed over the time to suppress hepatic glucose production and stimulate the glucose uptake from muscle and adipose tissue. Though lifestyle intervention is considered as first line of therapy but still most patients with diabetes are unable to control their glucose levels and require pharmacologic therapy. Metformin and Sulfonylureas are predominately used since long time and are proven both safe and effective.

The discovery of the first PPAR date back in 1990's in rodents and named after their property of peroxisome proliferation. PPARs are transducer proteins belonging to the nuclear receptor superfamily and originally identified in Xenopus frogs, the identification of PPARα as the leading regulator of the peroxisomal β-oxidation pathway paved the way for subsequent research efforts into the intriguing and diverse world of this nuclear receptor subtype. Initially, the medical significance of PPARs in human health was unclear. Later in 1999, Pioglitazone a new class of glucose-lowering medication known as the thiazolidinediones (TZDs) which work through activation of peroxisome proliferator activated receptors (PPARs) was approved for the treatment of hyperglycemia. Since then

PPAR members have become clinically validated targets for the treatment of type II diabetes and dyslipidemia.

Last decade and a half witnessed a rapid advancement in biological roles of peroxisome proliferator activated receptors (PPARs) and tremendous efforts towards the development of PPAR ligands for the treatment of metabolic disorder. The peroxisome is a cell organ involved in the removal of hydrogen peroxide, lipid synthesis, cholesterol biosynthesis/catabolism, and fatty acid oxidation [47]. Despite the name, PPAR activation does not result in peroxisome proliferation in humans; rather, PPAR is located in the cellular nucleus and regulates gene activity [48].

Till date three sub-types of PPAR's, classified as PPARα, PPARγ and PPARδ/β and cloned in most of the rodent and mammalian species. These three subtypes share a similar sequence and structural homology despite of that they are involved in significantly different physiological functions. The distinct tissue distribution and physiological roles of PPARs are well documented [49,50].

1.6.2 Protein structure of PPARs

Figure 2 : Schematic representation of the functional domains of PPARs
Domain C is a DNA binding domain, the A/B domain located at in the N-terminus with AF-1 is responsible for phosphorylation, domain D is the concern with docking region for cofactors and a domain E/F is the ligand binding domain (LBD) containing AF-2, which promotes the recruitment of cofactors required for the gene transcription

Like other nuclear receptors, 3D structure PPARs consists of four distinct functional regions called A/B, C, D and E/F (**Figure 2**). All three PPAR isoforms have similar structural and functional features [51]. N-terminal A/B domain

contains a ligand independent activation function 1 (AF-1) responsible for the phosphorylation of PPAR. DNA binding domain (DBD) or C domain is responsible for the binding of PPAR to the peroxisome proliferator response element (PPRE) in the promoter region of target genes [52]. The D site is a docking domain for cofactors. Nuclear receptor (NR) regulation of transcription involves important roles played by numerous coregulator proteins that bind the receptor/DNA complexes. Coregulators also termed as coactivators promotes transcriptional activation by binding the ligand bound form of the receptor and corepressor are involved in repression of transcription by binding the ligand free (apo) receptor . Each PPAR is associated with a corepressor that prevents basal transcription. The E domain or ligand binding domain (LBD) is responsible for ligand specificity and activation of PPAR binding to the PPRE (PPAR response elements), which increases the expression of targeted genes. The structure of LBD of all three isotypes of PPAR is common and resembles that of other nuclear receptors (NRs). Recruitment of PPAR co-factors to assist the gene transcription processes is carried out by the ligand-dependent activation function 2 (AF-2), which is located in the E/F domain [53].

1.6.3 Mechanism of action of PPAR agonists

When receptor encounter a typically small lipophilic synthetic ligand or a natural ligand, it binds and causes conformational changes in the receptor, which dissociates corepressor and recruit coactivator which turn into transcription factors in the nucleus controlling gene expression [54]. The receptors forms

heterodimers with another nuclear receptor, named retinoid X-receptor (RXR) resulting the complex (**Figure 3**).

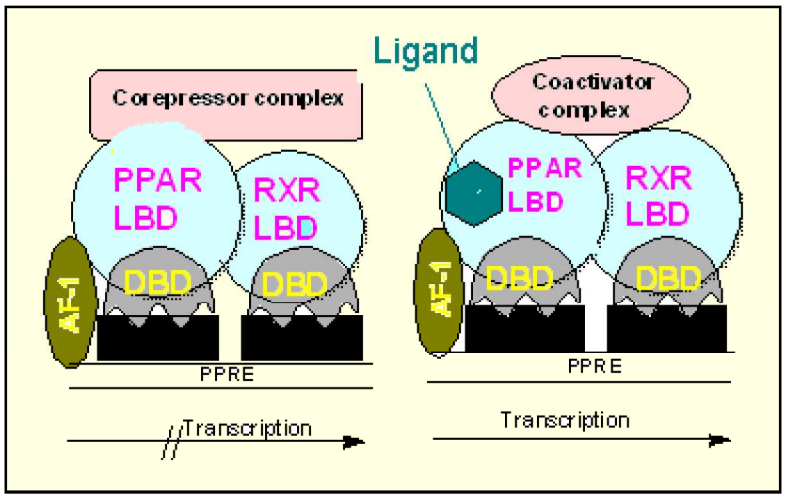


Figure 3 : PPAR's mechanism of gene transcription

Finally this complex binds to PPREs usually as homodimers or heterodimers along with auxiliary proteins which ultimately results in gene transcription. The major hetereodimer partner is retinoid X receptor (RXR) that belongs to the nuclear receptor superfamily and has high homology with the retinoic acid receptor [55].

1.7 PPARα

1.7.1 Receptor structure of PPARα

Peroxisome proliferator activated receptor (PPARα) belongs to the family of nuclear receptors, it is a ligand activated transcriptional factor. PPARα was first cloned from a mouse liver [56] and since then it has been cloned from most of rodent and mammalian species [57-60] including humans [61].

PPARα has a comparable structural organization as other nuclear receptors. As explained earlier receptor consists of four functional modules.

These are the modulator region, the DNA binding domain (DBD), the hinge region, and the ligand binding domain (LBD). The LBD mediates ligand binding and dimerization with RXRα [62]. Although the three PPAR receptors hold similar structural homology, their ligand binding domains (LBDs) exhibit lower homology. The difference in homology of LBD opened a way for possibility of designing selective PPARα ligand.

1.7.2 Tissue distribution of PPARα

PPARα is mainly expressed with high levels in metabolically active tissues like liver, heart, muscle, kidney, skeletal muscle, and brown fat having elevated mitochondrial and peroxisomal fatty acid β-oxidation rates [63,64] (**Figure 4**).

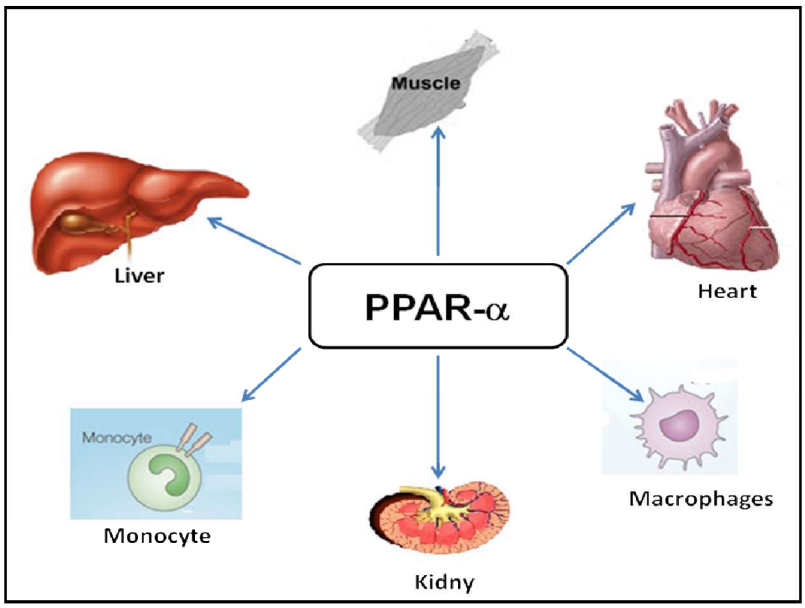


Figure 4 : Tissue distribution PPARα

1.7.3 Mechanism of action, pharmacology and physiology of PPARα

PPARα has a crucial role to play in lipid metabolism. The PPARα subtype is involved in the regulation of genes that control retrograde cholesterol and mainly controls the expression of genes involved in β-oxidation of fatty acids [65]. Specifically, PPARα upregulates fatty acid transport protein (FATP), which facilitates the uptake of long chain fatty acids by the liver. On the other hand activation of PPARα with endogenous or synthetic ligands reduces triglyceride (TG) levels. This is because of the induction of enzymes involved in the β-oxidation pathway in the liver, FFA (free fatty acid) metabolism is shifted from TG synthesis to catabolism. Consequently, the secretion of very low density lipoproteins (VLDL) particles by the liver is strongly reduced [66].

Additionally, PPARα activators decrease plasma triglyceride rich lipoproteins (TRLs) levels by increasing the activity of the enzyme lipoprotein lipase (LPL) [67]. PPARα activators also mediate favorable actions on high-density lipoprotein (HDL) metabolism and, therefore, affect the anti atherogenic reverse cholesterol transport (RCT). RCT is the process in which HDL particles mediate the uptake of cholesterol from lipid laden peripheral cells (including those in the vascular wall) with subsequent delivery back to the liver, where cholesterol is excreted into the bile as bile salts [68].

It was discovered that saturated and unsaturated fatty acids are the primary natural PPARα ligands [59]. Apart from natural ligands, Clofibrate was identified as ligand for PPARα. Apart from Clofibrate, other synthetic compounds can also activate PPARα, including Carbaprostacyclin [69,70] Pirinixic acid (also

known as WY-14643), phthalate ester plasticizers, and the second generation fibrates (e.g. Fenofibrate, Bezafibrate, and Gemfibrozil) [71].

1.7.4 History of PPARα ligands

PPARα activators in the form of fibrates have been used to investigate the influence of their hypolipidemic effects on the incidence of CHD (coronary heart disease) since 1966. Earlier Clofibrate was the only drug available in the treatment of ischaemic heart disease [72]. In the mid 1980s it was discovered that fibrates increase the transcription of peroxisomal fatty acid β-oxidation genes. Since than hypolipidemic fibrate drugs have been used for several years for the treatment of dyslipidemia and they continue to remain the treatment for patients with hypertriglyceridemia. Thereafter second generation fibrates such as Fenofibrate, Bezafibrate (**Figure 5**) were developed even though their mode of action was not deciphered until the discovery of PPARα in the 1990s.

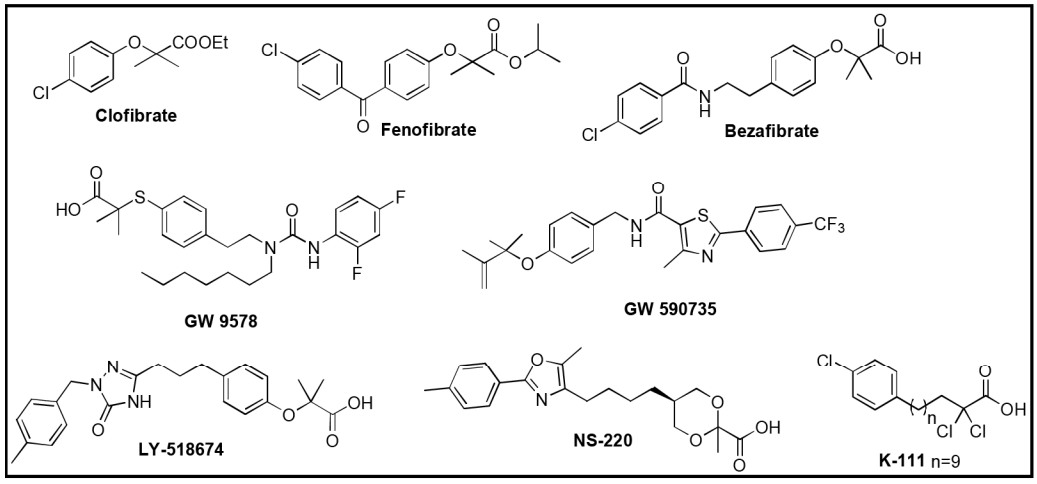


Figure 5 : PPARα agonists

Then slowly over a period of time a novel generation of PPARα agonists were under development which was supported by increased knowledge of PPARα structure and the mechanisms of action of fibrates. However high doses

were required for clinical efficacy (300-1200mg/day) and all compounds had EC_{50} values in the high micromolar range. Hence, uses of fibrates were limited by their weak potency as PPARα agonists. As the present fibrates are relatively weak and nonspecific ligands of PPARα, more specific designed PPARα activators could have increased efficacy and decreased adverse effects, especially in combination with statins. Till late 1990s no potent PPARα agonist was identified by several research groups of pharmaceutical industry or academia.

Further research towards the discovery of novel PPARα agonists has led to compounds with chemical and structural diversity from those of the fibrate group. Glaxo SmithKline identified a urea derivative GW-9578 (**Figure 5**) as potent and selective PPARα agonist. Studies showed that this compound, in addition to its lipid lowering activity prevented weight gain and the development of hyperinsulinemia in insulin resistant rats [73]. Lilly identified a LY-518674 (**Figure 5**) (EC_{50} of 42 nM) having 2,4-dihydo-3H-1,2,4 triazole-3-one (triazolone) core in the lipophilic tail part and fibric acid as acidic head. This compound was advanced for clinical studies [74]. However clinical results were disappointing as the compound displayed potent hypolipidemic activity and good bioavailability but efficacy was comparable to the weak PPARα agonist Fenofibrate in humans. Subsequently a GW-590735 (**Figure 5**) (EC_{50} of 4 nM) was discovered from novel series of substituted 2-[(4-aminomethyl)phenoxy]-2-methylpropionic acids through modification and optimization of the selective PPARβ/δ agonist GW-501516 (**Figure 8**) as a potent and selective PPARα agonist [75]. Clinical trials displayed reduced TG and apoB100 levels in patients. Progressing further K-111

[76] was identified as highly selective PPARα agonist. This compound was discontinued from phase-II clinical trials and does negligible cross reactivity against a panel of human nuclear receptors PPARγ and PPARδ even at high doses. Nippon developed a compound NS-220 (**Figure 5**) [77] as highly potent and selective PPARα agonist. This compound displayed potent hypolipidemic and anti-diabetic effects in animal models. Unfortunately the development of this compound has been terminated from phase-II for unknown reasons [78]. In 2010 discovery of an oxybenzylglycine based PPARα selective agonist was reported by Li et al [79].

Over a 15 year period, significant research effort provided many compounds featuring nanomolar PPARα potency (**Table 6**).

Table 6 : Transactivation profile of PPARα agonists

Compound	**Company**	**hPPARα EC_{50} (μM)**	**hPPARγ EC_{50}(μM)**	**Ref**
Clofibrate	Astrazeneca Wyth	55	500	[80]
Bezafibrate	Norwich Eaton Roche	50	60	[80]
Fenofibrate	Abbot fournier	30	300	[80]
GW-9578	Glaxo Smithkline	0.05	1.0	[80]
LY-518674	Eli Lilly	0.042	Inactive	[81]
GW-590735	Glaxo Smithkline	0.004	10	[75]
NS-220	Nippon Shinyaku	0.019	9.6	[76]

Translation of the *in vitro* potency was investigated at various stages of preclinical and clinical development. However, it appears that the progress made by these promising PPARα specific modulators has been terminated mainly due

to clinically observed safety issues and in some cases they were found to be less efficacious. As a result, a market still remains for the suitable potent PPARα agonists. A new generation of PPARα targeting treatments may result in an acceptable alternative as the medical need for the treatment of this complex disease.

1.8 PPARγ

1.8.1 Receptor structure of PPARγ

As mentioned earlier thiazolidinedione class of compounds having antidiabetic property were the first agonists with high affinity for PPARγ. Research on PPARγ is the most extensively investigated of the three PPAR subtypes so far. Like PPARα, PPARγ is also ligand activated transcriptional factor that belongs to the family of nuclear receptors. The receptor consists of DNA binding domain (DBD), the hinge region, and the ligand binding domain (LBD). Sequence comparison of their DNA binding domains (DBD) across variety of species shows that they are highly conserved with respect to PPARα. However the ligand-binding domains (LBD) have a slightly lower level of conservation across the subtypes. DNA binding domain of PPARγ has 83% identity with respect to PPARα. On the other hand ligand binding domain of PPARγ has only 68% identity [82-84].

1.8.2 Tissue distribution of PPARγ

In terms of tissue distribution PPARγ differs from PPARα, it is mainly expressed in adipose tissue with lower expression detected in a wide range of differing tissues like spleen, intestine, pancreas (**Figure 6**), colon, kidney,

skeletal muscle and macrophages [85]. Prostaglandins, polysaturated fatty acids, and leukotriene B4 are natural ligands for PPARγ.

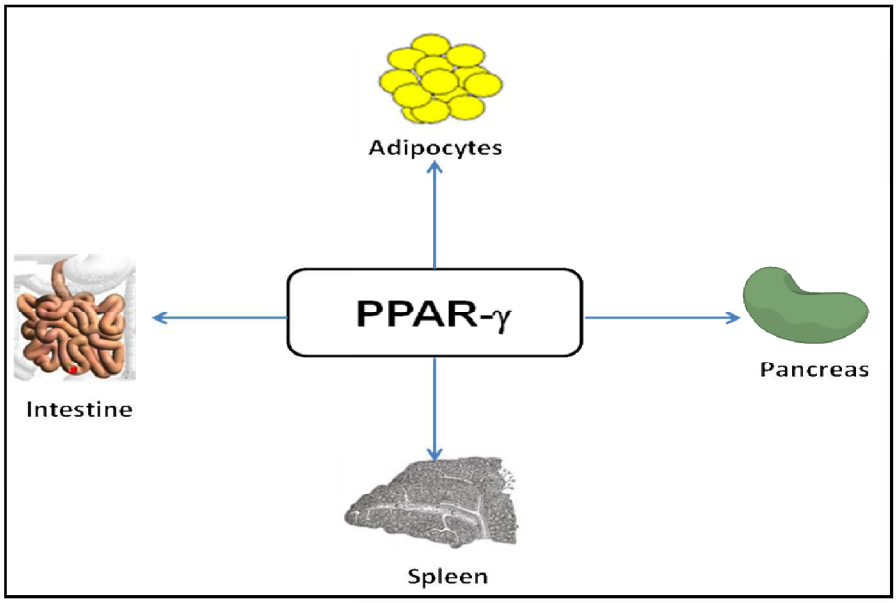


Figure 6 : Tissue distribution PPARγ

1.8.3 Mechanism of action PPARγ

Activation of PPARγ is known to improve insulin sensitivity mainly and control glucose homeostasis [86]. PPARγ agonists stimulate adipocyte differentiation, improve insulin sensitivity, reduce hyper glycaemia, and have shown experimental pleiotropic prevention of atherosclerosis [87]. PPARγ activation results in transcription of insulin-sensitive genes that regulate both carbohydrate and lipid metabolisms by increasing the uptake of both fatty acid and glucose [48] despite the fact that the PPARγ receptor is absent in skeletal muscle [47]. Glucose transport into muscle and adipose tissue is increased due to an increase in the number of glucose transporters and adiponectin (which increases insulin sensitivity by increasing muscle uptake of insulin and fatty acid oxidation). Hepatic insulin sensitivity is increased whereas hepatic glucose output

is decreased resulting in less circulating free fatty acids and less free fatty acids available to the liver for gluconeogenesis [Randle cycle] [88]. As a result, insulin sensitivity in peripheral tissues is increased whereas hepatic glucose production is decreased [89].

1.8.4 History of PPARγ ligands

PPARγ is the most studied among the other PPAR receptors. There are several PPARγ agonist thoroughly studied. In 1980's analogue of Clofibrate (2-chloro-3-phenylpropanoic acid ethyl ester) AL-294 (**Figure 7**) was identified by Takeda Pharmaceutical. This compound had the ability to effectively lower plasma glucose as well as triglycerides. Moving on from this medicinal chemistry efforts towards building Structure Activity Relationships (SAR) of analogues led to the discovery of Ciglitazone (**Figure 7**) [90,91]. Clinical development of Ciglitazone was ceased mainly because of insufficient efficacy. In 1988, Troglitazone (**Figure 7**) evoked as antidiabetic agent as it decrease insulin resistance by both increasing insulin stimulated glucose utilization and reducing hepatic gluconeogenesis. In 1995, scientists at GSK demonstrated that TZDs are high affinity agonist ligands for PPARγ [92]. These classes of compounds are commonly called as glitazones. Troglitazone (Rezulin) was the first of the TZD class of oral anti-diabetic agents to be launched in the United States in 1997. Later it was withdrawn worldwide in 2000 due to associated liver toxicity [93]. Progressing in the same direction further TZD drug discovery efforts also lead to the discovery of two other blockbuster compounds of thiazolidinedione class Rosiglitazone and Pioglitazone (**Figure 7**). Both of these compounds showed

positive effects on the glucose and lipid profiles in patients with type II diabetes, and were marketed as PPARγ agonists. However these drugs were not devoid of side effects. Treatment with these drugs causes weight gain and edema [94,95].

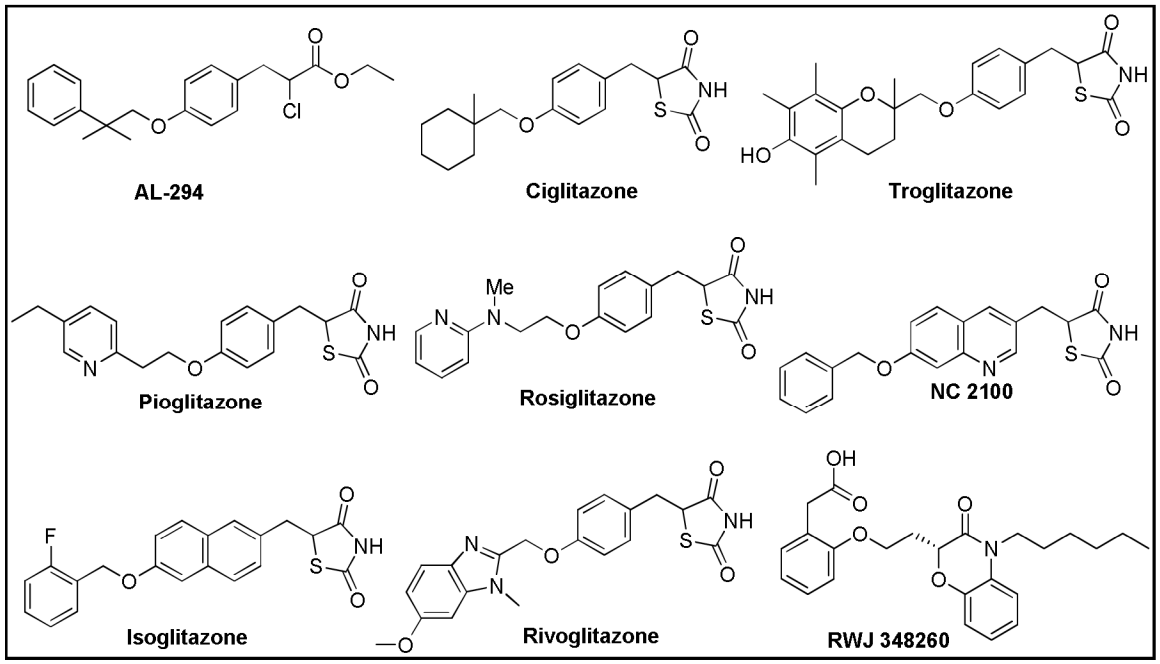


Figure 7 : PPARγ agonists

Further SAR development yielded another molecule Isoglitazone which is a structural homolog of Rosiglitazone, binds to PPARγ with approximately 10% affinity compared Rosiglitazone, it exhibited a more potent antidiabetic effect in animal experiments. Studies indicated Isoglitazone activity on PPARγ is dependent on its tissue distribution, with full to partial agonism display dependent on its localized effects. NC-2100, a structurally similar TZD to Isoglitazone (**Figure 7**) having EC_{50} values 30-50 fold higher than other comparable TZDs, also displays specific activity on PPARγ dependent on its tissue localisation. The results suggested TZD induced activation of PPARγ does not directly correlate with antidiabetic action. Another molecule Rivoglitazone (**Figure 7**) demonstrated

superior ADME profile efficacy in rats when compared to Rosiglitazone and Pioglitazone. By 2010 Rivoglitazone had entered advanced clinical trials [96]. Glitazones exert antidiabetic effects through insulin sensitization [72,82]. However treatment with glitazones is associated with adverse effects such as weight gain and edema. Discovery of several other selective PPARγ agonists non TZD derived molecules has also been explored. RWJ-348260 [97] is a novel non TZD PPARγ agonist (**Figure 7**).

Table 7 : Transactivation profile of PPARγ agonists

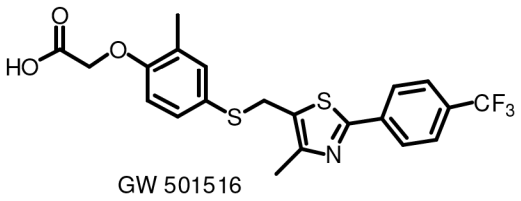
Compound	**Company**	**hPPARα EC_{50} (μM)**	**hPPARγ EC_{50}(μM)**	**Ref**
AL-294	Takeda			
Ciglitazone	Takeda			
Troglitazone	Daiichi Sankyo	IA	0.55	[80]
Rosiglitazone	Glaxo Smithkline	IA	0.043	[80]
Pioglitazone	Takeda	IA	0.58	[80]
NC-2100	Nippon			
Isoglitazone	Mitsubishi	ND	8	[98]
Rivoglitazone	Daiichi Sankyo	IA	0.005	[96]

IA- Inactive, ND – Not detected

in vitro potency of some of the PPARγ agonist is given in the **Table 7**. Like PPARα still there is possibility exist for the betterment of PPARγ agonist**.**

1.9 PPARδ

PPARδ also known as PPARβ, is ubiquitously expressed. It promotes fatty acid metabolism and suppresses macrophage derived inflammation [99]. Compounds such as GW-501516 (**Figure 8**), GW-610742 and GW-0742X are shown to have high selectivity to PPARδ [100].



GW 501516

Figure 8 : PPARδ agonist

Reduced cholesterol absorption upon PPARδ/β activation coincides with decreased intestinal expression of NPC1L1 [101]. Studies have demonstrated the role of PPARδ in ameliorating cardiovascular complications [100,102]. PPARδ/β agonists have been noted to reduce the expression of inflammatory mediators and adhesion molecules, suggesting their potential role in attenuating atherogenesis [100]. PPARα and PPARδ/β activators inhibit cytokine induced nuclear translocation of NF-kappaB and expression of VCAM-1 in EAhy926 endothelial cells [103].

1.10 Concept of dual agonist of PPARα/γ

As stated above PPARα plays crucial role in lipid metabolism. It regulates genes involved in fatty acid oxidation, It also dose the lowering of triglyceride (TG). Another important role of PPARα is that it is involved in lowering of cholesterol by uptake of cholesterol which is mediated through HDL. On the other hand PPARγ improves the insulin sensitivity, controls the glucose homeostasis thereby it reduce hyperglycemia. Combining all together targeting both PPARα and PPARγ simultaneously could produce synergistic anti diabetic and cardio protective effects, which means that concept of dual PPARα/γ agonists could regulate different metabolic pathways. However, It is still unclear what ratio of PPARα and PPARγ activity is required to maintain this balance which ultimately

can be translated as optimal efficacy in humans. Another question to be answered was by activation of both receptors what will be effect on both efficacy and toxicity? Fortunately researchers have successfully identified several PPARα/γ dual agonists that demonstrated both glucose and lipid-lowering efficacy in animal models that are comparable to effects obtained with selective PPARα and PPARγ agonists. Till date, a number of PPARα/γ dual agonists with structural diversity as well as diversity in ratio of PPARα/γ are reported. Many of them have advanced up to clinical trials, unfortunately majority of these dual agonists were dropped. History of last decade has proved that dual PPARα/γ agonists hold promise in patients with T2DM and cardiovascular risk or metabolic syndrome.

1.10.1 History of PPARα/γ dual agonist

The first PPARα/γ dual agonist to be reported was KRP-297 (MK-0767) [104]. KRP-297 (**Figure 9**) was thiazolidin class of compound and was discontinued following instances of carcinogenicity. A number of diverse PPARα/γ dual agonist has been evaluated and progressed for clinical trials. E.g., Tesaglitazar, Naveglitazar, Ragaglitazar, Farglitazar, Imiglitazar, JTT-501, Muraglitazar (**Figure 9**) and the list may go on.

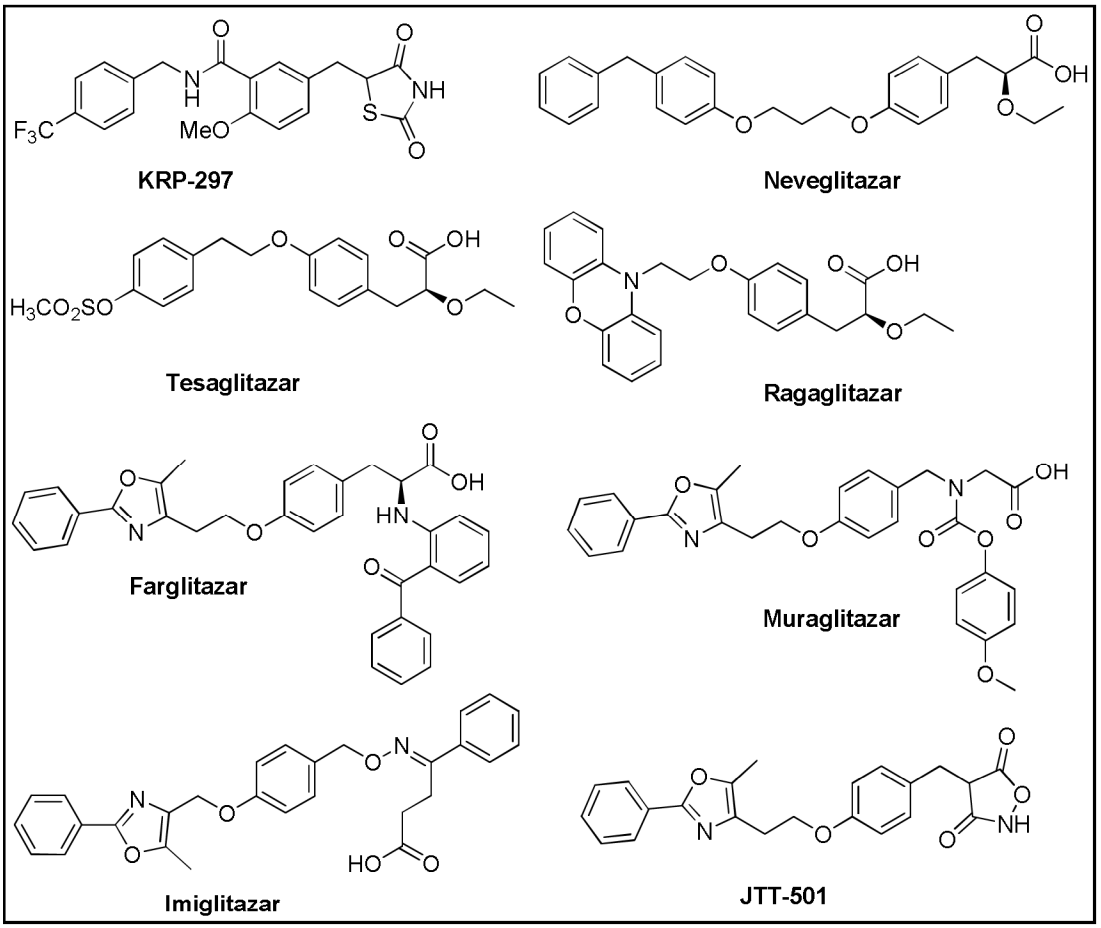


Figure 9 : PPARα/γ dual agonists.

From KRP-297 to till date Muraglitazar (BMS-298585) is the first PPARα/γ dual agonist reviewed by the FDA advisory committee. This non TZD oxybenzylglycine analogue Muraglitazar was reported to exhibit potent in vitro activities against both PPARα and PPARγ subtypes and exert excellent glucose and lipid lowering effects in rodent models [105]. A longer study of 24-104 weeks resulted in a significantly increased risk in the composite end point of death, myocardial infarction, stroke, transient ischemic attack, and congestive heart failure [106] leading to termination of further development of Muraglitazar. In between many structurally diversified compounds were discovered as PPARα/γ dual agonists. They were effective in animal models, however, further

development was discontinued due to various toxicological reasons or a risk-benefit assessment [107]. These include Farglitazar, MK-0676, Tesaglitazar (AZ-242) [108] Ragaglitazar (DRF-2725) [109], Imiglitazar (TAK-559) [110]. There are only a few PPARα/γ dual agonists now left in the development pipelines.

Table 8 : Dual PPARα/γ agonists efficacy and comparison [111]

Name	Company (Licence)	Status	TC	LDL	HDL	TG	HbA1C	FPG	FPI
Muraglitazar (BMS-298585)	Bristol-Myers	FDA Approval / Suspended	↓	↓	↑	↓	↓	↓	↓
Pargluva Tesaglitazar (AZ-242) Galida	AstraZeneca	Suspended after Phase III	↓	↓	↑	↓		↓	↓
Ragaglitazar (DRF-2725)	DRF (Novonordisk)	Suspended During Phase III	↓		↑	↓	↓	↓	↓
Imiglitazar TAK-559	Takeda	Suspended During Phase III	↓	↓	↑	↓	↓	↓	↓
KRP-297 MK-0767	Kyotin (Merck)	Suspended During Phase III	↓	↓	↑	↓	↓	↓	↓

↓ : indicates decrease, ↑ : indicates increase

The first dual agonist Farglitazar which is a potent PPARγ agonist with a moderate PPARα activation was dropped in an advanced stage due to the emergence of edema. Among several investigational compounds that have been discovered in the laboratory, glitazar group (Muraglitazar, Tesaglitazar, Ragaglitazar) reached phase III clinical trials. Adverse events with PPARα/γ dual agonists in experimental models and/or clinical trials included edema, weight gain, heart failure, hypertension, nasopharyngitis, arthralgia, headache, upper respiratory tract infections, gastrointestinal discomfort, pain, bone marrow

suppression, carcinogenesis, and renal failure [54]. In 2003, two glitazar molecules Ragaglitazar and MK-0676 were discontinued from late clinical development due to carcinogencity in rodent toxicity models and elevated serum creatinine & associated decrease in glomular filtration rate respectively [112]. The only dual agonist that has been advanced to NDA filing was Muraglitazar. Later when It was expected to became a blockbuster molecule from this class, it was dropped due to the higher incidence of edema, heart failure and cardiovascular deaths amongst the patients taking Muraglitazar compared with those receiving placebo or treated with Pioglitazone. These facts though appears to be discouraging the scientists continued the development of dual PPAR agonists with expectation that safer dual PPAR agonists can be develop by optimizing structural features.

Looking at the landscape of PPAR dual agonist our first aim was to search for available structures and *in vitro* activities of PPAR agonists to move further for designing novel compounds. Transactivation profile of many PPAR agonists are mentioned in the **Table 9**. Unfortunately majority of these dual agonists were dropped, as they had demonstrated appreciable dose-limiting side effects.

Since each compound showed different kind of side effect profile the ray of hope is that, reason for discontinuation of development could be compound specific [87,113]. It was thought that safety liabilities could be related to chemical structures. Hence there is a possible opportunity for successful development of new generation compounds of this class [114].

Table : 9. Transactivation profile of PPAR agonists

Compound	Company	hPPARα EC_{50} (μM)	hPPARγ EC_{50}(μM)	Ref
KRP-297	Kyorin	0.85	0.083	[49]
Tesaglitazar	Astrazeneca	1.7	0.25	[115]
Naveglitazar	Eli Lilly	2.86	0.36	[116]
Ragaglitazar	Dr.Reddy's	3.2	0.57	[109]
Farglitazar	Glaxo Smithkline	0.45	0.0003	[117]
Imiglitazar	Takeda	0.067	0.031	[118]
Muraglitazar	BMS	0.32	0.11	[105]

As it appears from the above table that most potent agonist has potency near to 1 nM. We aimed to have agonist having potency less than 1 nM range. We hypothesized that administration of very low dose of compounds would probably provide practical approach to minimize some of the adverse effects, as adverse effects exerted by this class of compounds are dose dependent. The reasons for the failure of all these compounds are quite different from each other. So there is a hope of developing new compounds with structural modifications.

Our goal obviously is to discover the compounds with very high *in vitro* potency that translates to *in vivo* efficacy to increase margin of safety in order to develop efficacious and relatively safer PPAR agonists.

1.11 References

1. Alberti KG, Zimmet P, Shaw J. **The metabolic syndrome-a new worldwide definition.** *Lancet* (**2005**) 366(9491):1059-1062.
2. Alberti KG, Zimmet P, Shaw J. **Metabolic syndrome-a new world-wide definition. A consensus statement from the international diabetes federation.** *Diabetic Medicine : A Journal of the British Diabetic Association* (**2006**) 23(5):469-480.
3. Vague J. *La Presse Medicale* (**1947**) 55(30):339.
4. Reaven GM. **Banting lecture 1988. Role of insulin resistance in human disease.** *Diabetes* (**1988**) 37(12):1595-1607.
5. Akiyama TE, Meinke PT, Berger JP. **PPAR ligands: Potential therapies for metabolic syndrome.** *Current Diabetes Reports* (**2005**) 5(1):45-52.
6. Shearer BG, Hoekstra WJ. **Recent advances in peroxisome proliferator-activated receptor science.** *Current Medicinal Chemistry* (**2003**) 10(4):267-280.
7. Verges B. **Clinical interest of PPARs ligands.** *Diabetes & Metabolism* (**2004**) 30(1):7-12.
8. Rosamond WD, Chambless LE, Folsom AR, Cooper LS, Conwill DE, Clegg L, Wang CH, Heiss G. **Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994.** *The New England Journal of Medicine* (**1998**) 339(13):861-867.
9. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. **Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The bogalusa heart study.** *The New England Journal of Medicine* (**1998**) 338(23):1650-1656.
10. Ravikiran M, Bhansali A, Ravikumar P, Bhansali S, Dutta P, Thakur JS, Sachdeva N, Bhadada S, Walia R. **Prevalence and risk factors of metabolic syndrome among asian indians: A community survey.** *Diabetes Research and Clinical Practice* (**2010**) 89(2):181-188.

11. Hossain P, Kawar B, El Nahas M. **Obesity and diabetes in the developing world-a growing challenge.** *The New England Journal of Medicine* (**2007**) 356(3):213-215.

12. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, Frick MH. **Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the helsinki heart study. Implications for treatment.** *Circulation* (**1992**) 85(1):37-45.

13. Cullen P, Schulte H, Assmann G. **The munster heart study (procam): Total mortality in middle-aged men is increased at low total and LDL cholesterol concentrations in smokers but not in nonsmokers.** *Circulation* (**1997**) 96(7):2128-2136.

14. Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, Buring JE. **Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction.** *Circulation* (**1997**) 96(8):2520-2525.

15. Kannel WB. **Risk stratification of dyslipidemia: Insights from the framingham study.** *Current Medicinal Chemistry Cardiovascular and Hematological Agents* (**2005**) 3(3):187-193.

16. Millan J, Pinto X, Munoz A, Zuniga M, Rubies-Prat J, Pallardo LF, Masana L, Mangas A, Hernandez-Mijares A, Gonzalez-Santos P, Ascaso JF *et al.* **Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention.** *Vascular Health and Risk Management* (**2009**) 5(757-765).

17. Miller NE, Hammett F, Saltissi S, Rao S, van Zeller H, Coltart J, Lewis B. **Relation of angiographically defined coronary artery disease to plasma lipoprotein subfractions and apolipoproteins.** *Br Med J (Clin Res Ed)* (**1981**) 282(6278):1741-1744.

18. Picardo M, Massey JB, Kuhn DE, Gotto AM, Jr., Gianturco SH, Pownall HJ. **Partially reassembled high density lipoproteins. Effects on cholesterol flux, synthesis, and esterification in normal human skin fibroblasts.** *Arteriosclerosis* (**1986**) 6(4):434-441.

19. Mackinnon M, Savage J, Wishart R, Barter P. **Metabolism of high density lipoproteins by the perfused rabbit liver.** *The Journal of Biological Chemistry* (**1986**) 261(6):2548-2552.

20. Ross R, Glomset JA. **The pathogenesis of atherosclerosis (first of two parts).** *The New England Journal of Medicine* (**1976**) 295(7):369-377.

21. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. **A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction.** *The New England Journal of Medicine* (**1991**) 325(6):373-381.

22. James WP. **The epidemiology of obesity: The size of the problem.** *Journal of Internal Medicine* (**2008**) 263(4):336-352.

23. Janero DR, Makriyannis A. **Cannabinoid receptor antagonists: Pharmacological opportunities, clinical experience, and translational prognosis.** *Expert Opinion on Emerging Drugs* (**2009**) 14(1):43-65.

24. Crowley VE, Yeo GS, O'Rahilly S. **Obesity therapy: Altering the energy intake-and-expenditure balance sheet.** *Nature Reviews Drug Discovery* (**2002**) 1(4):276-286.

25. Steinmetz A, Fenselau S, Schrezenmeir J. **Treatment of dyslipoproteinemia in the metabolic syndrome.** *Experimental and Clinical Endocrinology & Diabetes : Official Journal, German Society of Endocrinology [and] German Diabetes Association* (**2001**) 109(4):S548-559.

26. Kahn R, Buse J, Ferrannini E, Stern M. **The metabolic syndrome: Time for a critical appraisal: Joint statement from the american diabetes association and the european association for the study of diabetes.** *Diabetes Care* (**2005**) 28(9):2289-2304.

27. Gurfinkel R, Joy TR. **Anacetrapib: Hope for CETP inhibitors?** *Cardiovascular Therapeutics* (**2011**) 29(5):327-339.

28. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL *et al*. **Effects of Torcetrapib in patients at high risk for coronary events.** *The New England Journal of Medicine* (**2007**) 357(21):2109-2122.

29. Williams SJ, Best JD. **Novel microsomal triglyceride transfer protein inhibitors.** *Expert Opinion on Therapeutic Patents* (**2003**) 13(4):479-488.

30. Chang G, Ruggeri RB, Harwood HJ, Jr. **Microsomal triglyceride transfer protein (MTP) inhibitors: Discovery of clinically active inhibitors using high-throughput screening and parallel synthesis paradigms.** *Current Opinion in Drug Discovery & Development* (**2002**) 5(4):562-570.

31. Bays H, Stein EA. **Pharmacotherapy for dyslipidaemia--current therapies and future agents.** *Expert Opinion on Pharmacotherapy* (**2003**) 4(11):1901-1938.

32. Raval SK, Raval PS, Jain MR. **Emerging therapies for dyslipidemia: Known knowns and known unknowns of MTP inhibitors.** *Recent Patents on Endocrine, Metabolic & Immune Drug Discovery* (**2012**) 6(1):24-29.

33. Farmer JA. **Aggressive lipid therapy in the statin era.** *Progress in Cardiovascular Diseases* (**1998**) 41(2):71-94.

34. Harper CR, Jacobson TA. **The broad spectrum of statin myopathy: From myalgia to rhabdomyolysis.** *Current Opinion in Lipidology* (**2007**) 18(4):401-408.

35. Kiortsis DN, Filippatos TD, Mikhailidis DP, Elisaf MS, Liberopoulos EN. **Statin-associated adverse effects beyond muscle and liver toxicity.** *Atherosclerosis* (**2007**) 195(1):7-16.

36. Matschinsky FM, Magnuson MA, Zelent D, Jetton TL, Doliba N, Han Y, Taub R, Grimsby J. **The network of glucokinase-expressing cells in glucose homeostasis and the potential of glucokinase activators for diabetes therapy.** *Diabetes* (**2006**) 55(1):1-12.

37. Christesen HB, Jacobsen BB, Odili S, Buettger C, Cuesta-Munoz A, Hansen T, Brusgaard K, Massa O, Magnuson MΛ, Shiota C, Matschinsky FM *et al.* **The second activating glucokinase mutation (A456V): Implications for glucose homeostasis and diabetes therapy.** *Diabetes* (**2002**) 51(4):1240-1246.

38. Glaser B, Kesavan P, Heyman M, Davis E, Cuesta A, Buchs A, Stanley CA, Thornton PS, Permutt MA, Matschinsky FM, Herold KC. **Familial hyperinsulinism caused by an activating glucokinase mutation.** *The New England Journal of Medicine* (**1998**) 338(4):226-230.

39. Gloyn AL. **Glucokinase (GCK) mutations in hyper- and hypoglycemia: Maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemia of infancy.** *Human Mutation* (**2003**) 22(5):353-362.

40. Coghlan M, Leighton B. **Glucokinase activators in diabetes management.** *Expert Opinion on Investigational Drugs* (**2008**) 17(2):145-167.

41. Marguet D, Baggio L, Kobayashi T, Bernard AM, Pierres M, Nielsen PF, Ribel U, Watanabe T, Drucker DJ, Wagtmann N. **Enhanced insulin secretion and improved glucose tolerance in mice lacking CD26.** *Proceedings of the National Academy of Sciences of the United States of America* (**2000**) 97(12):6874-6879.

42. Gallwitz B. **Glucagon-like peptide-1-based therapies for the treatment of type 2 diabetes mellitus.** *Treatments in Endocrinology* (**2005**) 4(6):361-370.

43. Young AA, Gedulin BR, Bhavsar S, Bodkin N, Jodka C, Hansen B, Denaro M. **Glucose-lowering and insulin-sensitizing actions of exendin-4: Studies in obese diabetic (ob/ob, db/db) mice, diabetic fatty zucker rats, and diabetic rhesus monkeys (macaca mulatta).** *Diabetes* (**1999**) 48(5):1026-1034.

44. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim D, Baron AD. **Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes.** *Diabetes Care* (**2003**) 26(8):2370-2377.

45. Triplitt C, McGill JB, Porte D, Jr., Conner CS. **The changing landscape of type 2 diabetes: The role of incretin-based therapies in managed care outcomes.** *Journal of Managed Care Pharmacy : JMCP* (**2007**) 13(9 Suppl C):S2-16; quiz S17.

46. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. **Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: A randomized, double-blind, non-inferiority trial.** *Diabetes, Obesity & Metabolism* (**2007**) 9(2):194-205.

47. Vamecq J, Latruffe N. **Medical significance of peroxisome proliferator-activated receptors.** *Lancet* (**1999**) 354(9173):141-148.

48. Campbell IW. **The clinical significance of PPAR gamma agonism.** *Current Molecular Medicine* (**2005**) 5(3):349-363.

49. Willson TM, Brown PJ, Sternbach DD, Henke BR. **The PPARs: From orphan receptors to drug discovery.** *Journal of Medicinal Chemistry* (**2000**) 43(4):527-550.

50. Gani OA. **Are fish oil omega-3 long-chain fatty acids and their derivatives peroxisome proliferator-activated receptor agonists?** *Cardiovascular Diabetology* (**2008**) 7(6.

51. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schutz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, Evans RM. **The nuclear receptor superfamily: The second decade.** *Cell* (**1995**) 83(6):835-839.

52. Hillier TA, Fagot-Campagna A, Eschwege E, Vol S, Cailleau M, Balkau B. **Weight change and changes in the metabolic syndrome as the french population moves towards overweight: The D.E.S.I.R. Cohort.** *International Journal of Epidemiology* (**2006**) 35(1):190-196.

53. Kliewer SA, Umesono K, Noonan DJ, Heyman RA, Evans RM. **Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors.** *Nature* (**1992**) 358(6389):771-774.

54. Chang F, Jaber LA, Berlie HD, O'Connell MB. **Evolution of peroxisome proliferator-activated receptor agonists.** *The Annals of Pharmacotherapy* (**2007**) 41(6):973-983.

55. Keller H, Dreyer C, Medin J, Mahfoudi A, Ozato K, Wahli W. **Fatty acids and retinoids control lipid metabolism through activation of peroxisome proliferator-activated receptor-retinoid x receptor heterodimers.** *Proceedings of the National Academy of Sciences of the United States of America* (**1993**) 90(6):2160-2164.

56. Zhu Y, Qi C, Jain S, Rao MS, Reddy JK. **Isolation and characterization of pbp, a protein that interacts with peroxisome proliferator-activated receptor.** *The Journal of Biological Chemistry* (**1997**) 272(41):25500-25506.

57. Bell AR, Savory R, Horley NJ, Choudhury AI, Dickins M, Gray TJ, Salter AM, Bell DR. **Molecular basis of non-responsiveness to peroxisome proliferators:**

The guinea-pig PPARalpha is functional and mediates peroxisome proliferator-induced hypolipidaemia. *The Biochemical Journal* (**1998**) 332 (Pt 3)(689-693.

58. Dreyer C, Krey G, Keller H, Givel F, Helftenbein G, Wahli W. **Control of the peroxisomal beta-oxidation pathway by a novel family of nuclear hormone receptors.** *Cell* (**1992**) 68(5):879-887.

59. Gottlicher M, Widmark E, Li Q, Gustafsson JA. **Fatty acids activate a chimera of the clofibric acid-activated receptor and the glucocorticoid receptor.** *Proceedings of the National Academy of Sciences of the United States of America* (**1992**) 89(10):4653-4657.

60. Issemann I, Green S: **Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators.** *Nature* (**1990**) 347(6294):645-650.

61. Sher T, Yi HF, McBride OW, Gonzalez FJ. **CDNA cloning, chromosomal mapping, and functional characterization of the human peroxisome proliferator activated receptor.** *Biochemistry* (**1993**) 32(21):5598-5604.

62. Giguere V. **Orphan nuclear receptors: From gene to function.** *Endocrine Reviews* (**1999**) 20(5):689-725.

63. Braissant O, Foufelle F, Scotto C, Dauca M, Wahli W. **Differential expression of peroxisome proliferator-activated receptors (PPARs): Tissue distribution of ppar-α, -β, and -γ in the adult rat.** *Endocrinology* (**1996**) 137(1):354-366.

64. Auboeuf D, Rieusset J, Fajas L, Vallier P, Frering V, Riou JP, Staels B, Auwerx J, Laville M, Vidal H. **Tissue distribution and quantification of the expression of mrnas of peroxisome proliferator-activated receptors and liver x receptor-alpha in humans: No alteration in adipose tissue of obese and niddm patients.** *Diabetes* (**1997**) 46(8):1319-1327.

65. van Raalte DH, Li M, Pritchard PH, Wasan KM. **Peroxisome proliferator-activated receptor (PPAR)-alpha: A pharmacological target with a promising future.** *Pharmaceutical Research* (**2004**) 21(9):1531-1538.

66. Schoonjans K, Staels B, Auwerx J. **Role of the peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression.** *Journal of Lipid Research* (**1996**) 37(5):907-925.

67. Heller F, Harvengt C. **Effects of Clofibrate, Bezafibrate, Fenofibrate and probucol on plasma lipolytic enzymes in normolipaemic subjects.** *European Journal of Clinical Pharmacology* (**1983**) 25(1):57-63.

68. Fielding CJ, Fielding PE. **Molecular physiology of reverse cholesterol transport.** *Journal of Lipid Research* (**1995**) 36(2):211-228.

69. Hertz R, Berman I, Keppler D, Bar-Tana J. **Activation of gene transcription by prostacyclin analogues is mediated by the peroxisome-proliferators-activated receptor (PPAR).** *European Journal of Biochemistry / FEBS* (**1996**) 235(1-2):242-247.

70. Lehmann JM, Lenhard JM, Oliver BB, Ringold GM, Kliewer SA. **Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs.** *The Journal of Biological Chemistry* (**1997**) 272(6):3406-3410.

71. Gonzalez FJ, Peters JM, Cattley RC. **Mechanism of action of the nongenotoxic peroxisome proliferators: Role of the peroxisome proliferator-activator receptor alpha.** *Journal of the National Cancer Institute* (**1998**) 90(22):1702-1709.

72. **Trial of Clofibrate in the treatment of ischaemic heart disease. Five-year study by a group of physicians of the newcastle upon tyne region.** *British Medical Journal* (**1971**) 4(5790):767-775.

73. Brown PJ, Winegar DA, Plunket KD, Moore LB, Lewis MC, Wilson JG, Sundseth SS, Koble CS, Wu Z, Chapman JM, Lehmann JM *et al.* **A ureido-thioisobutyric acid (GW9578) is a subtype-selective PPARalpha agonist with potent lipid-lowering activity.** *Journal of Medicinal Chemistry* (**1999**) 42(19):3785-3788.

74. Xu Y, Mayhugh D, Saeed A, Wang X, Thompson RC, Dominianni SJ, Kauffman RF, Singh J, Bean JS, Bensch WR, Barr RJ *et al.* **Design and synthesis of a potent and selective triazolone-based peroxisome proliferator-activated receptor alpha agonist.** *Journal of Medicinal Chemistry* (**2003**) 46(24):5121-5124.

75. Sierra ML, Beneton V, Boullay AB, Boyer T, Brewster AG, Donche F, Forest MC, Fouchet MH, Gellibert FJ, Grillot DA, Lambert MH *et al*. **Substituted 2-[(4-aminomethyl)phenoxy]-2-methylpropionic acid PPARalpha agonists. 1. Discovery of a novel series of potent HDLc raising agents.** *Journal of Medicinal Chemistry* (**2007**) 50(4):685-695.

76. Schafer SA, Hansen BC, Volkl A, Fahimi HD, Pill J. **Biochemical and morphological effects of K-111, a peroxisome proliferator-activated receptor (PPAR)alpha activator, in non-human primates.** *Biochemical Pharmacology* (**2004**) 68(2):239-251.

77. Kuwabara K, Murakami K, Todo M, Aoki T, Asaki T, Murai M, Yano J. **A novel selective peroxisome proliferator-activated receptor alpha agonist, 2-methyl-c-5-[4-[5-methyl-2-(4-methylphenyl)-4-oxazolyl]butyl]-1,3-dioxane-r-2-ca rboxylic acid (NS-220), potently decreases plasma triglyceride and glucose levels and modifies lipoprotein profiles in kk-ay mice.** *The Journal of Pharmacology and Experimental Therapeutics* (**2004**) 309(3):970-977.

78. Kuwabara K, Murakami K, Todo M, Aoki T, Asaki T, Murai M, Yano J. **A novel selective peroxisome proliferator-activated receptor alpha agonist, 2-methyl-c-5-[4-[5-methyl-2-(4-methylphenyl)-4-oxazolyl]butyl]-1,3-dioxane -r-2-carboxylic acid (NS-220), potently decreases plasma triglyceride and glucose levels and modifies lipoprotein profiles in kk-ay mice.** *The Journal of Pharmacology and Experimental Therapeutics* (**2004**) 309(3):970-977.

79. Li J, Kennedy LJ, Shi Y, Tao S, Ye XY, Chen SY, Wang Y, Hernandez AS, Wang W, Devasthale PV, Chen S *et al*. **Discovery of an oxybenzylglycine based peroxisome proliferator activated receptor alpha selective agonist 2-((3-((2-(4-chlorophenyl)-5-methyloxazol-4-yl)methoxy)benzyl)(methoxycarb onyl)amino)acetic acid (BMS-687453).** *Journal of Medicinal Chemistry* (**2010**) 53(7):2854-2864.

80. Lee CH, Olson P, Hevener A, Mehl I, Chong LW, Olefsky JM, Gonzalez FJ, Ham J, Kang H, Peters JM, Evans RM. **PPARdelta regulates glucose metabolism and insulin sensitivity.** *Proceedings of the National Academy of Sciences of the United States of America* (**2006**) 103(9):3444-3449.

81. Shi GQ, Dropinski JF, Zhang Y, Santini C, Sahoo SP, Berger JP, Macnaul KL, Zhou G, Agrawal A, Alvaro R, Cai TQ *et al*. **Novel 2,3-dihydrobenzofuran-2-carboxylic acids: Highly potent and subtype-selective PPARalpha agonists with potent hypolipidemic activity.** *Journal of Medicinal Chemistry* (**2005**) 48(17):5589-5599.

82. Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R, Rosenfeld MG, Willson TM, Glass CK, Milburn MV. **Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma.** *Nature* (**1998**) 395(6698):137-143.

83. Uppenberg J, Svensson C, Jaki M, Bertilsson G, Jendeberg L, Berkenstam A. **Crystal structure of the ligand binding domain of the human nuclear receptor PPARgamma.** *The Journal of Biological Chemistry* (**1998**) 273(47):31108-31112.

84. Xu HE, Lambert MH, Montana VG, Parks DJ, Blanchard SG, Brown PJ, Sternbach DD, Lehmann JM, Wisely GB, Willson TM, Kliewer SA *et al*. **Molecular recognition of fatty acids by peroxisome proliferator-activated receptors.** *Molecular Cell* (**1999**) 3(3):397-403.

85. Escher P, Braissant O, Basu-Modak S, Michalik L, Wahli W, Desvergne B. **Rat PPARs: Quantitative analysis in adult rat tissues and regulation in fasting and refeeding.** *Endocrinology* (**2001**) 142(10):4195-4202.

86. Feige JN, Gelman L, Michalik L, Desvergne B, Wahli W. **From molecular action to physiological outputs: Peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions.** *Progress in Lipid Research* (**2006**) 45(2):120-159.

87. Balakumar P, Rose M, Ganti SS, Krishan P, Singh M. **PPAR dual agonists: Are they opening pandora's box?** *Pharmacological Research : The Official Journal of the Italian Pharmacological Society* (**2007**) 56(2):91-98.

88. Randle PJ, Garland PB, Hales CN, Newsholme EA. **The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus.** *Lancet* (**1963**) 1(7285):785-789.

89. Fu Y, Luo N, Klein RL, Garvey WT. **Adiponectin promotes adipocyte differentiation, insulin sensitivity, and lipid accumulation.** *Journal of Lipid Research* (**2005**) 46(7):1369-1379.

90. Sohda T, Mizuno K, Imamiya E, Sugiyama Y, Fujita T, Kawamatsu Y. **Studies on antidiabetic agents. Synthesis of 5-[4-(1-methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and its derivatives.** *Chemical & Pharmaceutical Bulletin* (**1982**) 30(10):3580-3600.

91. Sohda T, Mizuno K, Tawada H, Sugiyama Y, Fujita T, Kawamatsu Y. **Studies on antidiabetic agents. I. Synthesis of 5-[4-(2-methyl-2-phenylpropoxy)-benzyl]thiazolidine-2,4-dione (AL-321) and related compounds.** *Chemical & Pharmaceutical Bulletin* (**1982**) 30(10):3563-3573.

92. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. **An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma).** *The Journal of Biological Chemistry* (**1995**) 270(22):12953-12956.

93. Watkins PB, Whitcomb RW. **Hepatic dysfunction associated with Troglitazone.** *The New England Journal of Medicine* (**1998**) 338(13):916-917.

94. Mudaliar S, Chang AR, Henry RR. **Thiazolidinediones, peripheral edema, and type 2 diabetes: Incidence, pathophysiology, and clinical implications.** *Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* (**2003**) 9(5):406-416.

95. Wilding J. **Thiazolidinediones, insulin resistance and obesity: Finding a balance.** *International Journal of Clinical Practice* (**2006**) 60(10):1272-1280.

96. Truitt KE, Goldberg RB, Rosenstock J, Chou HS, Merante D, Triscari J, Wang ΛC. **A 26-week, placebo- and Pioglitazone-controlled, dose-ranging study of Rivoglitazone, a novel thiazolidinedione for the treatment of type 2 diabetes.** *Current Medical Research and Opinion* (**2010**) 26(6):1321-1331.

97. Rybczynski PJ, Zeck RE, Dudash J, Jr., Combs DW, Burris TP, Yang M, Osborne MC, Chen X, Demarest KT. **Benzoxazinones as PPARgamma agonists. 2. SAR of the amide substituent and in vivo results in a type 2 diabetes model.** *Journal of Medicinal Chemistry* (**2004**) 47(1):196-209.

98. Reginato MJ, Bailey ST, Krakow SL, Minami C, Ishii S, Tanaka H, Lazar MA. **A potent antidiabetic thiazolidinedione with unique peroxisome proliferator-activated receptor gamma-activating properties.** *The Journal of Biological Chemistry* (**1998**) 273(49):32679-32684.

99. Barish GD, Narkar VA, Evans RM. **PPAR delta: A dagger in the heart of the metabolic syndrome.** *The Journal of Clinical Investigation* (**2006**) 116(3):590-597.

100. Graham TL, Mookherjee C, Suckling KE, Palmer CN, Patel L. **The PPARdelta agonist GW0742X reduces atherosclerosis in LDLR(-/-) mice.** *Atherosclerosis* (**2005**) 181(1):29-37.

101. van der Veen JN, Kruit JK, Havinga R, Baller JF, Chimini G, Lestavel S, Staels B, Groot PH, Groen AK, Kuipers F. **Reduced cholesterol absorption upon PPARdelta activation coincides with decreased intestinal expression of NPC1l1.** *Journal of Lipid Research* (**2005**) 46(3):526-534.

102. Tesse A, Andriantsitohaina R, Ragot T. **PPARdelta activity in cardiovascular diseases: A potential pharmacological target.** *PPAR Research* (**2009**) 2009(745821.

103. Rival Y, Beneteau N, Taillandier T, Pezet M, Dupont-Passelaigue E, Patoiseau JF, Junquero D, Colpaert FC, Delhon A. **PPARalpha and PPARdelta activators inhibit cytokine-induced nuclear translocation of nf-kappab and expression of vcam-1 in eahy926 endothelial cells.** *European Journal of Pharmacology* (**2002**) 435(2-3):143-151.

104. Murakami K, Tobe K, Ide T, Mochizuki T, Ohashi M, Akanuma Y, Yazaki Y, Kadowaki T. **A novel insulin sensitizer acts as a coligand for peroxisome proliferator-activated receptor-alpha (PPAR-alpha) and PPAR-gamma: Effect of PPAR-alpha activation on abnormal lipid metabolism in liver of zucker fatty rats.** *Diabetes* (**1998**) 47(12):1841-1847.

105. Devasthale PV, Chen S, Jeon Y, Qu F, Shao C, Wang W, Zhang H, Cap M, Farrelly D, Golla R, Grover G *et al.* **Design and synthesis of n-[(4-methoxyphenoxy)carbonyl]-n-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]glycine [muraglitazar/BMS-298585], a novel**

peroxisome proliferator-activated receptor alpha/gamma dual agonist with efficacious glucose and lipid-lowering activities. *Journal of Medicinal Chemistry* (**2005**) 48(6):2248-2250.

106. Nissen SE, Wolski K, Topol EJ. **Effect of Muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus.** *JAMA : The Journal of the American Medical Association* (**2005**) 294(20):2581-2586.

107. Fievet C, Fruchart JC, Staels B. **PPARalpha and PPARgamma dual agonists for the treatment of type 2 diabetes and the metabolic syndrome.** *Current Opinion in Pharmacology* (**2006**) 6(6):606-614.

108. Fagerberg B, Edwards S, Halmos T, Lopatynski J, Schuster H, Stender S, Stoa-Birketvedt G, Tonstad S, Halldorsdottir S, Gause-Nilsson I. **Tesaglitazar, a novel dual peroxisome proliferator-activated receptor alpha/gamma agonist, dose-dependently improves the metabolic abnormalities associated with insulin resistance in a non-diabetic population.** *Diabetologia* (**2005**) 48(9):1716-1725.

109. Lohray BB, Lohray VB, Bajji AC, Kalchar S, Poondra RR, Padakanti S, Chakrabarti R, Vikramadithyan RK, Misra P, Juluri S, Mamidi NV *et al*. **(-)3-[4-[2-(phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid [(-)drf 2725]: A dual PPAR agonist with potent antihyperglycemic and lipid modulating activity.** *Journal of Medicinal Chemistry* (**2001**) 44(16):2675-2678.

110. Imoto H, Matsumoto M, Odaka H, Sakamoto J, Kimura H, Nonaka M, Kiyota Y, Momose Y. **Studies on non-thiazolidinedione antidiabetic agents. 3. Preparation and biological activity of the metabolites of TAK-559.** *Chemical & Pharmaceutical Bulletin* (**2004**) 52(1):120-124.

111. Catherine Fie´ vet J-CF, Bart Staels. **PPARα and PPARγ dual agonists for the treatment of type 2 diabetes and the metabolic syndrome.** *Current Opinion in Pharmacology* (**2006**) 6(606.

112. Ahmed I, Furlong K, Flood J, Treat VP, Goldstein BJ. **Dual PPAR alpha/gamma agonists: Promises and pitfalls in type 2 diabetes.** *American Journal of Therapeutics* (**2007**) 14(1):49-62.

113. Rubenstrunk A, Hanf R, Hum DW, Fruchart JC, Staels B. **Safety issues and prospects for future generations of PPAR modulators.** *Biochimica et Biophysica Acta* (**2007**) 1771(8):1065-1081.

114. Boden G, Zhang M. **Recent findings concerning thiazolidinediones in the treatment of diabetes.** *Expert Opinion on Investigational Drugs* (**2006**) 15(3):243-250.

115. Ljung B, Bamberg K, Dahllof B, Kjellstedt A, Oakes ND, Ostling J, Svensson L, Camejo G. **AZ 242, a novel PPARalpha/gamma agonist with beneficial effects on insulin resistance and carbohydrate and lipid metabolism in ob/ob mice and obese zucker rats.** *Journal of Lipid Research* (**2002**) 43(11):1855-1863.

116. Martin JA, Brooks DA, Prieto L, Gonzalez R, Torrado A, Rojo I, Lopez de Uralde B, Lamas C, Ferritto R, Dolores Martin-Ortega M, Agejas J *et al.* **2-alkoxydihydrocinnamates as PPAR agonists. Activity modulation by the incorporation of phenoxy substituents.** *Bioorganic & Medicinal Chemistry Letters* (**2005**) 15(1):51-55.

117. Xu HE, Lambert MH, Montana VG, Plunket KD, Moore LB, Collins JL, Oplinger JA, Kliewer SA, Gampe RT, Jr., McKee DD, Moore JT *et al.* **Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors.** *Proceedings of the National Academy of Sciences of the United States of America* (**2001**) 98(24):13919-13924.

118. Sorbera LAL, P. A.; Martin, L.; Castaner, J. **Peroxisome proliferator-activated receptor modulators.** *Drugs Fut* (**2001**) 26(354.