

Different Therapeutic Aspects of Peroxisomes Proliferator-Activated Receptors

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Abstract— Peroxisome proliferator-activated receptors (PPARs) was discovered in 1990 belong to the super family of steroid hormone receptors. Three subtypes of PPAR which have been identified so far- PPAR α , PPAR β/δ , and PPAR γ . Human peroxisome proliferator-activated receptors (hPPARs) were initially recognized as therapeutic targets for the development of drugs to treat metabolic disorders, such as diabetes and dyslipidemia but now they have been used in energy burning, dyslipidemia, diabetes, inflammation, Hepatic steatosis, liver cancer, diabetic neuropathy, atherosclerosis also. These are included in management of NIDDM, macrophage differentiation, adipose differentiation, anti-cancer, inhibition of TH2 cytokine production and rheumatoid arthritis. PPAR β/δ can use to treat Huntington's disease, fertility, dyslipidemia. The functions of a third PPAR isoform and its potential as a therapeutic target are currently under investigation.

Keywords— PPAR, Diabetes, Metabolic Disorder, rheumatoid arthritis etc.

I. INTRODUCTION

Peroxisome proliferator activated receptors (PPARs) are transducer proteins belonging to the nuclear receptor or steroid receptor superfamily (1). The nuclear hormone receptors (NRs) comprise of 48 members in humans and form a superfamily of ligand-dependent transcription factors that control diverse biological functions.(2) Examples of NRs include the receptors for thyroid hormones, retinoid, steroid hormone receptors and a variety of other ligands. After interaction with the specific ligands, nuclear receptors are translocated to the nucleus, where they change their structure and regulate gene transcription.(3)

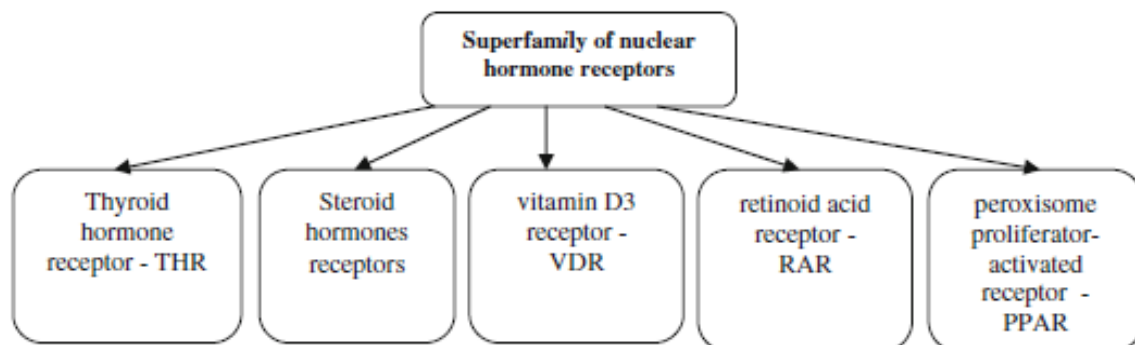


Fig.1: Superfamily of nuclear hormone receptor.(3)

Members of nuclear hormone receptor superfamily are activated by small lipophilic molecules, including hormones and vitamins that are derived directly and indirectly from dietary precursors such as thyroid hormone, retinoids, sterols, fatty acids and derivatives.(4) Three Peroxisome proliferator-activated receptors are members of the nuclear-hormone receptor superfamily, which are PPAR α (NR1C1), PPAR β/δ (NR1C2) and PPAR γ (NR1C3).(5)

II. HISTORY

Human peroxisome proliferator-activated receptors (hPPARs) were initially recognized as therapeutic targets for the development of drugs to treat metabolic disorders, such as diabetes and dyslipidemia.(2) The foundation for the discovery of the PPAR subfamily

of nuclear receptors was led in the 1990s.(5) These receptors were identified in the 1990s in rodents and named after their property of peroxisome proliferation.(1) Discovery and Designation of PPARs is the progressive work of over 25 years with peroxisome proliferators. Peroxisome proliferators are a group of chemicals that induce characteristic and predictable pleiotropic effects (multiple responses from a single gene).(6)

Initially, cloning of one isoform as a target of various xenobiotic compounds (non endogenous) was done and those xenobiotic induced proliferation of peroxisomes in the liver. The protein involved was named the peroxisome proliferator-activated receptor, now known as *PPAR* alpha (*PPAR* α). Within a few years, the family of *PPAR*s was expanded to include *PPAR* gamma (*PPAR* γ) and *PPAR* delta (*PPAR* δ).(7)

Mammalian *PPAR* γ was first described by O'Malley's group but adipocyte specific *PPAR* γ was discovered by Spiegelman. *PPAR* γ was discovered in *Xenopus* and mammals based on its similarity to *PPAR* α . There are two *PPAR* γ isoforms, γ 1 and γ 2, which are identical except, due to different first exons, *PPAR* γ 2 contains an additional 30 amino acids at its N-terminus. (4)

III. ISOLATION

*PPAR*s are members of the steroid hormone receptor superfamily, discovered in 1990.(8) Using electron microscopy, *microbodies* were first discovered in 1954 in mouse renal cells by Rhodin. Later in 1966, De Duve and Baudhuin were the first to isolate these organelles from rat liver and termed them *peroxisomes*. Peroxisomes were later found in all eukaryotic cells except in mature erythrocytes and sperms. (9)

Existence of a specific mediator for peroxisome proliferation was suggested by the tissue & cell specificity of the pleiotropic effects of chemicals called peroxisome proliferators. To identify such a molecular target, a cytosolic protein showing reversible stereospecific binding to nafenopin was detected in rat liver and then a receptor-mediated mechanism for peroxisome proliferation was postulated. A peroxisome proliferator-binding protein was later purified from rat liver cytosol and was identified as a dimer protein with a molecular weight of 140,000-160,000 KDa. This protein was capable of binding to chemicals called peroxisome proliferators which were structurally related to clofibrate. (8)

The ability of peroxisome proliferators to modulate specific gene transcription suggested that they could act via a mechanism similar to that of steroid hormones. This assumption paved the way to a significant discovery of a novel member of the steroid hormone receptor superfamily, isolated by screening a mouse cDNA library. The cloned receptor was found to be structurally related to steroid hormone receptors and was activated by a wide range of molecules including fatty acids and fibrates. The pattern of expression of the receptor mRNA and the tissue-specific effects of peroxisome proliferators were mirroring each other, so the identified receptor was thought to mediate the peroxisome proliferative response and eventually the receptor was named peroxisome proliferator-activated receptor (*PPAR*). (8)

Following the initial discovery of mouse *PPAR*, the receptor was identified in other species including rat and human. In addition, three related *xenopus* receptors belonging to nuclear hormone receptor superfamily were cloned and named *PPAR* α , *PPAR* β , and *PPAR* γ proving the existence of more than one form of *PPAR* in a given species. *PPAR* δ was initially identified in human as an additional form of *PPAR* but was found later to be closely related to *PPAR* β described in *xenopus*. (8)

IV. STRUCTURE OF PEROXISOMES

The peroxisome has a single membrane surrounding a fine granular matrix. All three *PPAR* isoforms possess similar structural and functional features. Principally, four functional domains have been identified, called A/B, C, D and E/F (Fig. 2). (1)



Fig.2: Representation of the functional domains of *PPAR*s.(1)

The N-terminal A/B domain contains a ligand-independent Activation Function-1 (AF-1) responsible for the phosphorylation of *PPAR*. The DNA binding domain (DBD) or C domain promotes the binding of *PPAR* to the peroxisome proliferator response element (PPRE) in the promoter region of target genes. The D site is a docking domain for cofactors. The E domain or ligand binding domain (LBD) is responsible for ligand specificity and activation of *PPAR* binding to the PPRE, which increases the

expression of targeted genes. 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.(1)

Enzymes

The matrix inside membrane of peroxisomes contains numerous enzymes such as Catalase, Manganese superoxide dismutase and Glutathione peroxidase. These enzymes are involved in several metabolic pathways such as Cholesterol biosynthesis, Plasmalogen biosynthesis, very long-chain Fatty Acid biosynthesis, Fatty Acid β -oxidation, Urate oxidation, Xanthine oxidation, and Polyamine oxidation. Catalase is the predominant peroxisomal protein in most specie. Since nutritional and environmental factors have a significant impact on peroxisomal enzyme, composition and function of peroxisomes differ among the organisms as well as the cells and tissues. (9)

V. TYPES OF PPAR

Three major types of *PPAR* which are encoded by separate genes, have been identified. They are *PPAR α* (NR1C1), *PPAR β/δ* (NR1C2), and *PPAR γ* (NR1C3). These three isotypes differ from each other in terms of their tissue distributions, ligand specificities and physiological roles. (1)

Differential promoter usage and alternative splicing of the gene generates 4 mRNA isoforms of *PPAR γ* which are *PPAR γ 1*, γ 2, γ 3 and γ 4. However, γ 3 and γ 4 encode the same protein as *PPAR γ 1*.(10)

VI. SITES

Peroxisomes are most abundant in the Liver playing numerous important roles. Kidney also possesses an abundance of peroxisomes exhibiting both similar and distinctive functions as compared to hepatic peroxisomes. In the Brain, peroxisomes play a significant physiological role such that some inherited peroxisomal disorders can be characterized by impairment of brain structure and function. (5)

The three subtypes *PPAR α* , *PPAR δ* , and *PPAR γ* , are differentially expressed in a tissue-specific manner. (2)

- a) *PPAR α* - expressed in tissues with high fatty acid oxidation activities like liver, kidney, small intestine, heart, and skeletal muscle.(6)
- b) *PPAR β* - expressed with relatively higher levels in brain, adipose tissue, and skin.(6)
- c) *PPAR γ* - expressed at a relatively high level in adipose. (6).) *PPAR γ 1* and γ 2 are predominantly expressed in adipocytes, *PPAR γ 1* is expressed in the tissues e.g., breast, colon, liver, vascular cells while expression of *PPAR γ 2* isoform appears
- d) to be completely adipocyte specific.(4)

VII. ROLES OF PPAR

Human peroxisome proliferator-activated receptors (hPPARs) are activated by endogenous saturated and unsaturated fatty acids, their metabolites, and synthetic ligands.(2) The *PPAR* proteins regulate diverse biological processes such as reproduction, development and immune function.(2) *PPARs* mediate neuroprotective effects in CNS, *PPAR α* and *PPAR γ* activation have opposite regulatory effects in bone formation.(8)

All three members of *PPAR* subfamily either activate or suppress different genes important in cell differentiation and various metabolic processes, especially lipid and glucose homeostasis. (3)

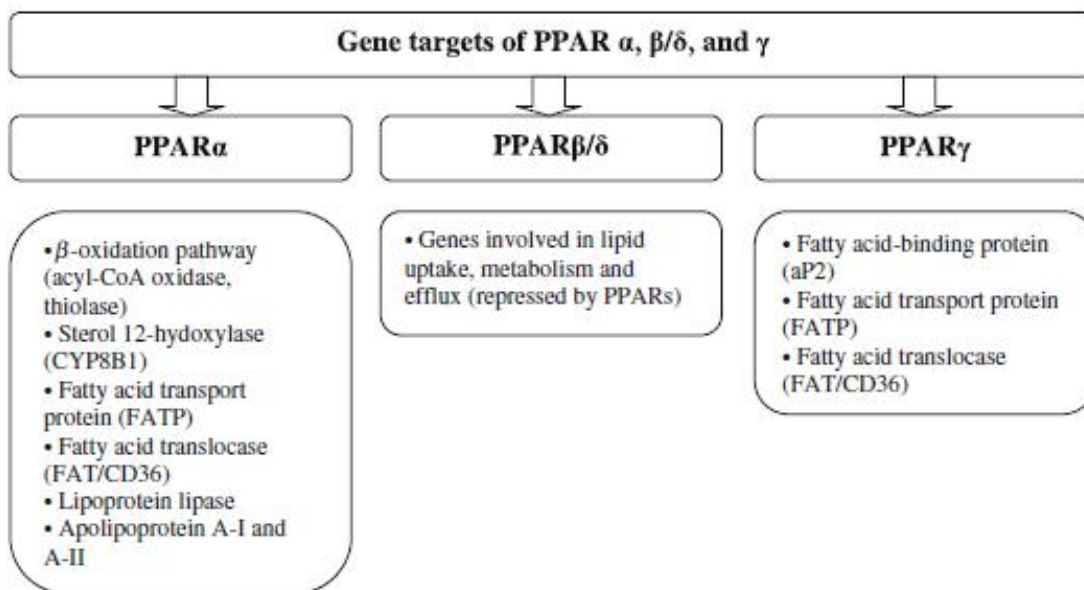


Fig.3: PPARs and their targets (3)

Many selective PPAR agonists have been reported and the structures of well Known PPAR full agonists and ligands are shown in Figure 4.

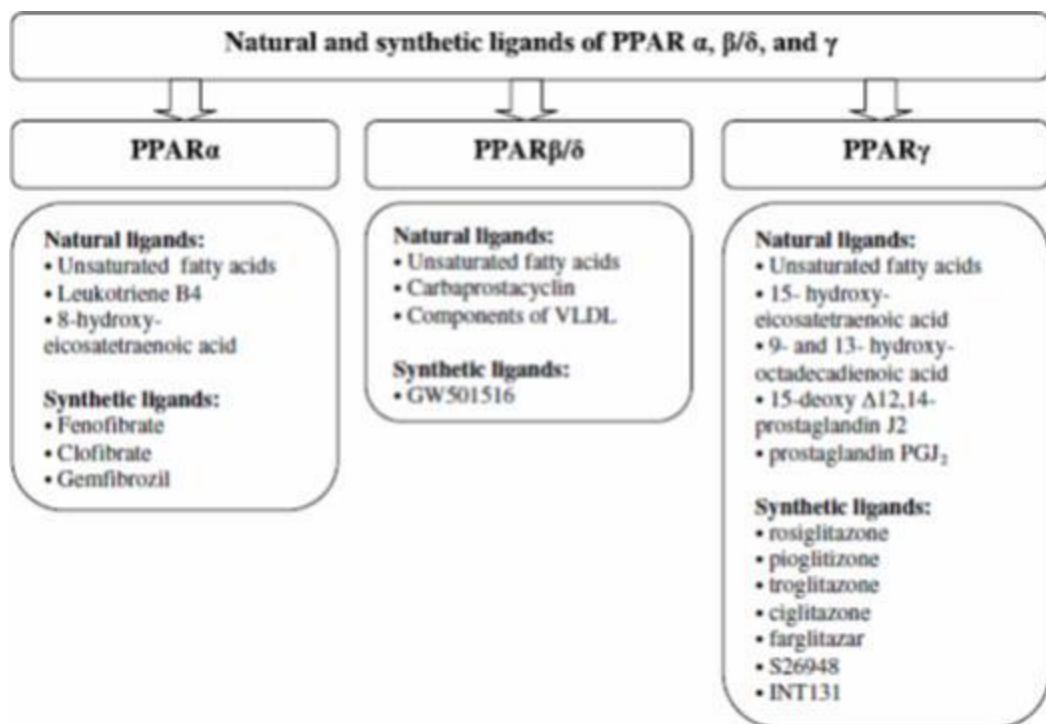


Fig.4: Natural and synthetic ligands of PPARs.(3)

a) PPAR α

PPAR α is highly expressed in metabolically active tissues, such as liver, heart, skeletal muscle, intestinal mucosa and brown adipose tissue. This receptor is implicated in fatty acid metabolism and its activation lowers lipid levels. (3) PPAR α also plays a role in lipoprotein synthesis, inflammatory responses and the development of cancer in the rodent liver. (6) Few roles have been discussed in details below.

• ENERGY BURNING

All three members of the PPAR subfamily of nuclear receptors have been shown to participate in energy metabolism. PPAR α function mostly as catabolic regulators of energy expenditure and regulates all three fatty acid oxidation systems. Some of the key enzymes involved in these three fatty acid oxidation systems are regulated by PPAR α . Hyperactivation of PPAR α by pharmacological intervention might prove to be useful as an adjuvant to exercise in combating obesity in individuals. (5)

• HEPATIC STEATOSIS

PPAR α appears to play a significant role in the pathogenesis of hepatic steatosis. PPAR α influences the expression of hepatic lipogenic genes by regulating the primary transcription factors SREBP-1c and liver X receptor α (LXR α). Second, in conditions for increased demand for fatty acid oxidation, such as starvation, PPAR α is essential for the up regulation of some of the enzymes necessary for the process. Under fasted conditions, PPAR α senses the lipid influx into the liver and upregulates all three fatty acid oxidation systems to burn the energy and minimize hepatic steatosis. Furthermore, ethanol is known to inhibit fatty acid oxidation and this is attributed to ethanol inhibition of PPAR α transcription. Hypo-activity of PPAR α might play a role in the severity of alcohol liver disease in the human. (5)

• DYSLIPIDEMIA (HYPOLIPIDEMIC EFFECTS)

In humans, Fibrates activate PPAR α and have the lipid-lowering activity. Fibrates are effective at lowering serum triglycerides and raising HDL cholesterol (HDLc), primarily through increased clearance and decreased synthesis of triglyceride-rich VLDL. (11) PPAR α ligands reduce VLDL production and enhance the catabolism of TG-rich particles, which indirectly decreases small dense LDL (sdLDL) particles which enhances the formation of HDL particles and hepatic elimination of excess cholesterol. PPAR α activation by fibrates and other compounds, elicits a normolipidemic response. (5) Potent subtype-selective PPAR α agonists, such as GW 9578, are more effective than the current fibrate drugs at lowering apoC-III levels in rodents (Figure 7). (11)

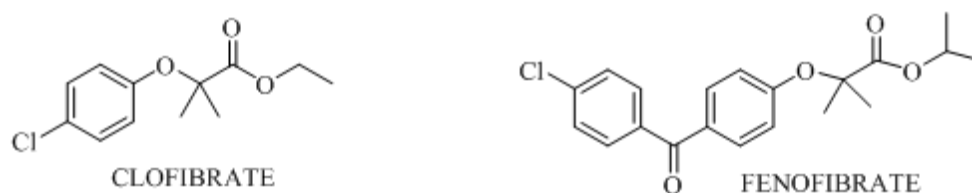
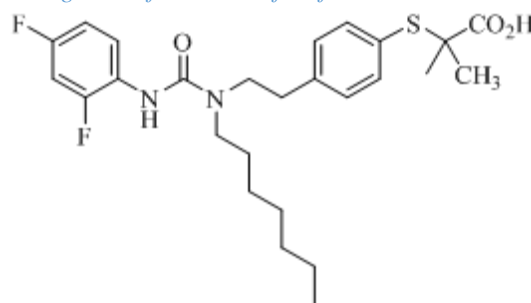


Fig.5: Clofibrate and fenofibrate structures.



GW 9578

Fig.6: PPAR α agonists GW 9578. (11)

- **DIABETES**

The clinically used fibrates are only moderately selective for *PPAR α* over *PPAR β* , thus it is not clear whether activation of the *PPAR α* is responsible for any observed effects in case of diabetes or not. (11)

- **INFLAMMATION**

Activation of this receptor appears to influence both acute and chronic inflammatory disorders involving neutrophils and macrophages. Leukotriene B₄ (LTB₄), a powerful chemotactic inflammatory eicosanoid, is an endogenous *PPAR α* ligand. Like other *PPAR α* ligands, it induces transcription of genes of the β - and ω -oxidation pathways that neutralize and degrade LTB₄ itself to regulate the inflammatory response. Absence of *PPAR α* prolongs the LTB₄-induced inflammatory response. *PPAR α* ligands exert potential anti-inflammatory effects in modulating various inflammatory processes such as atherogenesis and hepatitis. *PPAR α* ligands significantly reduce the levels of pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS). It has important role for *PPAR α* in modulating inflammation in vascular endothelial cells, cartilage and bone tissue, kidney, adipose tissue, and glial cells in the central nervous system (CNS).

Recent studies may point toward potential new roles for *PPAR α* and *PPAR α* target genes as therapeutic targets in disorders involving inflammation such as atherosclerosis, joint disease, and autoimmune disorders such as multiple sclerosis. (5)

- **LIVER CANCER**

The development of hepatocellular carcinomas (HCC) in mice fed a diet containing nafenopin, a potent peroxisome proliferator, was first reported in 1976. Subsequently, several hypolipidemic compounds and plasticizers such as DEHP and DEHA have also been shown to induce liver tumors in rats and mice. With chronic exposure, hepatic adenomas and hepatocellular carcinomas develop in these rodents.

Peroxisome proliferator-induced liver tumors differ from those induced by classic genotoxic hepatocarcinogens. Since peroxisome proliferators are neither DNA damaging nor mutagenic, it was proposed that these compounds constitute a novel class of nongenotoxic hepatocarcinogens and this concept laid the foundation for the receptor-mediated hepatocarcinogenesis.

In normal liver, hydrogen peroxide is produced as a byproduct of many oxidative reactions. Peroxisomal catalase degrades hydrogen peroxide in normal liver. Imbalance between the expression of enzymes capable of producing- and degrading- hydrogen peroxide and other reactive oxygen species in hepatocytes contribute to oxidative stress, lipid peroxidation and oxidative DNA damage. DNA damage through oxidative stress and hepatocellular proliferation, together, are considered as possible mechanisms responsible for the development of hepatocellular carcinomas in rodents chronically exposed to peroxisome proliferators. Exposure to synthetic peroxisome proliferators results in sustained activation of *PPAR α* and transcriptional activation of *PPAR α* responsive genes that affect intermediary metabolism in liver. These metabolic changes, along with the anti-apoptotic effects of *PPAR α* activation, contribute to oxidative DNA damage and increased hepatocellular proliferation leading to liver cancer. (5)

- **DIABETIC NEPHROPATHY**

Many factors contribute to the induction and progression of diabetic nephropathy but hyperlipidemia is considered as major determinant of progression of renal disease in patients with diabetes mellitus. It was found that high lipids could induce renal inflammation and injury. (12)

Studies suggest that the hypolipidemic drugs like *PPAR α* agonists can bring possible therapeutic outcome in preventing the development and progression of diabetic nephropathy. A *PPAR α* agonist, **fenofibrate** was noted to have renoprotection by reducing the occurrence of albuminuria and glomerular lesions in experimental diabetic mice. However, numerous experimental and clinical studies demonstrated that *PPAR γ* agonists like Thiazolidinedione class also have therapeutic potential of preventing the development of diabetic nephropathy as these may be worthy in attenuating insulin resistance, chronic hyperglycemia and inflammation-associated progression of diabetic nephropathy. Thus, *PPAR α* / γ dual agonist not only improves insulin resistance, glycemic control and lipid profile; but also markedly attenuates albuminuria and renal glomerular fibrosis by reducing the collagen deposition and TGF- β expression in the kidney of diabetic mice. However, further clinical studies are needed to elucidate the protective effects of *PPAR α* & *PPAR γ* ligands on the renal function in patients with diabetes mellitus. (13)

- **ATHEROSCLEROSIS**

Evidence is emerging that *PPAR α* agonists may have direct effects in the arterial wall, which could contribute to the beneficial effects of these drugs in atherosclerosis prevention studies. Atherosclerotic lesion formation requires recruitment of monocytes

into the arterial wall through expression of adhesion molecules by activated endothelial cells. Expression of the adhesion molecule VCAM-1 was down-regulated by *PPARα* agonists in human vascular endothelial cells. This proves the role of *PPARα* in atherosclerosis. (11)

b) *PPAR β/δ*

PPARβ/δ is the least known isoform, which has not been so intensely studied as *PPARα* and *PPARγ*. *PPARβ/δ* mainly facilitate energy combustion.(4) However, is also involved in lipid metabolism, fatty acid oxidation mainly in skeletal and cardiac muscles, regulates blood cholesterol concentrations and glucose levels.(3) Activation of *PPARδ* has been shown to increase physical performance and improve endurance performance hence abused by athletes. For the same reason *PPARδ* agonists are characterized as *exercise mimetic*.(8) In the liver, *PPARβ* can be activated by plasma free fatty acids which are influxed during fasting conditions.(6)

Few roles have been discussed in details below.

• HUNTINGTON'S DISEASE

HD is a progressive autosomal-dominant neurodegenerative disorder in which individuals develop motor and cognitive impairments. Different *PPARs* were evaluated and an interaction between *PPARδ* and HTT (huntingtin protein) was found. The role of *PPARδ* repression in HD was investigated and found. The *PPARδ* agonist KD3010 rescues neurological phenotypes and neurodegeneration. KD3010 chemically is (S)-4-[cis-2,6-dimethyl-4-(4-trifluoromethoxy-phenyl)-piperazine-1- sulfonyl]-indan-2-carboxylic acid tosylate and is a highly selective and potent *PPARδ* agonist.(14)

• FERTILITY

PPARδ activators such as carbaprostacyclin or L-165041 in combination with 9-cis-retinoic acid were shown to restore implantation in COX2-/- mice. Thus, prostacyclin or its metabolites may be regulators of embryo implantation though activation of *PPARδ*. (11)

• DYSLIPIDEMIA

It is likely that *PPARδ* is involved in lipid homeostasis because, like the other two subtypes, fatty acids and fatty acid metabolites activate the receptor.(11)

c) *PPARγ*

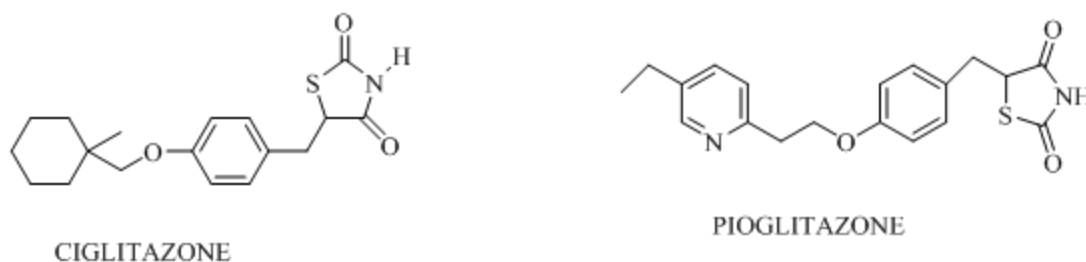
PPARγ plays a key role in the regulation of adipogenesis, energy balance, and lipid biosynthesis. This receptor also participates in insulin sensitivity.(3) Adipogenesis and fat storage in adipocytes by *PPARγ*, accounts for the insulin sensitizing effect of the anti-diabetic drug Thiazolidinediones.(6).

Few roles have been discussed in details below.

• NON-INSULIN-DEPENDENT-DIABETES MELLITUS (NIDDM)

Insulin resistance plays a major pathophysiological role in NIDDM. Ligands for *PPARγ* include fatty acids and eicosanoids. Thiazolidinediones (TZDs) are a group of *PPARγ*-agonists used in the treatment of type 2 diabetes (T2D) since 1997. (7) TZDs have very high affinity and enhance insulin sensitivity in humans. The classic *PPARγ* target in adipocytes is the fatty acid binding protein (aP2) gene, which is induced by TZDs and contains a well-characterized *PPAR/RXR* binding site for *PPARγ* ligands and insulin sensitivity.(4) TZDs also increase insulin biosynthesis and release as well as glucose transport in β-cells by up-regulating expression of genes involved in these processes.(8)

The TZDs are a relatively new class of oral antidiabetic drugs, and they are often referred to as 'insulin sensitizers'. The first of this type of compounds was Ciglitazone, which was synthesized in 1982, and subsequently Pioglitazone, Englitazone, Troglitazone, Rosiglitazone, and Darglitazone were synthesized. Only Troglitazone, Pioglitazone, and Rosiglitazone were evaluated in clinical studies, and Troglitazone was approved for clinical use by the US Federal Drug Administration (FDA) in 1997, but were subsequently withdrawn from the market in March 2000 because of idiosyncratic liver toxicity. Rosiglitazone and Pioglitazone were approved by FDA in 1999 in the US. These three *PPARγ* agonists contain the same active TZD ring, they have different side chain, causing differ in their pharmacological potency.(7)

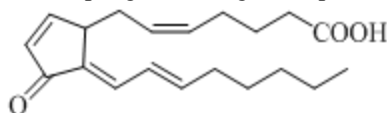
Fig.7: *PPAR* γ agonists.

The beneficial metabolic effects of *PPAR* γ Agonist in treatment of human type II diabetics includes reduction in postprandial glucose, fasting plasma glucose and HbA1c, increased insulin sensitivity, improved pancreatic Island β -cell function, increase in HDL levels, variable lowering of LDL levels, lowering of diastolic blood pressure and decreased microalbuminuria.(7)

The *PPAR* γ agonists in use show good tolerability, the major adverse events being weight gain, oedema, upper respiratory tract infection and headache. A major drawback of treatment with TZD is body fat gain. (7)

• MACROPHAGE DIFFERENTIATION

PPAR γ is a regulator of adipogenesis and is abundant in fat cells and at lower levels in other cell types including macrophages. *PPAR* γ ligands such as Modified fatty acids, Prostaglandin D2 metabolite 15d-PGJ2 and Thiazolidinedione (TZD) can dampen macrophage inflammatory responses by reducing the expression of matrix degrading metalloproteinases, cytokines, nitric oxide and the modified lipoprotein receptors known as macrophage-scavenger receptor class A (SRA) an enable foam cell formation.(15)

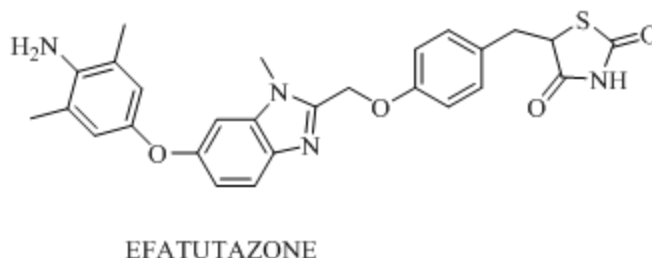


15d-PGJ2

Fig.8: Structure of 15d-PGJ2.

• ADIPOSE DIFFERENTIATION

PPAR γ forms a heterodimer with retinoid X receptor (RXR) and the dimer binds to *PPAR* response element (*PPRE*). Consequently regulating the expression of adipose-related genes that code adipocyte-related proteins, represented by adipocyte fatty acid-binding protein 2 (aP2), adipose differentiation-related protein (ADFP) and adiponectin. In this way, *PPAR* γ agonists promote the differentiation of adipose tissues, and there are many reports demonstrating that *PPAR* γ agonists strongly promote the differentiation of fibroblast-like cells such as 3T3-L1 cells to adipocytes. Indeed, Efatutazone (CS-7017), a potent *PPAR* γ full agonist, showed differentiation-inducing activity in anaplastic thyroid carcinoma, non-small cell lung cancer, and pancreatic cancer under low concentrations in vitro. (16)

Fig.9: *PPAR* γ agonist Efatutazone.

• ANTI-CANCER

According to author Keisuke Yamamoto, *PPAR* γ activation potentially induces the differentiation of cancer cells. Indeed, Efatutazone (CS-7017), a potent *PPAR* γ full agonist, showed differentiation-inducing activity in anaplastic thyroid carcinoma, non-

small cell lung cancer, and pancreatic cancer under low concentrations in vitro, while such differentiation effects have not been reported for any other *PPAR* γ agonists. In addition, a recent phase I clinical study of efatutazone demonstrated that its treatments prolonged the overall survival of anaplastic carcinoma patients. However, several patients have reported adverse effects, such as localized edema, likely due to the chemical structure of the TZD moiety. New *PPAR* γ ligands has been found of Dihydrodibenzo [b,e]oxepine scaffold with very potent in vitro differentiation-inducing activity and a unique binding mode to the *PPAR* γ LBD. (16)

• INHIBITION OF TH2 CYTOKINE PRODUCTION

Yellow pigment monascin (MS) is a secondary metabolite isolated from *Monascus*-fermented products and has numerous physiological activities. MS and the synthetic *PPAR* γ ligand, rosiglitazone (RG) significantly inhibited the production of Th2 cytokines, including IL-4, IL-5, and IL-13, in PMA/ionomycin-activated mouse EL-4 T cells. This was due to cellular *PPAR* γ translocation. (17)

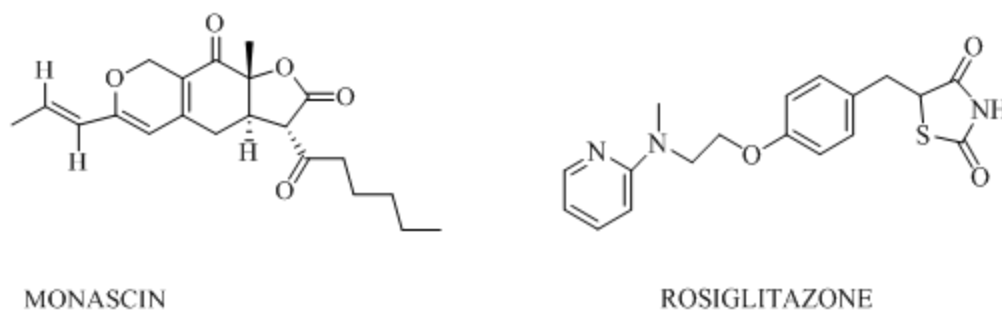


Fig.10: Monascin and Rosiglitazone structures.

These results indicate that MS and RG promote *PPAR* γ –DNA interactions and suggest that the regulatory effects of MS and RG on Th2 cytokine production could be abolished with *PPAR* γ antagonist treatment. However, the potential use of MS for immunomodulation remains unclear.(17)

• RHEUMATOID ARTHRITIS

PPAR γ has been remarkably known to have anti-inflammatory and anti-proliferation activities. *PPAR* γ might contribute to the persistent expression of pro-inflammatory cytokines in RA. In RA, the expression of *PPAR* γ down-regulates FLS (Fibroblast-like-synoviocytes). *PPAR* γ inhibitor *PPAR* γ siRNA can increase observably FLSs proliferation and migration in normal and Adjuvant Arthritis (AA). *PPAR* γ agonist Pioditazone or pEGFP-N1-*PPAR* γ could suppress substantially FLSs proliferation and migration in normal and Adjuvant Arthritis. (18)

• LUNG INFLAMMATION

PPAR γ agonists may modulate the oxidative stress pathway to decrease the development of airway inflammation. Oxidative stress has been shown to play an important role between inflammation and lung damage. The lungs combat oxidative injury in part by the nuclear factor-erythroid 2 related factor 2 (Nrf-2). One of the major ligand-activated transcription factors up-regulated by Nrf-2 is *PPAR* γ , which is involved in anti-inflammatory effects in the lung and other organs. *PPAR* γ enhances the transcription of anti-inflammatory and antioxidant genes several of which are also up-regulated by Nrf-2. (19)

Yellow pigment monascin (MS), isolated from *Monascus*-fermented products, is a secondary metabolite with an azaphilone structure and has been reported to have cytotoxic and anti-inflammatory activities via *PPAR* γ . The effect of *Monascus*-fermented metabolite monascin (MS) and rosiglitazone (Rosi) on oxidative stress-induced lung inflammation was evaluated a study and it was found that MS attenuated oxidative stress-induced ROS generation. It can be said that MS has the potential to protect airway epithelial cells against oxidative injury. (19)

• NON ALCOHOLIC STEATO HEPATITIS & ANTI-FIBROTIC

Non Alcoholic Steato Hepatitis (NASH) is a highly prevalent multifactorial and multi-step disease associated with increasing risk of cardiovascular mortality and development of severe liver conditions such as cirrhosis and hepatocellular carcinoma. NASH is characterized by histopathological changes in the liver which include steatosis, inflammation, ballooning, necro inflammation and

perisinusoidal fibrosis. Fibrosis stage is the strongest predictor for all-cause and disease-specific mortality in NASH patients. Although the pathogenesis of NASH is not fully understood, there is a consensus that metabolic disorders and hepatic steatosis play a key role in the initiation of the disease. (20)



Fig.11: Compound 4 led to the formation of Lanofibranor 5

According to author Benaissa Boubia, Compound 4 is a *PPAR* activator which led to the discovery of lanifibranor 5 (IVA337). This compound has balanced activity on all *PPARs* subtypes and it demonstrated significant anti-fibrotic activity in the mouse CCl₄- induced liver fibrosis model. Development of lanifibranor 5 for the treatment of NASH is on the way. (20)

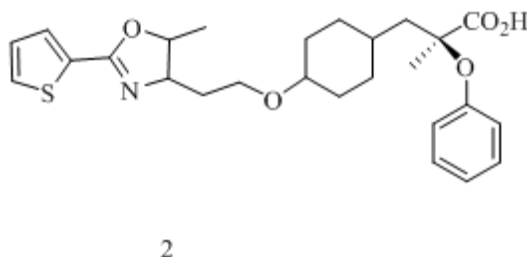
- **HYPERTENSION**

TZDs have been shown to decrease blood pressure in a number of animal models, including Dahl S rats, obese Zucker rats spontaneously hypertensive rats Watanabe rabbits, and obese insulin-resistant rhesus monkeys. (11)

8) LIGANDS

Various ligands which are at the various stages of developmental stages of a drug are described under this heading. Few of them are in clinical trials or are about to be sent for clinical trials after proper investigation. The ligands have been described below.

a) α -ARYLOXY- α -METHYLHYDROCINNAMIC ACIDS



2

Fig.12: Compound 2 is (S)-2-methyl-3-[4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)ethoxy]phenyl]-2-phenoxypropionic acid.

Dual *PPAR* α/γ agonistic activity of compound 2 for the treatment of type 2 diabetes and associated dyslipidemia have been described by the author Xu Y. In his research, compound 2 was identified as a balanced dual *PPAR* α/γ agonist with high-affinity binding to h *PPAR* α and h *PPAR* γ and potent agonist activity in cell-based cotransfection assay. Preclinically, compound 2 exhibited remarkably potent activity on *PPAR* γ -mediated endpoints (insulin-sensitization and glucose lowering) but appeared less potent on *PPAR* α -mediated endpoints (HDL cholesterol elevation). Overall, the results of that research supported the hypothesis that 2 will stimulate both *PPAR* α and *PPAR* γ at similar plasma exposures in the clinical setting, thus providing optimal control of both hyperglycemia and dyslipidemia. Thus 2 was selected for advancement to clinical trials for the treatment of type 2 diabetes and associated dyslipidemia and is currently undergoing evaluation in man. (21)

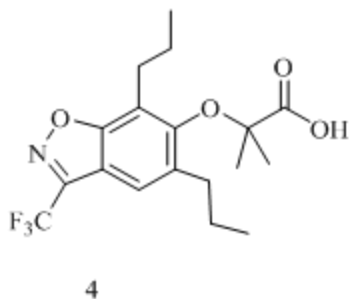
b) α/γ DUAL AGONISTS FOR TYPE 2 DIABETES AND DYSLIPIDEMIA

Fig.13: Compound 4 as $PPAR\alpha/\gamma$ dual agonist.

According to author Liu K, in a research compound 4 was identified as a $PPAR\alpha/\gamma$ dual agonist with relative $PPAR\alpha$ selectivity. Compound 4 demonstrated potent efficacy in lowering both glucose and lipids in animal models without causing body weight gain. $PPAR\alpha$ activity of 4 appeared to have played a significant role in lowering glucose levels in db/db mice. The $PPAR\alpha$ activity of 4 appeared to have played a significant role in glucose lowering in db/db mice. On the basis of its in vitro and in vivo profiles, compound 4 was selected for further evaluation in man.(23)

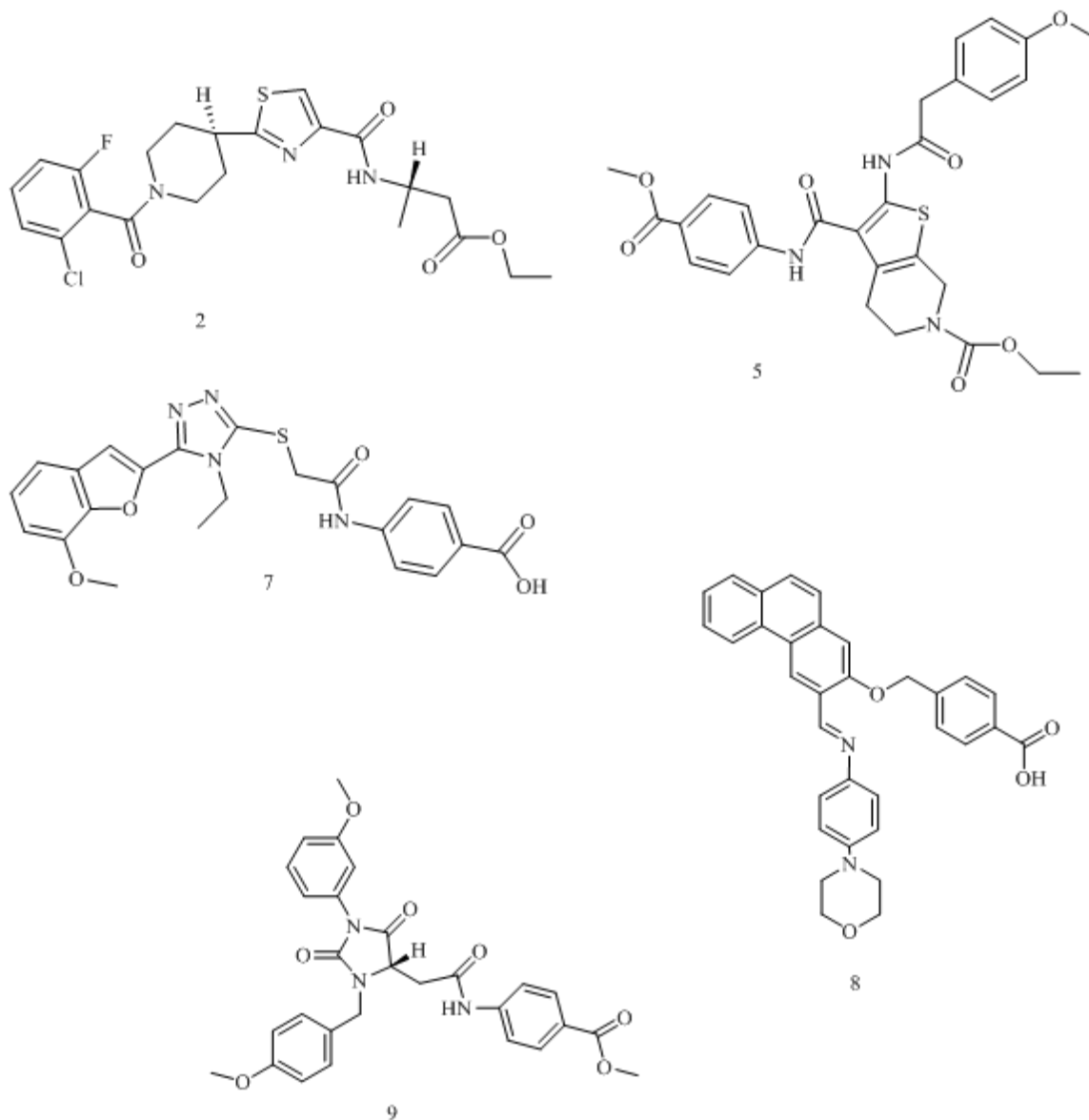
c) NOVEL *PPAR* $\alpha\gamma\delta$ LIGANDS

Fig.14: Compounds 5, 7, and 8 were identified as *PPAR* α/γ agonists, whereas compounds 2 and 9 showed agonistic activity for *PPAR* γ , compound 9 was identified as a *PPAR*- δ Antagonist.

According to author Markt P., in a research Compounds 5, 7, and 8 were identified as *PPAR* α agonists, whereas compounds 2 and 9 showed agonistic activity for h *PPAR* γ , compound 9 was identified as a *PPAR* δ , Antagonist. These were the *PPAR* ligands that could be useful for drug development in the area of atherosclerosis, dyslipidaemia, and type 2 diabetes. Evidences suggested that agonists of the delta subtype are useful in the treatment of type 2 diabetes and diet-induced obesity. Elevated expression of *PPAR* δ has been observed in cancer cells, antagonists of *PPAR* δ are investigated for their use in anticancer therapy Novel *PPAR* ligands 2, 5, 7, 8, and 9 could be structurally optimized in order to obtain new drugs for the therapy of atherosclerosis, dyslipidaemia, and type 2 diabetes. (22)

d) **A3 ADENOSINE RECEPTOR LIGANDS WITH *PPAR* γ PARTIAL AGONIST AND *PPAR* δ ANTAGONIST AS ANTIDIABETIC**

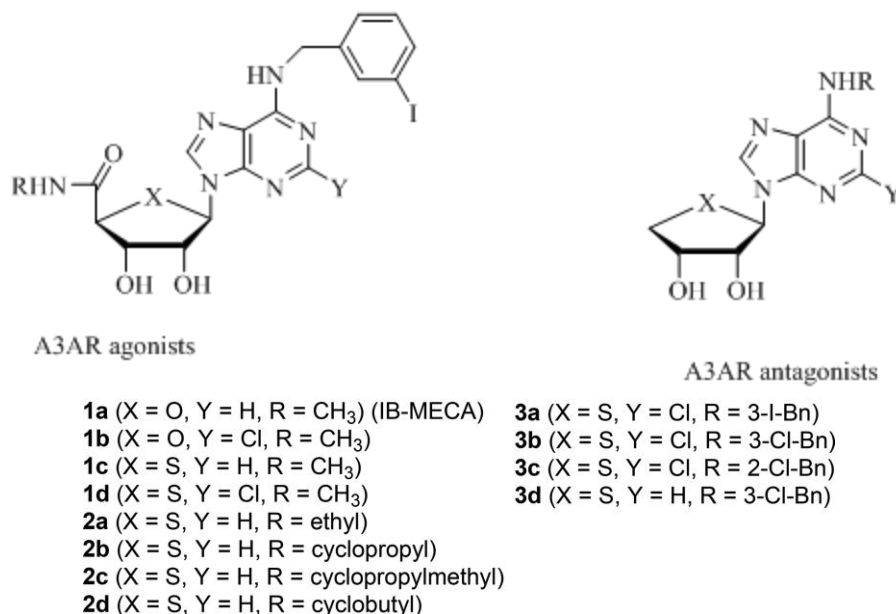
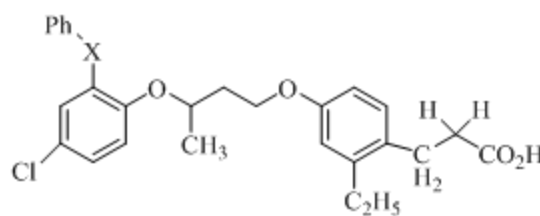


Fig.15: A study demonstrated that the antidiabetic potential of 1a and related A3 AR ligands.

A study demonstrated that the antidiabetic potential of **1a** and related A3 AR ligands is associated with previously undetected interactions, i.e., both *PPAR* γ partial agonism and *PPAR* δ antagonism. In order to develop these compounds to treat human metabolic diseases, further studies will be necessary because clinical outcomes associated with efficacy or toxicity have not yet been clearly addressed depending on their A3 AR agonist or A3 AR antagonist activity. In addition, when 1a and related A3 AR ligands are clinically developed as A3 AR modulators to treat A3 AR-associated clinical conditions, the adverse effects or clinical benefits associated with *PPAR* γ partial agonism and *PPAR* δ antagonism should be considered. (24)

e) **DUAL *PPAR* γ/δ AGONISTS AS EUGLYCEMIC AGENTS**



20

Fig.16: Dual *PPAR* γ/δ agonist (R)-3-{4-[3-(4-chloro-2-phenoxy-phenoxy)-butoxy]-2-ethyl-phenyl}-propionic acid.

According to author Xu Y, the compound 20 possesses a potent dual *PPAR* γ/δ agonist profile for the treatment of type 2 diabetes and associated dyslipidemia. In preclinical models, the compound improves insulin sensitivity and reverses diabetic hyperglycemia with less weight gain at a given level of glucose control relative to Rosiglitazone. The studies suggested that a *PPAR* γ/δ dual agonist approach can attenuate the weight gain side effect commonly associated with marketed TZDs. The SAR suggested that, a *PPAR* γ/δ agonist with a properly controlled g/d ratio can be effective on glucose control with less weight gain relative to Rosiglitazone in the preclinical models. (25)

f) **LINOLEIC ACID OXIDATION MODULATES *PPAR* β/δ SUPPRESSION OF *PPAR* γ ACTIVITY.**

In colon cancer cells, 15-LOX-1 (15-lipoxygenase-1) expression is lost and *PPAR*- β/δ is over expressed, resulting in the suppression of *PPAR* γ transcriptional activity (Figure 5g). However, restoring 15-LOX-1 expression produces 13-S-HODE (13-S-

hydroxyoctadecadienoic acid, is the main product of (15-LOX-1), which down regulates $PPAR\text{-}\beta/\delta$ expression and thus promotes $PPAR\gamma$ activity (Figure 5h).

Adding linoleic acid to the culture medium enhanced 13-S-HODE production in the 15-LOX-1-transfected cells, whereas adding caffeic acid (a 15-LOX-1 inhibitor) in a concentration that specifically inhibits 15-LOX-1 enzymatic activity. Future studies will be needed to further elucidate how the signaling of polyunsaturated fatty acid oxidative metabolic pathways modulates the interaction between $PPARs$ to influence important biologic events such as apoptosis in cells. (26)

g) $PPAR\text{-}\gamma$ AGONIST AS ANTI-INFLAMMATORY AGENT

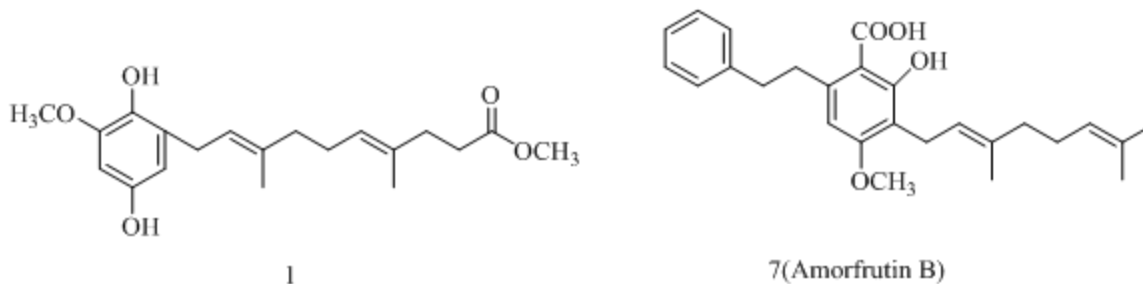


Fig.17: New meroterpene derivative, chrysogenester (1) & natural $PPAR\gamma$ agonist amorfrutin.

An investigation of the jellyfish-derived fungus *Penicillium chrysogenum* J08NF-4 led to the isolation of two new meroterpene derivatives, chrysogenester (1) and 5-farnesyl-2-methyl-1-O-methylhydroquinone, and four known farnesyl meroterpenes. Docking analysis of 1 showed that it binds $PPAR\gamma$ in the same manner as the natural $PPAR\gamma$ agonist amorfrutin B (7). Main biological functions of $PPAR\text{-}\gamma$ agonists is to suppress inflammatory response. An in vitro study was performed to explore the anti-inflammatory potency of 1 and the mechanism involved. In RAW 264.7 macrophages, 1 suppressed the expression of the pro-inflammatory mediators iNOS, NO, COX-2, TNF- α , IL-1 β , and IL-6. Their findings suggested that 1 can be viewed as a starting point for the development of anti-inflammatory therapeutics. (27)

h) INDANYLACETIC ACID DERIVATIVES- $PPAR\alpha/\delta/\gamma$ PAN AGONISTS

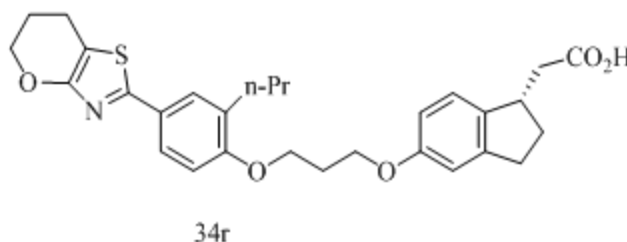
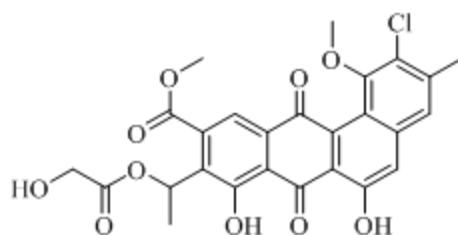


Fig.18: Recently identified Indanylacetic acid moiety as a well-tunable $PPAR$ agonist.

In a research, 4-Thiazolylphenyl groups were identified as novel $PPAR$ agonist tail portions. In combination with the recently established indanylacetic acid head group, these compounds gave balanced $PPAR\alpha/\gamma/\delta$ pan agonistic activities in vitro and good selectivities against other nuclear hormone receptor family members, including androgen, estrogen, glucocorticoid, and progesterone receptors. Optimization efforts within the thiazolylphenyl series led to the identification of 34r, a compound with a good in vitro pharmacology profile and excellent ADME properties. Compound 34r was found to dose dependently reduce blood glucose and was significantly more potent than the standard of care agent rosiglitazone in db/db mice. 34r displayed a highly attractive in vivo pharmacology profile. The magnitude of effects seen in the in vivo experiments was equal or superior to standard. Hence, $PPAR\alpha/\gamma/\delta$ pan agonists hold potential for the treatment of diabetes and associated dyslipidemia. (28)

i) CHLOROCYCLINONES (A-D) ANTAGONIZING $PPAR\text{-}\gamma$ ACTIVATION

Structure 3, named chlorocyclinone C is methyl 2-chloro-6,8-dihydroxy-9-[1-[(hydroxyacetyl)oxy]ethyl]-1-methoxy-3-methyl-7,12-dioxo-7,12-dihydro-tetraphene-10-carboxylate. (29)

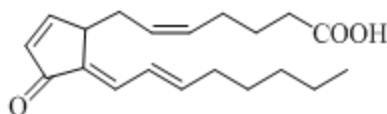


3

Fig.19: Chlorocyclinone C isolated from the mycelium of *Streptomyces* sp. strain DSM 17045.

According to author Potterat O, In course of screening to identify novel $PPAR\gamma$ modulators for the potential treatment of type 2 diabetes, four new chlorinated angucyclinones, chlorocyclinones A-D(1-4) were isolated from the mycelium of *Streptomyces* sp. strain DSM 17045. The compounds proved to be active in a cell-based reporter gene assay as well, antagonizing rosiglitazone-induced $PPAR\gamma$ activity. Chlorocyclinone C exhibited the most potent activity in all assays. Not only were the compounds able to antagonize the rosiglitazone-induced $PPAR\gamma$ activation but due to overlapping binding sites, they precluded rosiglitazone from binding. Chlorocyclinone C was the most active and displaced rosiglitazone.(29)

j) 15d-PGJ2— NATURAL $PPAR\gamma$ LIGAND



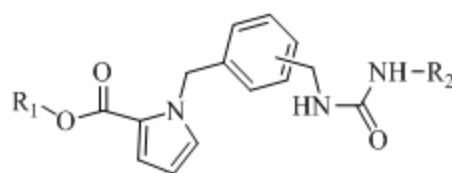
15d-PGJ2

Fig.20: Natural ligands for $PPAR\gamma$ is 15d-PGJ2 (15-deoxy-D12,14-prostaglandin J2).

Recent studies demonstrated that the full length $PPAR\gamma$ was indeed expressed in activated T, B cells and monocytes/macrophages. The ligands for $PPAR\gamma$ include 15-deoxy-D12,14-prostaglandin J2 (15d-PGJ2)—a natural ligand from the prostaglandin synthesis pathway, and “glitazones”—drugs utilized in the treatment of patients with diabetes. Emerging evidence indicates that $PPAR\gamma$ and its ligands are indeed important for the modulation of immune and inflammatory reactions

Therapeutic efficacy of $PPAR\gamma$ agonists has been tested on the animal models. The results showed that the compound can attenuate acute and chronic inflammation. However, cautions have been raised for the potential application of 15d -PGJ2 on human subjects due to some of its proinflammatory effects observed from the studies of human cells. Further research is needed in this direction. (30)

k) DUAL MODULATORS OF SOLUBLE EPOXIDE HYDROLASE & $PPAR\gamma$ s



6

name	R ₁	R ₂	subst
------	----------------	----------------	-------

6e	H	adamantyl	m-
6f	H	adamantyl	p-
6h	H	Ph-pOCF ₃	m-
6i	H	Ph-pOCF ₃	p-

Fig.21: Dual sEH/PPAR modulators as potential agents for the treatment of metabolic syndrome.

In a study by author Buscato E, an acidic pyrrole headgroup, known as a pharmacophore important for PPAR dual agonistic activity, was combined with different hydrophobic urea derivatives in order to introduce an epoxide mimetic. The resulting compounds displayed high inhibition on sEH and different patterns of PPAR agonistic activity. Regarding dual modulation of sEH/PPAR, two compounds were obtained that partially activated PPAR. (6e, 6f) and inhibited sEH with moderate potency. Compound 6h inhibited sEH and activated PPAR $\alpha/\gamma/\delta$. Compound 6i inhibited sEH and activated PPAR α/γ , resulting in an interesting compound to be evaluated in further experiments. (31)

That study demonstrated that the pharmacophores of PPAR agonists and sEH inhibitors could be easily combined, resulting in a simplified blueprint of a dual sEH/PPAR modulator. Further in vivo pharmacological evaluation studies are needed in order to shows the most promising profile for treatment of metabolic syndrome. (31)

1) PPAR γ MODULATORS- ANTI-INFLAMMATORY

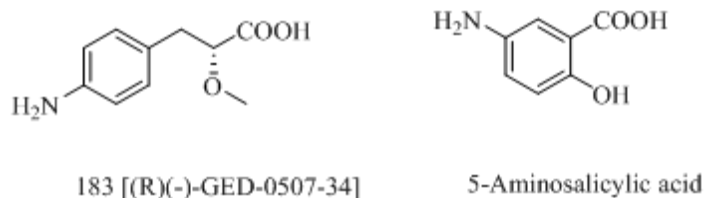


Fig.22: Ligand for PPAR with Anti-Inflammatory Activity.

According to author Speca S, Compound 183 demonstrated 100 to 150 fold higher anti-inflammatory activity than 5-ASA in a study. 5-Aminosalicylic acid (5-ASA) (Figure _) is an anti-inflammatory drug currently used to treat inflammation of the digestive tract, inflammatory bowel disease, ulcerative colitis and mild-to-moderate Crohn's disease. Its mechanism of action has been clarified as being PPAR γ dependent. Compound 183 gave promising results in both in vitro and in vivo experimental models of colitis, and its specificity appeared to be very good, without any adverse events. It is currently in phase 2 of clinical trials. (32)

m) PPAR γ AGONISTS WITH INDOLEGLYOXYLYL MOIETIES

Seven new amino acid derivatives (1-4 and 6-8) were isolated from MeOH extracts of the marine ascidian *Herdmania momus*. Analogues with indoleglyoxylyl moieties (5, 6, and 8) showed significant PPAR γ activation in Ac2F rat liver cells. Since, PPAR γ have emerged as potent agents in the treatment of type II diabetes, inflammatory disorders of CNS, CVD and tissue injury associated with ischemia and reperfusion these compounds could be utilized for the same after further research. (33)

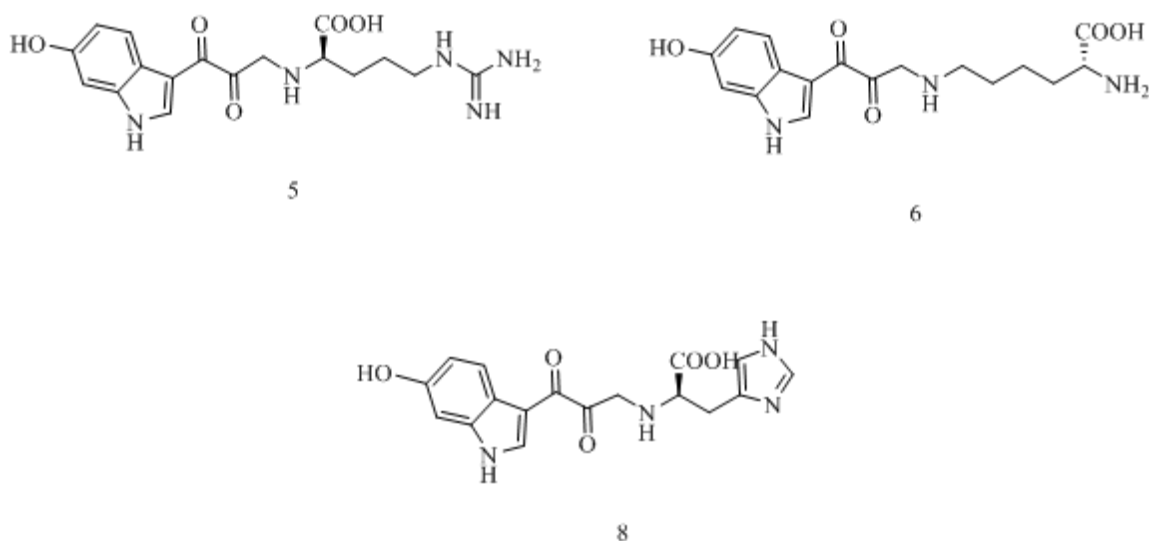


Fig.23: Analogues with indoleglyoxyl moieties (5, 6, and 8) showed significant PPAR γ activation in Ac2F rat liver cells.

n) NSAIDS IN CANCER

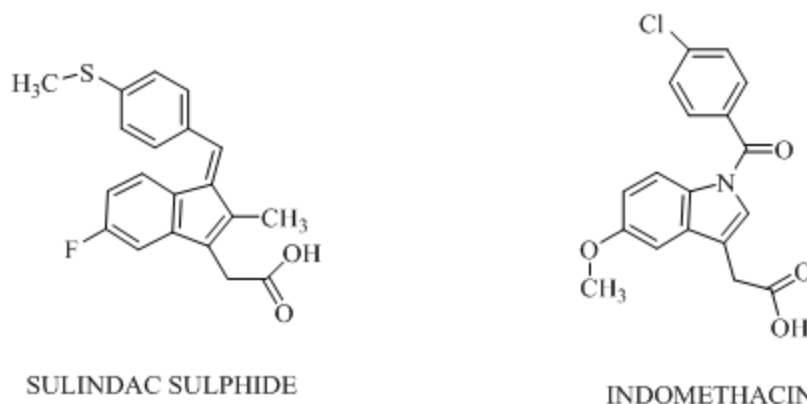


Fig.24: NSAIDs mediate their anti-tumorigenic activity in colorectal cancer through PPAR δ .

A recent report has suggested that NSAIDs mediate their anti-tumorigenic activity in colorectal cancer in part through PPAR δ . High micromolar concentrations of the NSAIDs sulindac and indomethacin suppressed PPAR δ activity in a transactivation assay. This proposal has yet to be tested using more potent PPAR δ ligands. (11)

o) NOVEL INDOLE-BASED PPAR AGONISTS

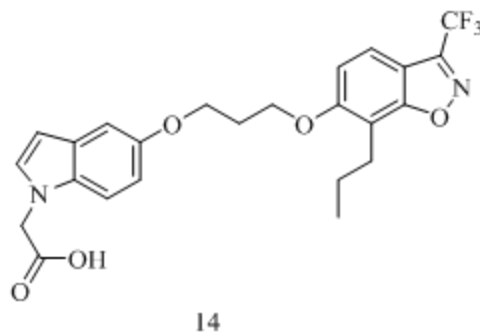


Fig.25: Lead compound 14, an Indole compound with a benzisoxazole tail displayed potent PPAR agonistic activity.

According to author Mahindroo N, in vitro evaluation led to identification of a novel series of indole compounds with a benzisoxazole tail as potent *PPAR* agonists with the lead compound 14 (BPR1H036). Structural biology studies of compound 14 showed that the indole ring contributes strong hydrophobic interactions with *PPAR* γ and could be an important moiety for the binding to the protein. Compound 14 displayed excellent pharmacokinetic profile in BALB/c mice and an efficacious glucose lowering activity in KKAY mice. It also exhibited strong insulin sensitizer activity. The overall in vitro profile of 14 indicated that it could be a very promising antidiabetic candidate. (34)

p) NOVEL AND SELECTIVE *PPAR* SCAFFOLDS

Three novel *PPAR* scaffolds displaying distinct chemotypes have been identified, namely, 5-(4-(benzyloxy)-3-chlorobenzylidene) dihydro-2-thioxopyrimidine-4,6(1H,5H)-dione (MDG 548), 3-((4-bromophenoxy)methyl)-N-(4-nitro-1H-pyrazol-1-yl)benzamide (MDG 559), and ethyl 2-[3-hydroxy-5-(5-methyl-2-furyl)-2-oxo-4-(2-thienylcarbonyl)-2,5-dihydro-1H-pyrrol-1-yl]-4-methyl-1,3-thiazole-5-carboxylate (MDG 582). These compounds displayed high affinity competitive binding to the *PPAR* γ -LBD. (35)

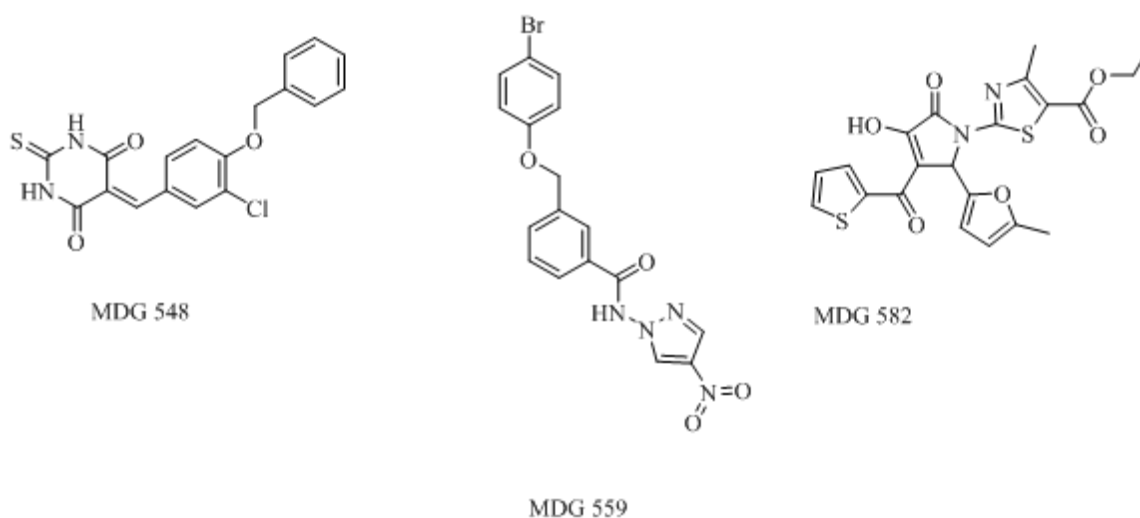


Fig.26: Compounds display high affinity competitive binding to the *PPAR* γ .

MDG 548 displayed specific binding within tested concentrations against *PPAR* γ , with an affinity approximately double that of Rosiglitazone. MDG 559 showed differing levels of affinity for three *PPAR* receptor subtypes. MDG 559 displayed preferential binding to *PPAR* γ but retained potency (decreasing) against *PPAR* α and *PPAR* δ . It has been postulated that agonism of all three *PPAR* subtypes could have benefits in a broad spectrum of metabolic diseases. Compound MDG 582 was shown to have dual affinity for both *PPAR* γ and *PPAR* δ . On the basis of the intricate involvement of *PPAR* γ/δ on lipid metabolism, dual target modulation has been suggested as a potentially beneficial approach toward treatment of hyperlipidemia, insulin resistance, and attenuation of atherogenesis. (35)

VIII. CONCLUSION

Peroxisome proliferator-activated receptors (PPARs) belong to the super family of steroid hormone receptors and were discovered in the year 1990. There are three subtypes of PPAR which have been identified- *PPAR* α , *PPAR* β/δ , and *PPAR* γ . *PPAR* α have been implicated in energy burning, Hepatic steatosis, dyslipidemia, diabetes, inflammation, liver cancer, diabetic neuropathy, atherosclerosis. *PPAR* γ is involved in NIDDM, macrophage differentiation, adipose differentiation, anti-cancer, inhibition of TH2 cytokine production and rheumatoid arthritis. *PPAR* β/δ is involved in Huntington's disease, fertility, dyslipidemia. The functions of a third PPAR isoform and its potential as a therapeutic target are currently under investigation.

Some of the PPAR ligands are under use for therapeutic purpose like Fibrates and TZDs. However researches are being underway to explore new ligands. Various new ligands have been explained in this project, which are in the various developmental stages. Clinical trials with such ligands have shown therapeutic benefits in treating various chronic diseases like atherosclerosis, diabetes

mellitus, cardiovascular diseases, cancer, lung inflammation etc. These ligands have opened new doors for further exploration in direction of the therapeutic aspects of PPARs and make life of living creature disease free.

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