Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

DIFFERENT THERAPEUTIC ASPECTS OF PEROXISOMES PROLIFERATOR-ACTIVATED RECEPTORS

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ARTICLE INFO

Received:
12th Nov 2018
Received in revised form:
22th Apr 2019
Accepted:
19th May 2019
Available online:
28th June 2019

Keywords: PPAR, Diabetes, Metabolic Disorder, Rheumatoid arthritis.

ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) were discovered in 1990 and belong to the steroid hormone receptors superfamily. Three PPAR subtypes have been discovered so far: PPARα, PPARβ/δ, and PPARγ. Human peroxisome proliferator-activated receptors (h*PPAR*s) were initially identified as therapeutic targets for production of drugs to treat metabolic disorders, such as diabetes and dyslipidemia but now they are used in energy burning, dyslipidemia, diabetes, inflammation, hepatic steatosis, liver cancer, diabetic neuropathy, and atherosclerosis. These are included in the management of NIDDM, macrophage differentiation, adipose differentiation, anti-cancer processes, inhibition of TH2 cytokine production and rheumatoid arthritis. PPARβ/δ can be used to treat Huntington's disease, fertility disorders, and dyslipidemia. The functions of third PPAR isoforms and their ability as a therapeutic target are still unknown.

To Cite This Article: Shivali Singla, Chetna Jhagta, Sachin Goyal, Abhishek Kumar, (2019), "Different Therapeutic Aspects of Peroxisomes Proliferator-Activated Receptors", ***Pharmacophore, 10(3),*** *39-56*.

Introduction

Peroxisome proliferator-activated receptors (*PPAR*s) are transducer proteins belonging to the steroid receptor or nuclear receptor superfamily [1]. The nuclear hormone receptors (NRs) comprise of 48 members in humans and form the ligand-dependent transcription factors superfamily that control diverse biological functions [2]. Examples for NRs include the receptors of thyroid hormones, retinoid, steroid hormone receptors, and other various ligands. These receptors interact with specific ligands, translocate to the nucleus, change their structure and finally regulate the transcription of the target gene [3].

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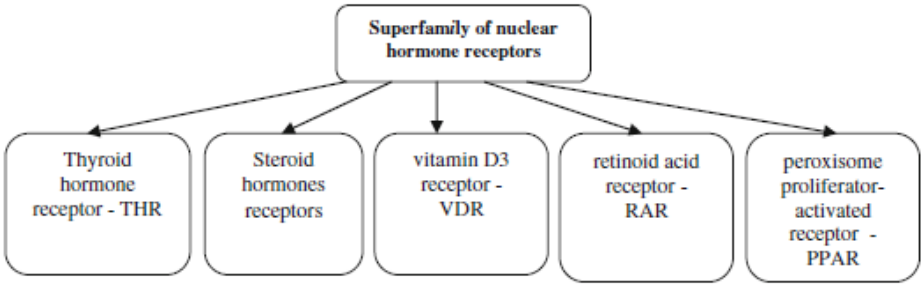


Figure 1. Nuclear hormone receptor superfamily [3]

Small lipophilic molecules, such as vitamins and hormones which are derived from dietary precursors directly or indirectly including retinoids, thyroid hormone, sterols, fatty acids, and their derivatives activate the members of the of NRs superfamily [4]. Three Peroxisome proliferator-activated receptors which are as nuclear hormone receptor superfamily members are *PPAR*α (NR1C1), *PPARβ/δ* (NR1C2) and *PPAR*γ (NR1C3) [5].

Background

Human peroxisome proliferator-activated receptors (h*PPAR*s) were initially identified as therapeutic targets for the production of drugs to treat metabolic disorders, such as diabetes and dyslipidemia [2]. The PPAR nuclear receptors subfamily was discovered in the 1990s [5]. These receptors were discovered in the 1990s in rodents and they were named according their peroxisome proliferation property [1]. Discovery and design of PPARs is the progressive process of over twenty five years with peroxisome proliferators. Peroxisome proliferators are chemicals which induce predictable and characteristic pleiotropic effects (multiple responses from a single gene) [6].

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

O'Malley's group was first described mammalian *PPAR*γ and Spiegelman discovered adipocyte-specific *PPAR*γ. *PPAR*γ was discovered in Xenopus and mammals based on the similarity to *PPAR*α. There are two isoforms of *PPAR*γ, γ1, and γ2, which are identical except, their first exons, *PPAR*γ2 that contains 30 additional amino acids at the N-terminus [4].

ISOLATION

PPARs are the members of the superfamily of steroid hormone receptor, which have been discovered in 1990 [8]. The microbodies were discovered by Rhodin in 1954 in the renal cells of mouse by using an electron microscope. Later in 1966, Baudhuin and De Duve isolated these organelles from the liver of rat and termed them *peroxisomes*. Peroxisomes were later discovered in all eukaryotic cells except in sperms and mature erythrocytes [9].

Existence of a specific mediator for peroxisome proliferation was suggested through the specificity of tissue and cell of the pleiotropic effects of chemicals called peroxisome proliferators. To discover this target, a cytosolic protein with a reversible stereospecific binding to nafenopin was detected in rat liver and then a receptor-mediated mechanism was postulated for peroxisome proliferation. A peroxisome proliferator-binding dimer protein with the molecular weight of 140,000-160,000 kDa was later isolated from the cytosol of rat liver. This protein could bind to chemicals called peroxisome proliferators which were structurally related to clofibrate [8].

It is suggested that the peroxisome proliferators act similar to the mechanism of steroid hormones because of their potential to modulate the transcription of specific genes. This assumption caused a significant discovery of a new member of the steroid hormone receptor superfamily, which was isolated by screening the cDNA library of a mouse. The cloned receptor was structurally related to steroid hormone receptors and was activated by various molecules including fatty acids and fibrates. The pattern of the receptor's mRNA expression and the tissue-specific effects of peroxisome proliferators were mirroring each other; therefore, it was thought that the identified receptor mediates the peroxisome proliferative response and it eventually was named peroxisome proliferator-activated receptor *(PPAR*) [8].

Following the initial discovery of mouse *PPAR*, it was recognized in other species including rat and human. Moreover, 3 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 it was found later to have a close relation to *PPAR*β, expressed in *Xenopus* [8].

STRUCTURE OF PEROXISOMES

The peroxisome has a single membrane surrounding a fine granular matrix. All three *PPAR* isoforms have similar functional and structural features. Mainly, 4 functional domains have been identified, called A/B, C, D and E/F (Fig. 2) [1].

Figure 2. The functional domains of PPARs [1]

The N-terminal A/B domain has a ligand-independent Activation Function-1 (AF-1), which is responsible for *PPAR* phosphorylation. The C domain or DNA binding domain (DBD) promotes the *PPAR* binding to the peroxisome proliferator response element (PPRE) in the target genes' promoter region. The D site is a docking domain for cofactors. The ligand binding domain (LBD) or E domain is responsible for ligand specificity and binding the *PPAR* to PPRE, which increases the target genes expression. Recruitment of *PPAR* co-factors to assist the processes of gene transcription is done by the ligand-dependent Activation Function-2 (AF-2), located in the E/F domain [1].

Enzymes

The matrix of the inside membrane of peroxisomes contains numerous enzymes such as Catalase, Manganese superoxide dismutase and Glutathione peroxidase. These enzymes are involved in several metabolic pathways including 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 species. Since nutritional and environmental factors have a significant impact on the peroxisomal enzyme, composition and function of peroxisomes differ among the organisms as well as the cells and tissues [9].

TYPES OF PPAR

Three major types of *PPAR* have been identified: *PPAR*α (NR1C1), *PPAR*β/δ (NR1C2), and *PPAR*γ (NR1C3). These 3 isotypes differ from each other in the ligand specificities, tissue distributions, physiological roles, and their encoding genes [1].

Alternative splicing of the gene and differential promoter usage generate 4 mRNA isoforms of *PPAR*γ which are PPARγ1, γ2, γ3, and γ4. However, γ3 and γ4 encode the same protein as PPARγ1 [10].

SITES

Peroxisomes are most abundant in the liver, playing numerous important roles. The 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 i.e. *PPAR*α, *PPAR*δ, and *PPAR*γ, are differentially expressed in a tissue-specific manner [2].

a) **PPARα-** expressed in the tissues with high fatty acid oxidation activities including liver, kidney, small intestine, heart, and skeletal muscle [6].

b) ***PPARβ-*** expressed with almost higher levels in the adipose tissue, skin, and brain [6].

c) ***PPARγ-*** expressed at a relatively high level in adipose [6]. *PPAR*γ1 and γ2 are predominantly expressed in adipocytes, *PPAR*γ1 is expressed in the tissues e.g., breast, colon, liver, vascular cells while expression of *PPAR*γ2 isoform appears to be completely adipocyte-specific [4].

ROLES OF PPAR

Human peroxisome proliferator-activated receptors (h*PPAR*s) are activated by endogenous saturated and unsaturated fatty acids, their metabolites, and synthetic ligands [2]. The *PPAR* proteins regulate many biological processes including reproduction, development and immune function [2]. *PPAR*s mediate neuroprotective effects in CNS, *PPARα,* and *PPAR*γ activation have opposite regulatory effects in bone formation [8].

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

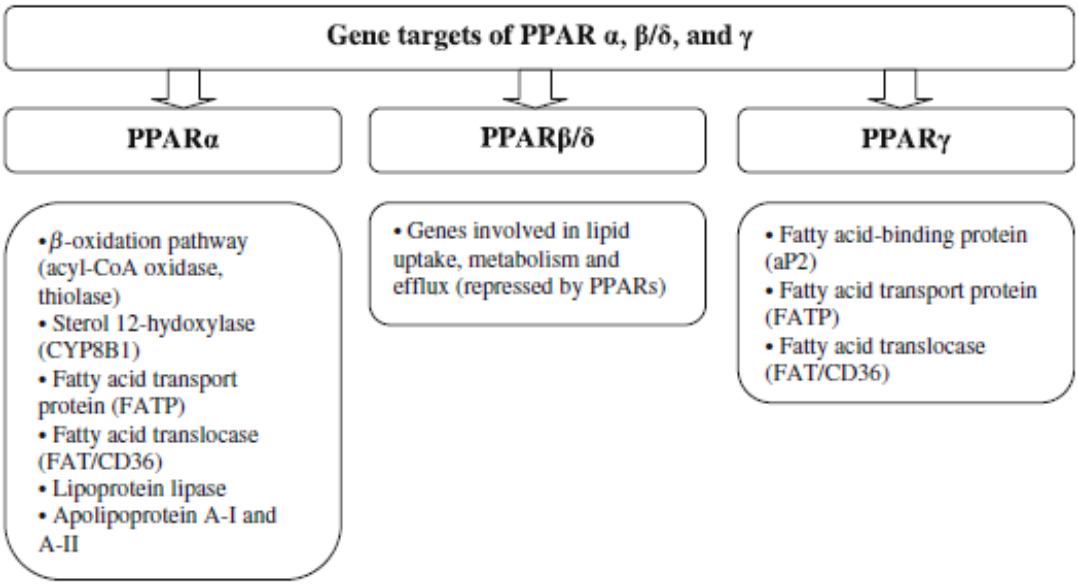


Figure 3. PPARs and their targets [3]

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

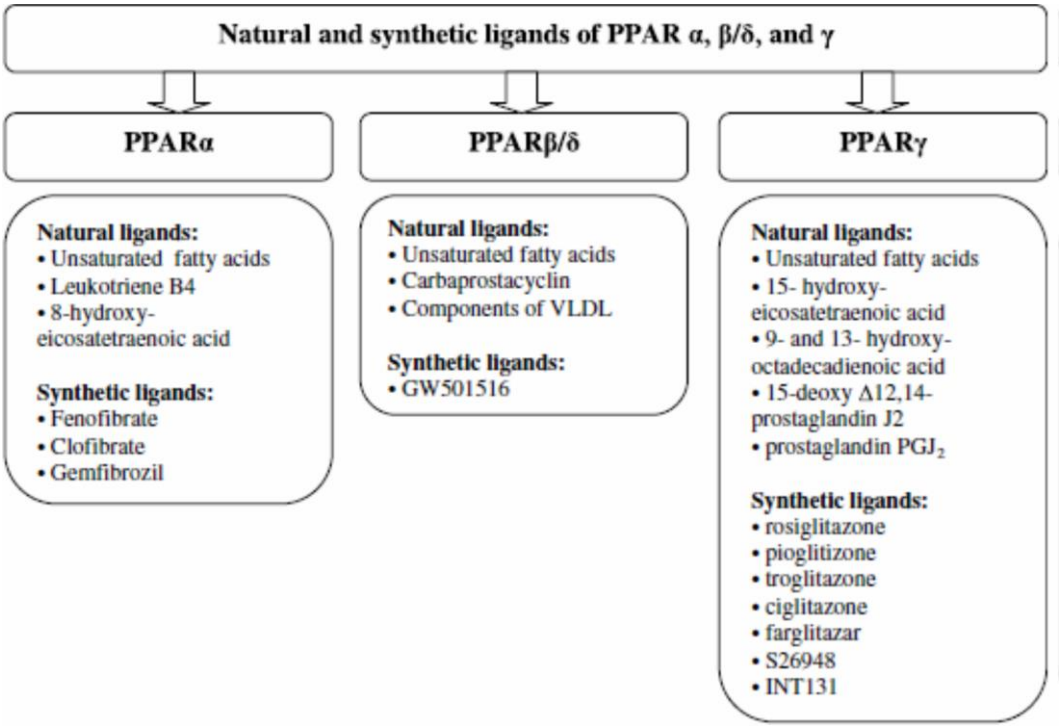


Figure 4. Synthetic and natural ligands of PPARs [3]

a) *PPARα*

PPARα is highly expressed in tissues, which metabolically are active, such as brown adipose tissue, liver, skeletal muscle, intestinal mucosa, and heart. This receptor is implicated in the metabolism of fatty acid and its activation lowers the lipid levels [3]. Moreover, *PPARα* is necessary for inflammatory responses, lipoprotein synthesis, and expansion of cancer in the rodent liver [6]. A few roles have been discussed in details below.

- **ENERGY BURNING**

All 3 types of the *PPAR* subfamily of nuclear receptors participate in the metabolism of energy. *PPARα* mostly is a catabolic energy regulator expenditure and regulates all 3 fatty acid oxidation systems. Some key enzymes, which are involved in these 3 fatty acid oxidation systems are regulated by *PPARα*. Hyperactivation of *PPARα* by drug intervention can be useful as an adjuvant to combat obesity in individuals [5].

- **HEPATIC STEATOSIS**

PPARα is important in the hepatic steatosis pathogenesis. *PPARα* influences the expression of hepatic lipogenic genes by regulating the primary transcription factors SREBP-1c and liver X receptor α (LXRα). Second, in conditions of increased demand for fatty acid oxidation, like starvation, *PPARα* is essential for up-regulation of some enzymes, which are necessary for the process. Under fasted conditions, *PPARα* senses the influx of lipid into the liver and upregulates all 3 systems of fatty acid oxidation to burn energy and lower hepatic steatosis. Furthermore, ethanol is known to inhibit fatty acid oxidation and this is attributed to ethanol inhibition of *PPARα* transcription. Hypo-activity of *PPARα* might play a role in the severity of alcoholic liver disease in the human [5].

- **DYSLIPIDEMIA (HYPOLIPIDEMIC EFFECTS)**

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

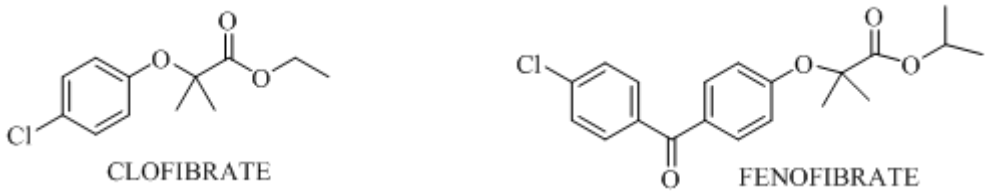


Figure 5. Clofibrate and fenofibrate structures

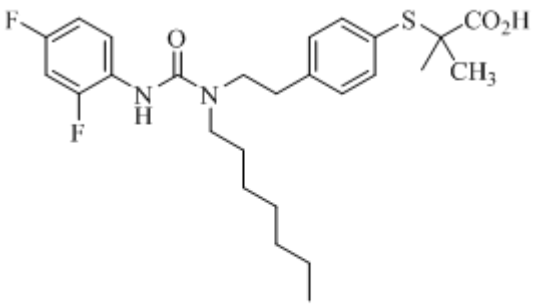


Figure 6. PPARα agonists GW 9578 [11]

- **DIABETES**

The clinically used fibrates are only moderately selective for *PPARα* over *PPARβ*, thus it is not clear whether activation of *PPARα* is responsible for any observed effects in case of diabetes or not [11].

- **INFLAMMATION**

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

Recent studies have shown new potential roles of *PPARα* and *PPARα* target genes as therapeutic targets in disorders involving inflammation including autoimmune disorders such as MS (multiple sclerosis), joint disease, and atherosclerosis [5].

- **LIVER CANCER**

The hepatocellular carcinomas (HCC) was first reported in 1976 in mice fed a diet which was contained of nafenopin that is a potent peroxisome proliferator. After that, several plasticizers and hypolipidemic compounds such as DEHA and DEHP induce liver tumors in mice and rats. With chronic exposure, hepatocellular carcinomas and hepatic adenomas develop in the rodents.

Peroxisome proliferator-induced liver tumors differ from tumors induced by classic genotoxic hepatocarcinogens. Since peroxisome proliferators are not mutagenic or DNA damage, it was suggested that these compounds form a new class of nongenotoxic hepatocarcinogens and this concept provides a basis for the receptor-mediated hepatocarcinogenesis**.**

In normal liver, hydrogen peroxide (H_2O_2) is produced as a byproduct of many oxidative reactions. Peroxisomal catalase degrades H_2O_2 in normal liver. An imbalance between the expression of enzymes capable of producing- and degrading-hydrogen peroxide and other reactive oxygen species in hepatocytes contributes to oxidative stress, oxidative DNA damage, and lipid peroxidation, DNA damage through oxidative stress and hepatocellular proliferation, together, are possible mechanisms responsible of hepatocellular carcinomas in rodents chronically exposed to peroxisome proliferators. Exposure to synthetic peroxisome proliferators activates *PPARα* and the transcription of its responsive genes, and these processes affect intermediary metabolism of the liver. These metabolic changes, along with the anti-apoptotic effect of *PPARα* activation, result in the oxidative damage of DNA and increased hepatocellular proliferation, which finally lead to liver cancer [5].

- **DIABETIC NEPHROPATHY**

Different factors contribute to induce and progress diabetic nephropathy but hyperlipidemia is considered as the main determinant of renal disease progression in diabetes mellitus patients. It was found that a high amount of lipids can lead to renal inflammation and injury [12].

Studies suggest that the hypolipidemic drugs like *PPARα* agonists can bring possible therapeutic outcome in preventing the development and progression of diabetic nephropathy. A *PPARα* agonist, fenofibrate**,** was noted to have renoprotection by reducing the glomerular lesions and albuminuria occurrence in experimental diabetic mice. However, numerous experimental and clinical studies showed that *PPARγ* agonists like thiazolidinedione class also have the therapeutic potential to prevent the nephropathy development in diabetics as these may be worthy in attenuating chronic hyperglycemia, insulin resistance, and inflammation-associated progression of diabetic nephropathy. Thus, *PPARα/γ* dual agonist not only improves lipid profile, glycemic control, and insulin resistance; but also significantly attenuates renal glomerular fibrosis and albuminuria by reducing the TGF-b expression and collagen deposition in the diabetic mice kidney. However, additional clinical studies are necessary to identify the protective effects of *PPARα* & *PPARγ* ligands on the renal function in diabetes mellitus patients [13].

- **ATHEROSCLEROSIS**

Evidence is emerging that *PPARα* 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 the 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 facilitates energy combustion [4]. However, they are also involved in lipid metabolism; fatty acid oxidation mainly in cardiac and skeletal muscles; and regulating blood glucose and cholesterol concentrations [3]. Activation of *PPARδ* increases physical performance and improve endurance performance hence abused by athletes. For the same reason, *PPARδ* agonists are characterized as *exercise mimetic* [8]. In liver, the free fatty acids of plasma, which are influxed during fasting conditions, can activate *PPARβ* [6]. Some roles have been discussed in details below.

- **HUNTINGTON'S DISEASE**

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

- **FERTILITY**

PPARδ activators including L-165041 or carbaprostacyclin 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 through activation of *PPARδ* [11].

- **DYSLIPIDEMIA**

It is likely that *PPARδ* is involved in lipid homeostasis because, like the other two subtypes, fatty acids and their metabolites activate this receptor [11].

c) PPARγ

PPARγ plays a major role in the regulation of energy balance, lipid biosynthesis, and adipogenesis. Moreover, this receptor participates in insulin sensitivity [3]. Adipogenesis and fat storage in adipocytes by *PPARγ* account for the insulin-sensitizing effect of the anti-diabetic drug, thiazolidinedione [6]. Few roles have been discussed in details, below.

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

Insulin resistance plays a key pathophysiological role in NIDDM. Fatty acids and eicosanoids are the ligands of *PPARγ*. Thiazolidinediones (TZDs) are a group of *PPARγ*-agonists, used to treat type 2 diabetes (T2D) since 1997. [7] TZDs have a very high affinity and increase insulin sensitivity in humans. The fatty acid binding protein (aP2) gene is the target of classic *PPARγ* in adipocytes, which is induced by TZDs and it has 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-cell by up-regulating the expression of genes which are involved in these processes [8].

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

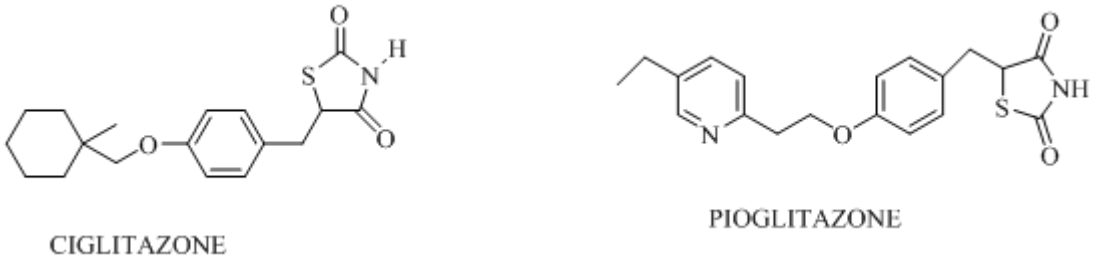


Figure 7. PPARγ agonists

The helpful metabolic effects of *PPARγ* agonist in the human type II diabetics treatment include a reduction in fasting plasma glucose, HbA1c, and postprandial glucose; increase in insulin sensitivity; improvement of pancreatic island β-cell function; increase in HDL levels; variable lowering of LDL levels; lowering diastolic blood pressure; and decrease the microalbuminuria [7].

Although the *PPARγ* agonists in use have good tolerability, the major side effects include upper respiratory tract infection, weight gain, headache, and edema. The main disadvantage of treatment with TZD is body fat gain [7].

- **MACROPHAGE DIFFERENTIATION**

PPARγ is an adipogenesis regulator and is plentiful in fat cells and at lower levels in other types of cells including macrophages. *PPARγ* ligands such as modified fatty acids, prostaglandin D2 metabolite 15d-PGJ2, and thiazolidinedione (TZD) can adjust macrophage inflammatory responses by reducing the expression of matrix-degrading nitric oxide, cytokines, metalloproteinases, and the modified lipoprotein receptors, which are known as macrophage-scavenger receptor class A (SRA) and enabling foam cell formation [15].

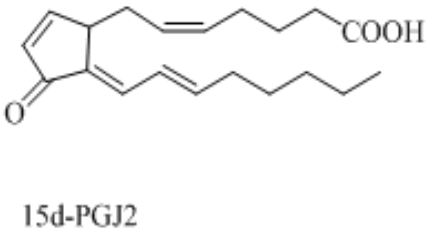
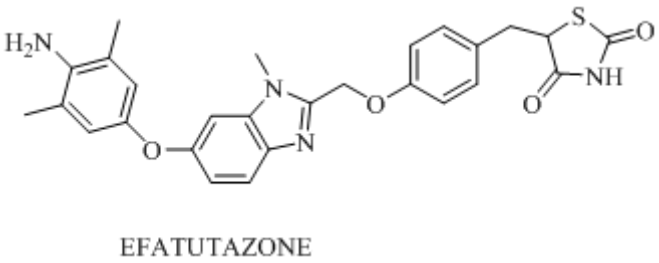


Figure 8. Structure of 15d-PGJ2

- **ADIPOSE DIFFERENTIATION**

PPARγ along with retinoid X receptor (RXR) forms a heterodimer and the dimer binds to *PPAR* response element (*PPRE*) and consequently regulate 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, *PPARγ* agonists promote the adipose tissues' differentiation, and there are many reports demonstrating that *PPARγ* agonists strongly promote the differentiation of fibroblast-like cells such as 3T3-L1 cells to adipocytes. Indeed, Efatutazone (CS-7017), a potent *PPARγ* full agonist, shows a differentiation-inducing activity in anaplastic thyroid carcinoma, non-small cell lung cancer, and pancreatic cancer under low concentrations in vitro [16].



EFATUTAZONE

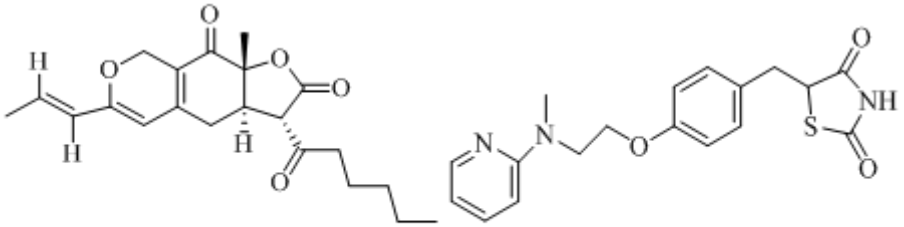
Figure 9. PPARγ agonist Efatutazone

- **ANTI-CANCER**

According to Keisuke Yamamoto's study, the activation of *PPARγ* potentially induces the differentiation of cancer cells. Indeed, Efatutazone (CS-7017), a potent *PPARγ* full agonist, shows 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 *PPARγ* agonists. In addition, a recent phase 1 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 *PPARγ* ligands have been found of Dihydrodibenzo [*b,e*]oxepine scaffold with very potent in vitro differentiation-inducing activity and a unique binding mode to the *PPARγ* LBD [16].

- **INHIBITION OF TH2 CYTOKINE PRODUCTION**

Yellow pigment monascin (MS) is a secondary metabolite, which is isolated from Monascus-fermented products and it has various physiological activities. MS and rosiglitazone (RG), that is the synthetic *PPARγ* ligand, considerably inhibit the production of Th2 cytokines, such as IL-4, IL-5, and IL-13, in PMA/ionomycin-activated mouse EL-4 T cells. This is due to cellular *PPARγ* translocation [17].



MONASCIN ROSIGLITAZONE

Figure 10. Monascin and Rosiglitazone structures

These results demonstrate that RG and MS promote the interactions of DNA −*PPARγ* and it is suggested that the regulatory effects of RG and MS on Th2 cytokine production could be abolished with *PPARγ* antagonist treatment. Nevertheless, the use of MS for immunomodulation is not known, yet [17].

- **RHEUMATOID ARTHRITIS**

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

- **LUNG INFLAMMATION**

*PPAR*γ agonists can modulate the pathway of oxidative stress to decrease the airway inflammation development. Oxidative stress is important in inflammation and lung damage. The lungs combat oxidative injury in part by the nuclear factor-erythroid 2 related factors 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 azaphilonoid structure and has cytotoxic and anti-inflammatory activities via *PPAR*γ. The effect of rosiglitazone (Rosi) and Monascus-fermented metabolite monascin (MS) on lung inflammation, induced by oxidative stress was evaluated in 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 STRATO HEPATITIS & ANTI-FIBROTIC**

Non-Alcoholic Steato Hepatitis (NASH) is a highly prevalent multifactorial and multi-step disease associated with the increased risk of cardiovascular mortality and development of severe liver conditions including hepatocellular carcinoma and cirrhosis. NASH is characterized by histopathological changes in the liver, including steatosis, inflammation, ballooning, necroinflammation, and perisinusoidal fibrosis. Fibrosis stage is the strongest predictor for all-cause and disease-specific mortality in NASH patients. Although the NASH pathogenesis is almost unclear, there is a consensus that hepatic steatosis and metabolic disorders are important in the initiation of the disease [20].

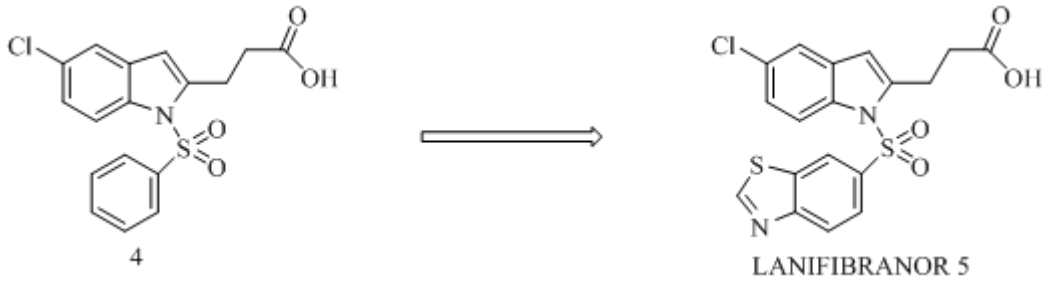


Figure 11. Compound 4 led to the formation of Lanofibranor 5

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

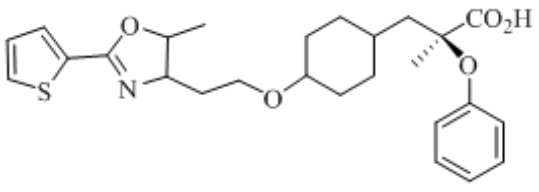
- **HYPERTENSION**

TZDs decreases 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].

LIGANDS

Various ligands, at various 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 investigations. The ligands have been described below.

a) α -ARYLOXY- α -METHYLHYDROCINNAMIC ACIDS



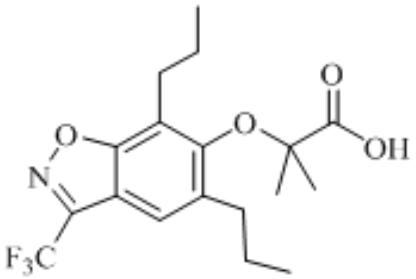
2

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

Xu Y described Dual *PPAR*α/γ agonistic activity of compound 2 for type 2 diabetes treatment and associated dyslipidemia. 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 co-transfection assay. Preclinically, compound 2 exhibited a remarkably

potent activity on *PPARγ*-mediated endpoints (insulin-sensitization and glucose lowering) but it appeared less potent on *PPARα*-mediated endpoints (HDL cholesterol elevation). Overall, the results of that research supported the hypothesis that compound 2 will stimulate both *PPARα* and *PPARγ* at similar plasma exposures in the clinical setting, thus providing optimal control of both hyperglycemia and dyslipidemia. Thus, compound 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



4

Figure 13. Compound 4 as PPARα/γ dual agonist

In Liu K's research, compound **4** was identified as *PPARα*/γ dual agonist with relative *PPARα* selectivity. Compound 4 showed a potent efficacy in lowering both lipids and glucose in animal models without causing any body weight gain. *PPARα* activity of compound 4 appeared to play an important role in decreasing glucose levels in db/db mice. The *PPARα* activity of compound 4 appeared to play a significant role in glucose lowering in db/db mice. On the basis of its in vivo and in vitro profiles, compound 4 was selected for further evaluation in man [22].

c) NOVEL *PPAR* α/γ/δ LIGANDS

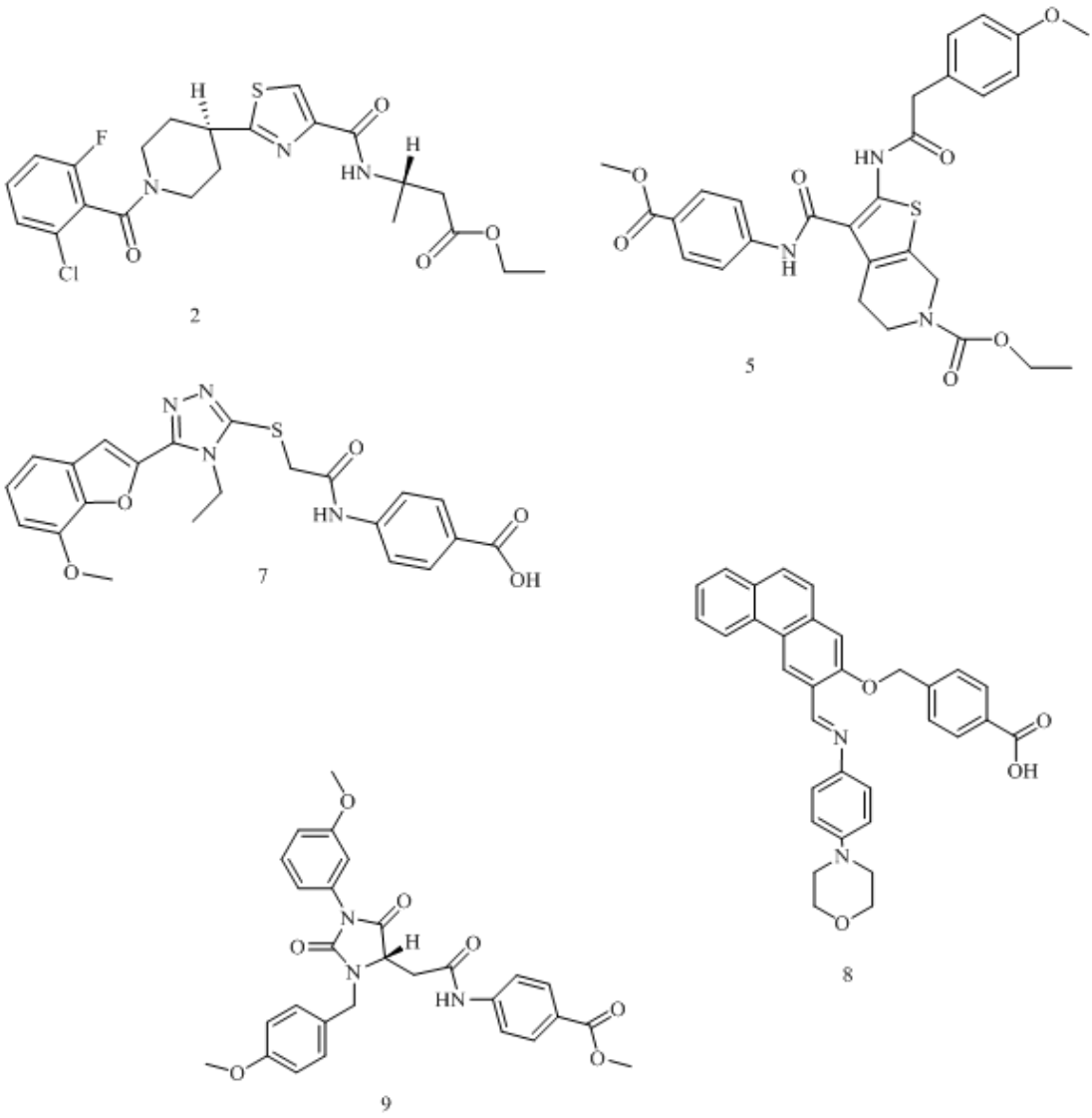
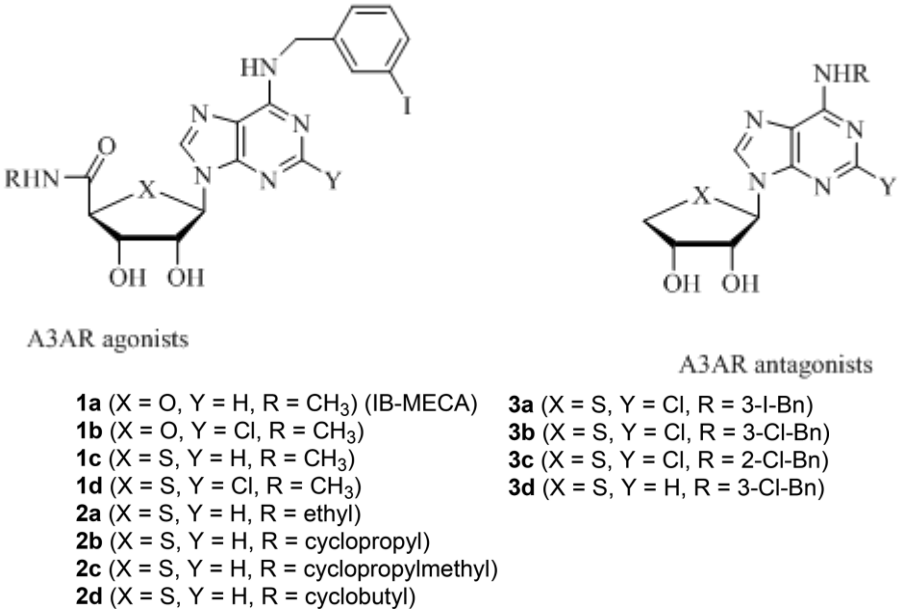


Figure 14. Compounds 5, 7, and 8 were identified as PPARα/γ agonists, whereas compounds 2 and 9 showed an agonistic activity for PPARγ, compound 9 was identified as a PPAR-d antagonist.

According to Markt P's research, compounds 5, 7, and 8 were identified as *PPAR*α agonists, while compounds 2 and 9 showed an agonistic activity for h*PPAR*γ and compound 9 was identified as *PPAR*δ antagonist. These were the *PPAR* ligands that can be used as drugs for atherosclerosis, dyslipidemia, and type 2 diabetes. Evidence suggested that agonists of the delta subtype are useful in the type 2 diabetes treatment and diet-induced obesity. Elevated expression of *PPAR*δ has been observed in cancer cells and thus, antagonists of *PPAR*δ are investigated for their use in novel anticancer therapy and *PPAR* ligands 2, 5, 7, 8, and 9 could be structurally optimized in order to obtain new drugs to treat atherosclerosis, dyslipidemia, and type 2 diabetes [23].

d) A3 ADENOSINE RECEPTOR LIGANDS WITH *PPARγ* PARTIAL AGONIST AND *PPARδ* ANTAGONIST AS ANTIDIABETIC



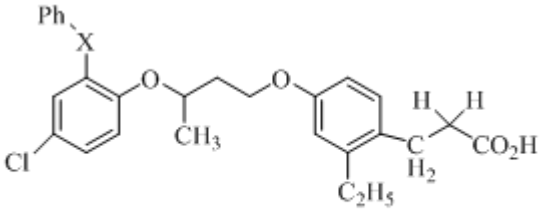
1a (X = O, Y = H, R = CH_3) (IB-MECA)
1b (X = O, Y = Cl, R = CH_3)
1c (X = S, Y = H, R = CH_3)
1d (X = S, Y = Cl, R = CH_3)
2a (X = S, Y = H, R = ethyl)
2b (X = S, Y = H, R = cyclopropyl)
2c (X = S, Y = H, R = cyclopropylmethyl)
2d (X = S, Y = H, R = cyclobutyl)

3a (X = S, Y = Cl, R = 3-I-Bn)
3b (X = S, Y = Cl, R = 3-Cl-Bn)
3c (X = S, Y = Cl, R = 2-Cl-Bn)
3d (X = S, Y = H, R = 3-Cl-Bn)

Figure 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 A3AR ligands is associated with previously undetected interactions, i.e., both *PPARγ* partial agonism, and *PPARδ* 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 A3AR agonist or A3AR antagonist activity. In addition, when 1a and related A3AR ligands are clinically developed as A3AR modulators to treat A3AR-associated clinical conditions, the adverse effects or clinical benefits associated with *PPARγ* partial agonism and *PPARδ* antagonism should be considered [24].

e) DUAL PPARγ/δ AGONISTS AS EUGLYCEMIC AGENTS



20

Figure 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, compound 20 possesses a potent dual h *PPAR*γ/δ agonist profile to treat type 2 diabetes and associated dyslipidemia. In preclinical models, compound 20 improves the sensitivity of insulin 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].

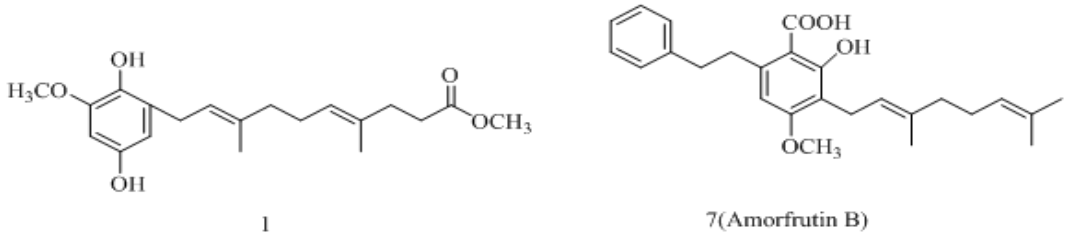
f) LINOLEIC ACID OXIDATION MODULATES PPAR β/δ SUPPRESSION OF PPARγ ACTIVITY

In colon cancer cells, 15-LOX-1 (15-lipoxygenase-1) expression is lost and *PPAR*-β/δ is overexpressed, 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 downregulates *PPAR*-β/δ expression and thus promotes *PPAR*γ activity (Figure 5h).

Adding linoleic acid to the culture medium increased the production of 13-S-HODE in the 15- LOX-1-transfected cells, while adding caffeic acid (a 15-LOX-1 inhibitor) in a certain concentration specifically inhibited the enzymatic activity of 15-LOX-1. Additional studies are necessary to further elucidate how the signaling of polyunsaturated fatty acid oxidative

metabolic pathways modulates the interaction between *PPAR*s to influence important biologic events such as apoptosis in the cells [26].

g) *PPAR*-γ AGONIST AS ANTI-INFLAMMATORY AGENT

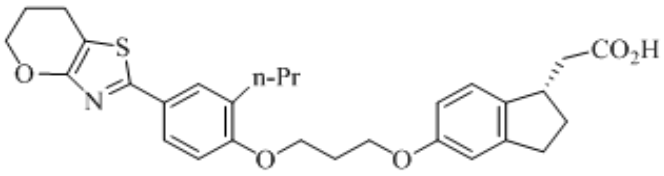


1 7(Amorfrutin B)

Figure 17. New meroterpene derivative, chrysogenester [1] & natural *PPARγ* agonist amorfrutin

A study on *Penicillium chrysogenum* J08NF-4, a jellyfish-derived fungus led to the isolation of 4 known farnesyl meroterpenes, as well as 2 new meroterpene derivatives, 5- farnesyl-2-methyl-1-O-methyl-hydroquinone and chrysogenester [1]. Docking analysis of chrysogenester demonstrated that it binds to *PPARγ* similar to the natural *PPARγ* agonist amorfrutin B [7]. Suppressing the inflammatory response is the main biological function of PPARγ agonists is to. An in vitro study was conducted to evaluate the anti-inflammatory potency of chrysogenester and the involved mechanism. In RAW 264.7 macrophages. Chrysogenester suppressed the expression of the pro-inflammatory mediators iNOS, COX-2, NO, TNF-a, IL-1ß, and IL-6. Their findings suggested that chrysogenester could be viewed as a starting point for the development of anti-inflammatory therapeutics [27].

h) INDANYLACETIC ACID DERIVATIVES- *PPARα*/δ/γ PAN AGONISTS



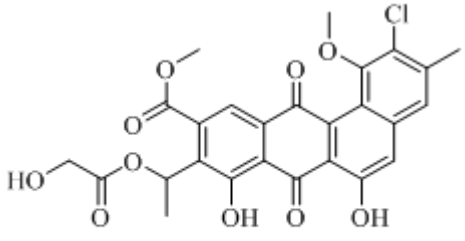
34r

Figure 18. Recently identified indanylacetic acid moiety as a well-tunable *PPAR* agonist

In s study, 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 *PPARα/γ/δ* 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 the standard. Hence, *PPARα/γ/δ* pan agonists hold potential for treatment of diabetes and associated dyslipidemia [28].

i) CHLOROCYCLINONES (A-D) ANTAGONIZING PPAR-γ 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-dihydrotetraphene-10 carboxylate [29].

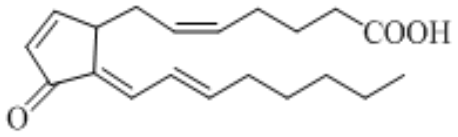


3

Figure 19. Chlorocyclinone C, isolated from the mycelium of Streptomyces sp. strain DSM 17045

According to Potterat O's study, 4 new chlorinated angucyclinones, chlorocyclinones A-D(1-4) were isolated from the mycelium of Streptomyces sp. strain DSM 17045 in the screening to identify new *PPARγ* modulators to treat type 2 diabetes. It was proved that the compounds were active in antagonizing rosiglitazone-induced *PPARγ* activity as well as in a cell-based reporter gene assay. Chlorocyclinone C showed the most potent activity in all assays. The compounds were not only able to antagonize the rosiglitazone-induced *PPARγ* activation, but also precluded rosiglitazone from binding due to overlapping binding sites. Chlorocyclinone C was the most active and displaced rosiglitazone [29].

j) 15d-PGJ2— NATURAL *PPARγ* LIGAND



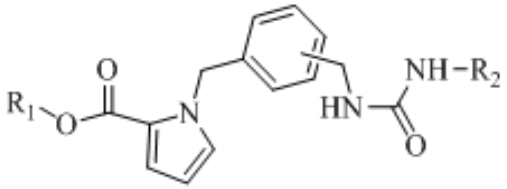
15d-PGJ2

Figure 20. Natural ligands for *PPARγ* is 15d-PGJ2 (15-deoxy-D12,14-prostaglandin J2)

Recent studies showed that the full-length *PPARγ* was indeed expressed in activated monocytes/macrophages and B, T cells. The ligands for *PPARγ* include 15-deoxy-D12,14-prostaglandin J2 (15d-PGJ2)—a natural ligand from the pathway of prostaglandin synthesis, and ''glitazones''—drugs, utilized in the treatment of diabetes. New evidence shows that *PPARγ* and its ligands are important for the modulation of inflammatory and immune reactions.

Therapeutic efficacy of *PPARγ* agonist has been tested on animal models. The results showed that the compound could attenuate chronic and acute 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. Additional research is necessary in this direction [30].

k) DUAL MODULATORS OF SOLUBLE EPOXIDE HYDROLASE & *PPAR*s



6

name	R_1	R_2	subst
6e	H	adamantyl	*m*-
6f	H	adamantyl	*p*-
6h	H	Ph-*p*OCF_3	*m*-
6i	H	Ph-*p*OCF_3	*p*-

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

In a study by Buscato E, an acidic pyrrole head group, known as a pharmacophore important for *PPAR* dual agonistic activity, was combined with different hydrophobic urea derivatives to introduce an epoxide mimetic. The resulting compounds highly inhibited on sEH and different patterns of *PPAR* agonistic activity. Regarding dual modulation of sEH/*PPAR*, two compounds were obtained the partially activated *PPAR*. (6e, 6f) and inhibited sEH with moderate potency. Compound 6h inhibited sEH and activated *PPARα/γ/δ*. Compound 6i inhibited sEH and activated *PPARα/γ*, resulting in an interesting compound for evaluation in further experiments [31].

That study demonstrated that the pharmacophores of *PPAR* agonists and sEH inhibitors could be easily combined and result in a simplified blueprint of a dual sEH/*PPAR* modulator. Further in vivo pharmacological evaluation studies are necessary to show the most promising profile for the metabolic syndrome treatment [31].

l) *PPAR* γ MODULATORS- ANTI-INFLAMMATORY

183 [(R)(-)-GED-0507-34] 5-Aminosalicylic acid

Figure 22. Ligand for *PPAR* with Anti-Inflammatory Activity

According to the study of Speca S, compound 183 demonstrated 100 to 150 fold higher anti-inflammatory activity than 5-ASA. 5-Aminosalicylic acid (5-ASA) (Figure 22) is an anti-inflammatory drug, currently used to treat inflammatory bowel disease, inflammation of the digestive tract, ulcerative colitis, and mild-to-moderate Crohn's disease. Its mechanism of action has been clarified as being *PPARγ* dependent. Compound 183 gave promising results in both in vivo and in vitro experimental models of colitis, and its specificity appeared to be very good, without any adverse events. It currently is in phase 2 of clinical trials [32].

m) *PPARγ* AGONISTS WITH INDOLEGLYOXYLYL MOIETIES

7 new amino acid derivatives (1-4 and 6-8) were isolated from MeOH extracts of the marine ascidian Herdmania momus. Analogs with indoleglyoxylyl moieties (5, 6, and 8) showed a significant *PPARγ* activation in Ac2F rat liver cells. Since *PPARγ* is a potent agent to treat type II diabetes, inflammatory disorders of CNS, CVD and tissue injury associated with ischemia and reperfusion, it could be utilized for the same after further research [33].

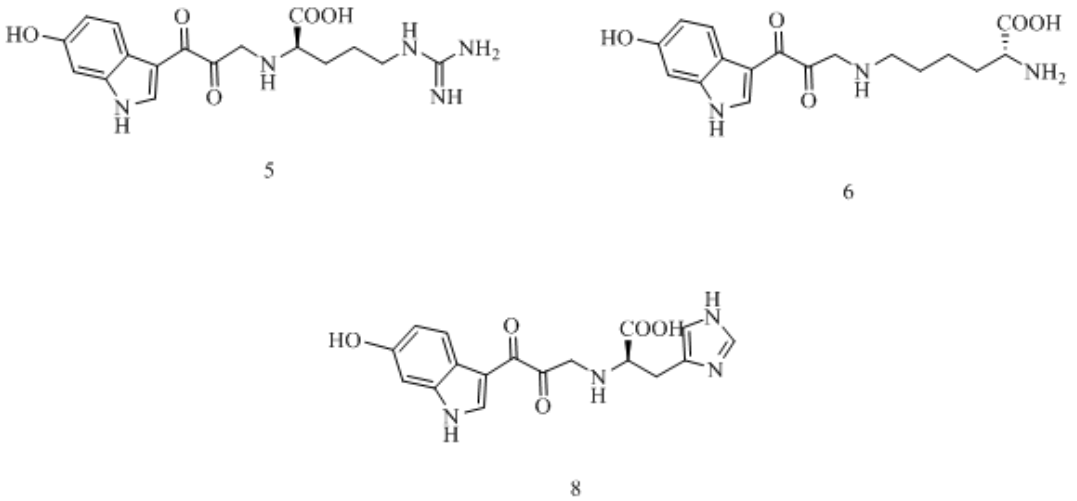
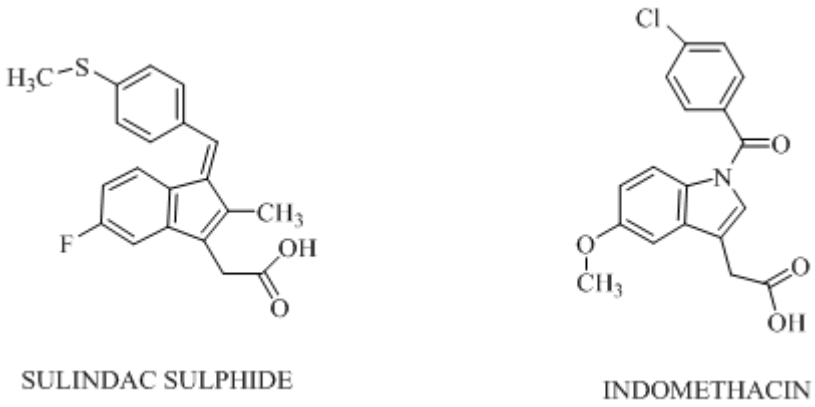


Figure 23. Analogs with indoleglyoxyl moieties (5, 6, and 8) showed significant PPARγ activation in Ac2F rat liver cells

n) NSAIDS IN CANCER

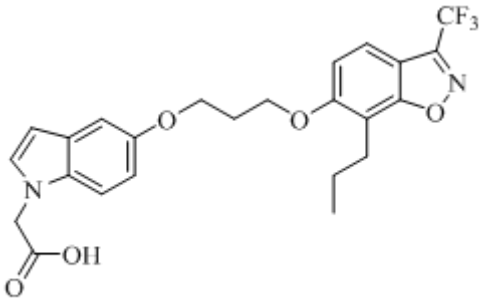


SULINDAC SULPHIDE INDOMETHACIN

Figure 24. NSAIDs mediate their anti-tumorigenic activity in colorectal cancer through *PPARδ*

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



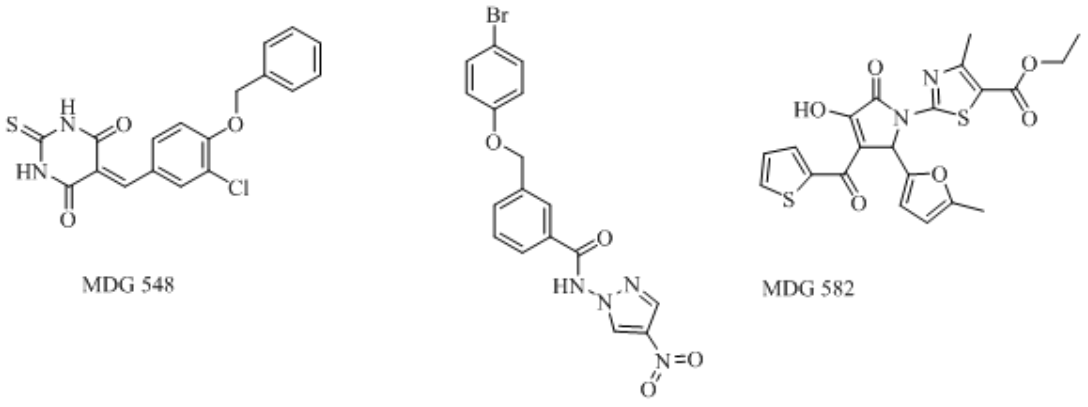
14

Figure 25. Lead compound 14, an indole compound with a benzisoxazole tail displayed a potent *PPAR* agonistic activity

According to the investigation of Mahindroo N, in vitro evaluation led to the identification of new indole compounds with a benzisoxazole tail as potent *PPAR* agonists with the lead compound 14 (BPR1H036). Structural biology studies of compound 14 demonstrated that the indole ring had strong hydrophobic interactions with *PPARγ* and could be an important moiety for binding to the protein. Compound 14 displayed efficacious glucose lowering activity in KKAy mice and a great pharmacokinetic profile in BALB/c 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-pyrazole-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].



MDG 548

MDG 559

MDG 582

Figure 26. Compounds display high-affinity competitive binding to the *PPAR*γ

MDG 548 displayed a 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 3 subtypes of *PPAR* could have benefits in a wide range of metabolic diseases. Compound MDG 582 was shown to have a dual affinity for both *PPAR*γ and *PPAR*δ. On the basis of the intricate involvement of *PPAR*γ/δ on lipid metabolism, a dual target modulation has been suggested as a potentially beneficial approach toward the treatment of hyperlipidemia, insulin resistance, and attenuation of atherogenesis [35].

Conclusion

Peroxisome proliferator-activated receptors (PPARs) belong to the steroid hormone receptors superfamily and were discovered in the year 1990. PPAR has 3 subtypes which have been identified as *PPARα, PPARβ/δ*, and *PPARγ. PPARα* has been implicated in energy burning, hepatic steatosis, dyslipidemia, diabetes, inflammation, liver cancer, diabetic neuropathy, atherosclerosis. *PPARγ* is involved in NIDDM, macrophage differentiation, adipose differentiation, anti-cancer, inhibition of TH2 cytokine production and rheumatoid arthritis. *PPARβ/δ* is involved in Huntington's disease, fertility, dyslipidemia. The functions of the third PPAR isoform and its ability as a therapeutic target are under studying.

Some of the PPAR ligands are under use for therapeutic purposes like Fibrates and TZDs. However, researches are ongoing 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 different chronic diseases like diabetes mellitus, atherosclerosis cardiovascular diseases, cancer, lung inflammation, etc. These ligands have given new insights in further exploration in the direction of the therapeutic aspects of PPARs and make a disease-free life.

References

1. Kota BP, Huang TH, Roufogalis BD. An overview on biological mechanisms of PPARs. Pharmacological Research. 2005 Feb 1;51(2):85-94.
2. Kuwabara N, Oyama T, Tomioka D, Ohashi M, Yanagisawa J, Shimizu T, Miyachi H. Peroxisome proliferator-activated receptors (PPARs) have multiple binding points that accommodate ligands in various conformations: phenylpropanoic acid-type PPAR ligands bind to PPAR in different conformations, depending on the subtype. Journal of medicinal chemistry. 2012 Jan 10;55(2):893-902.
3. Grygiel-Górniak B. Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications-a review. Nutrition journal. 2014 Dec;13(1):17.
4. Lazar MA. PPARγ, 10 years later. Biochimie. 2005 Jan 1;87(1):9-13.
5. Pyper SR, Viswakarma N, Yu S, Reddy JK. PPARα: energy combustion, hypolipidemia, inflammation and cancer. Nuclear receptor signaling. 2010 Jan;8(1):nrs-08002.
6. Viswakarma N, Jia Y, Bai L, Vluggens A, Borensztajn J, Xu J, Reddy JK. Coactivators in PPAR-regulated gene expression. PPAR research. 2010;2010.
7. Larsen TM, Toubro S, Astrup A. PPARgamma agonists in the treatment of type II diabetes: is increased fatness commensurate with long-term efficacy?. International journal of obesity. 2003 Feb;27(2):147.
8. Badr MZ, Youssef JA, editors. Peroxisome proliferator-activated receptors (PPARs): methods and protocols. Humana Press; 2013.
9. Youssef JA, Badr MZ. Peroxisome proliferator-activated receptors: discovery and recent advances. Springer Science & Business Media; 2013 Apr 18.
10. Wang N, Yin R, Liu Y, Mao G, Xi F. Role of peroxisome proliferator-activated receptor-γ in atherosclerosis. Circulation Journal. 2011;75(3):528-35.
11. Willson TM, Brown PJ, Sternbach DD, Henke BR. The PPARs: from orphan receptors to drug discovery. Journal of medicinal chemistry. 2000 Feb 24;43(4):527-50.
12. Balakumar P, Kadian S, Mahadevan N. Are PPAR alpha agonists a rational therapeutic strategy for preventing abnormalities of the diabetic kidney?. Pharmacological Research. 2012 Apr 1;65(4):430-6.
13. Balakumar P, Arora MK, Singh M. Emerging role of PPAR ligands in the management of diabetic nephropathy. Pharmacological research. 2009 Sep 1;60(3):170-3.
14. Dickey AS, Pineda VV, Tsunemi T, Liu PP, Miranda HC, Gilmore-Hall SK, Lomas N, Sampat KR, Buttgereit A, Torres MJ, Flores AL. PPAR-δ is repressed in Huntington's disease, is required for normal neuronal function and can be targeted therapeutically. Nature medicine. 2016 Jan;22(1):37.
15. Moore KJ, Rosen ED, Fitzgerald ML, Randow F, Andersson LP, Altshuler D, Milstone DS, Mortensen RM, Spiegelman BM, Freeman MW. The role of PPAR-γ in macrophage differentiation and cholesterol uptake. Nature medicine. 2001 Jan;7(1):41.
16. Yamamoto K, Tamura T, Henmi K, Kuboyama T, Yanagisawa A, Matsubara M, Takahashi Y, Suzuki M, Saito JI, Ueno K, Shuto S. Development of Dihydrodibenzooxepine Peroxisome Proliferator-Activated Receptor (PPAR) Gamma Ligands of a Novel Binding Mode as Anticancer Agents: Effective Mimicry of Chiral Structures by Olefinic E/Z-Isomers. Journal of Medicinal Chemistry. 2018 Oct 23;61(22):10067-83.
17. Hsu WH, Lee BH, Hsu YW, Pan TM. Inhibition of Th2 cytokine production in T cells by monascin via PPAR-γ activation. Journal of agricultural and food chemistry. 2013 Aug 14;61(34):8126-33.
18. Li XF, Sun YY, Bao J, Chen X, Li YH, Yang Y, Zhang L, Huang C, Wu BM, Meng XM, Li J. Functional role of PPAR-γ on the proliferation and migration of fibroblast-like synoviocytes in rheumatoid arthritis. Scientific reports. 2017 Oct 4;7(1):12671.

19. Hsu WH, Lee BH, Pan TM. Monascin attenuates oxidative stress-mediated lung inflammation via peroxisome proliferator-activated receptor-gamma (PPAR-γ) and nuclear factor-erythroid 2 related factor 2 (Nrf-2) modulation. Journal of agricultural and food chemistry. 2014 Jun 3;62(23):5337-44.
20. Boubia B, Poupardin O, Barth M, Binet J, Peralba P, Mounier L, Jacquier E, Gauthier E, Lepais V, Chatar M, Ferry S. Design, Synthesis, and Evaluation of a Novel Series of Indole Sulfonamide Peroxisome Proliferator Activated Receptor (PPAR) α/γ/δ Triple Activators: Discovery of Lanifibranor, a New Antifibrotic Clinical Candidate. Journal of medicinal chemistry. 2018 Feb 15;61(6):2246-65.
21. Xu Y, Rito CJ, Etgen GJ, Ardecky RJ, Bean JS, Bensch WR, Bosley JR, Broderick CL, Brooks DA, Dominianni SJ, Hahn PJ. Design and synthesis of α-aryloxy-α-methylhydrocinnamic acids: a novel class of dual peroxisome proliferator-activated receptor α/γ agonists. Journal of medicinal chemistry. 2004 May 6;47(10):2422-5.
22. Liu K, Xu L, Berger JP, MacNaul KL, Zhou G, Doebber TW, Forrest MJ, Moller DE, Jones AB. Discovery of a novel series of peroxisome proliferator-activated receptor α/γ dual agonists for the treatment of type 2 diabetes and dyslipidemia. Journal of medicinal chemistry. 2005 Apr 7;48(7):2262-5.
23. Markt P, Petersen RK, Flindt EN, Kristiansen K, Kirchmair J, Spitzer G, Distinto S, Schuster D, Wolber G, Laggner C, Langer T. Discovery of novel PPAR ligands by a virtual screening approach based on pharmacophore modeling, 3D shape, and electrostatic similarity screening. Journal of medicinal chemistry. 2008 Sep 27;51(20):6303-17.
24. Yu J, Ahn S, Kim HJ, Lee M, Ahn S, Kim J, Jin SH, Lee E, Kim G, Cheong JH, Jacobson KA. Polypharmacology of N 6-(3-Iodobenzyl) adenosine-5′-N-methyluronamide (IB-MECA) and Related A3 Adenosine Receptor Ligands: Peroxisome Proliferator Activated Receptor (PPAR) γ Partial Agonist and PPARδ Antagonist Activity Suggests Their Antidiabetic Potential. Journal of medicinal chemistry. 2017 Aug 28;60(17):7459-75.
25. Xu Y, Etgen GJ, Broderick CL, Canada E, Gonzalez I, Lamar J, Montrose-Rafizadeh C, Oldham BA, Osborne JJ, Xie C, Shi Q. Design and synthesis of dual peroxisome proliferator-activated receptors γ and δ agonists as novel euglycemic agents with a reduced weight gain profile. Journal of medicinal chemistry. 2006 Sep 21;49(19):5649-52.
26. Potterat O, Puder C, Wagner K, Bolek W, Vettermann R, Kauschke SG. Chlorocyclinones A− D, Chlorinated Angucyclinones from Streptomyces sp. Strongly Antagonizing Rosiglitazone-Induced PPAR-γ Activation. Journal of natural products. 2007 Nov 29;70(12):1934-8.
27. Liu S, Su M, Song SJ, Hong J, Chung HY, Jung JH. An Anti-inflammatory PPAR-γ Agonist from the Jellyfish-derived Fungus Penicillium chrysogenum J08NF-4. Journal of natural products. 2018 Feb 1;81(2):356-63.
28. Rudolph J, Chen L, Majumdar D, Bullock WH, Burns M, Claus T, Dela Cruz FE, Daly M, Ehrgott FJ, Johnson JS, Livingston JN. Indanylacetic Acid Derivatives Carrying 4-Thiazolyl-phenoxy Tail Groups, a New Class of Potent PPAR α/γ/δ Pan Agonists: Synthesis, Structure− Activity Relationship, and In Vivo Efficacy. Journal of medicinal chemistry. 2007 Mar 8;50(5):984-1000.
29. Potterat O, Puder C, Wagner K, Bolek W, Vettermann R, Kauschke SG. Chlorocyclinones A− D, Chlorinated Angucyclinones from Streptomyces sp. Strongly Antagonizing Rosiglitazone-Induced PPAR-γ Activation. Journal of natural products. 2007 Nov 29;70(12):1934-8.
30. Zhang X, Young HA. PPAR and immune system—what do we know?. International immunopharmacology. 2002 Jul 1;2(8):1029-44.
31. Buscató EL, Blöcher R, Lamers C, Klingler FM, Hahn S, Steinhilber D, Schubert-Zsilavecz M, Proschak E. Design and synthesis of dual modulators of soluble epoxide hydrolase and peroxisome proliferator-activated receptors. Journal of medicinal chemistry. 2012 Nov 19;55(23):10771-5.
32. Pirat C, Farce A, Lebègue N, Renault N, Furman C, Millet R, Yous S, Speca S, Berthelot P, Desreumaux P, Chavatte P. Targeting peroxisome proliferator-activated receptors (PPARs): development of modulators. Journal of medicinal chemistry. 2012 Feb 27;55(9):4027-61.
33. Li JL, Xiao B, Park M, Yoo ES, Shin S, Hong J, Chung HY, Kim HS, Jung JH. PPAR-γ agonistic metabolites from the ascidian Herdmania momus. Journal of natural products. 2012 Nov 28;75(12):2082-7.
34. Mahindroo N, Huang CF, Peng YH, Wang CC, Liao CC, Lien TW, Chittimalla SK, Huang WJ, Chai CH, Prakash E, Chen CP. Novel indole-based peroxisome proliferator-activated receptor agonists: design, SAR, structural biology, and biological activities. Journal of medicinal chemistry. 2005 Dec 29;48(26):8194-208.
35. Nevin DK, Peters MB, Carta G, Fayne D, Lloyd DG. Integrated virtual screening for the identification of novel and selective peroxisome proliferator-activated receptor (PPAR) scaffolds. Journal of medicinal chemistry. 2012 May 24;55(11):4978-89.