Int J Pharm Bio Sci 2015 Oct; 6(4): (P) 46 - 69

**Review Article** **Medicinal chemistry**

**International Journal of Pharma and Bio Sciences** **ISSN 0975-6299**

# DIABETES MELLITUS: RECENT ADVANCEMENT IN PPAR AGONISTS AS THERAPEUTIC AGENTS

**GOPAL L. KHATIK***

*School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar (Punjab), India–144411*

## ABSTRACT

Diabetes mellitus is known as metabolic disorder related to glucose intolerance which is characterized by hyperglycemia. Diabetes mellitus can be treated by insulin and oral hypoglycemic agents. Most of known oral hypoglycemic are peroxisome proliferator-activated receptors (PPAR) agonist. There are three different subtypes of PPARs are identified and they are involved in glucose metabolism. A balanced PPARs agonist is required to avoid consequences related to over activation of one of the receptor subtypes. PPAR agonist has a good influence on activation of PPAR due to their chirality, therefore this review discusses the advancement and role of chirality on PPAR activation by PPAR agonists.

**KEYWORDS:** **Diabetes mellitus, hypoglycemia, PPAR agonist, oral hypoglycemic.**

**GOPAL L. KHATIK**
**School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar (Punjab), India–144411**

***Corresponding author**

# 1. INTRODUCTION

Among the life style diseases obesity and diabetes are increasing at a tremendous rate all over the world. An estimate by the International Diabetes Federation says that the cases of diabetes in India have more than doubled from 1995 (19.4 millions) to 2013 (49.7 millions), and are projected to increase approximately up to 69.7 million (approximately) by 2025 (Figure 1)[1,2]. This is probably the highest number of diabetics in any country. World Health Organization also estimated that mortality related to heart disease and diabetes costs nearly $210 billion each year and is expected to rise to $335 billion in the coming 10 years[1,2].

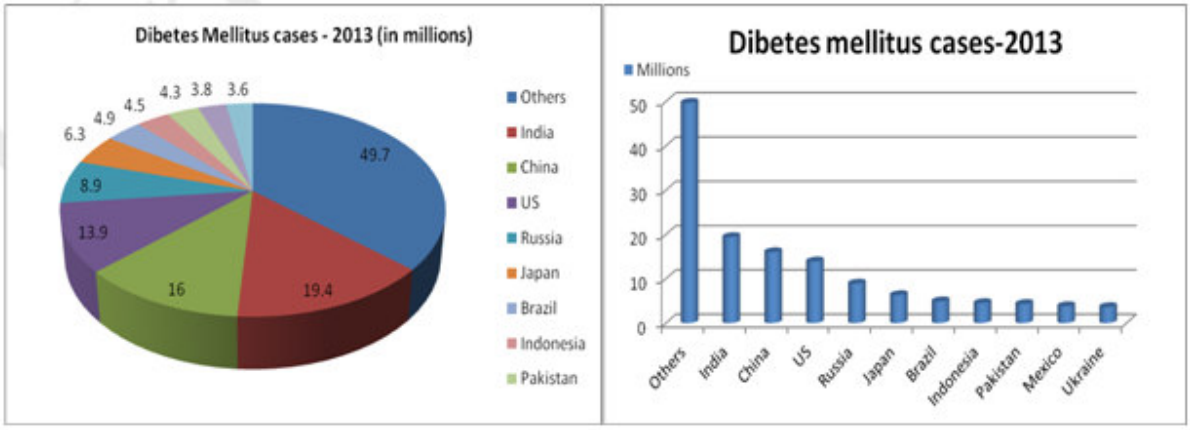


**Figure 1**
***Estimated number of adults with diabetes, 2013[1,2].***

Diabetes mellitus (DM) is characterized by hyperglycemia which is a consequence of changed metabolism of carbohydrates, lipids, proteins. Diabetes can be classified as Type 1 or Type 2 DM. Type 1 DM (insulin dependent), is caused by lack of insulin, which must be injected or inhaled to sustain the patient. Type 2 DM (non-insulin dependent) is a metabolic disorder characterized by increased blood glucose level. In India, approximately 95% of the diabetic patients are of Type 2 DM[1,2].

## *2. HISTORY OF DIABETES*

Diabetes mellitus, as described by an Egyptian priest, is characterized by excessive urination and weight loss and the urine of a diabetic patient attracting insects like ants and bees. Progress of scientific study of diabetes began only in the 18th century i.e. after the development of the microscope which helped in identification of Langerhan's containing β cell in the pancreas[3]. "Diabetes" is derived from Greek and it means "to siphon out". Its symptoms are excessive loss of water through polyuria, and urination. "Mellitus", derived from Latin, means "sweet". So diabetes mellitus is also known as sweet urine disease. Diabetes mellitus is considered as a metabolic disease of unknown cause resulting in deficiency of insulin (the pancreatic hormone) and an irregularity in the release of glucagon (a polypeptide hormone). It may promote many other symptoms or diseases such as arteriosclerosis, blindness etc. The normal blood sugar in human is between 80 to 120 mg/dl (empty stomach), and 120 to 160 mg/dl after meal. But during bedtime, it varies from 100 to 140 mg/dl. Any kind of variation from the above mentioned value range is indicative of diabetes.

### *Complications caused by Diabetes*

(i) Diabetic nephropathy: Causes swelling in the legs and feet, which progresses further into other body parts.
(ii) Diabetic retinopathy: Pain in the eyes, which may lead to loss of vision.

(iii) Diabetic neuropathy: Tingling, burning, tightness, numbness, shooting pain in the feet, hands and other body parts.

## *3. TREATMENT OF DIABETES*

### *3.1 Insulin therapy*

Insulin used currently is in seven forms classified as per their duration of action, i.e. fast, intermediate, or long-acting. A majority of the insulin is being prepared from beef or beef/pork pancreas. This insulin contains pancreatic enzymatic impurities such as somatostatin, glucagon, pancreatic proinsulin and polypeptide. This impure insulin was reported to have adverse effects on many patients. Normally the body of an organism refuses foreign protein or abnormal protein injected into it, recognizing it as a poison which is quickly excreted by the body.

### *3.2 Oral hypogycemic agents*

Janbon et al. reported that sulfonamides are found to be hypoglycemic. Thereafter, 1-butyl-3-sulfonylurea (carbutamide) was clinically used first as an effective treatment for diabetes. Although later it was withdrawn due to its side effect like bone marrow depression. This compound led to the discovery and development of the sulfonylureas class of drugs (Figure 2, Table 1). Tolbutamide was the first widely used drug in patients having Type 2 DM. Repaglinid, a new compound related to insulin secretagogues was developed and was called as meglitinides derivatives. This was further approved as a cure for diabetes. Thereafter in 1920s, a new class of antidiabetic agent was developed and categorized into biguanides, but was surpassed due to the discovery of insulin. The hypoglycemic effect of antimalarial agent chloroguanide, promoted for the development of this class of compounds. Phenformin from his class was withdrawn due to lactic acidosis associated with its use. Further developed biguanides such as metformin is being used broadly in Europe and the United States without any noteworthy undesirable effects.

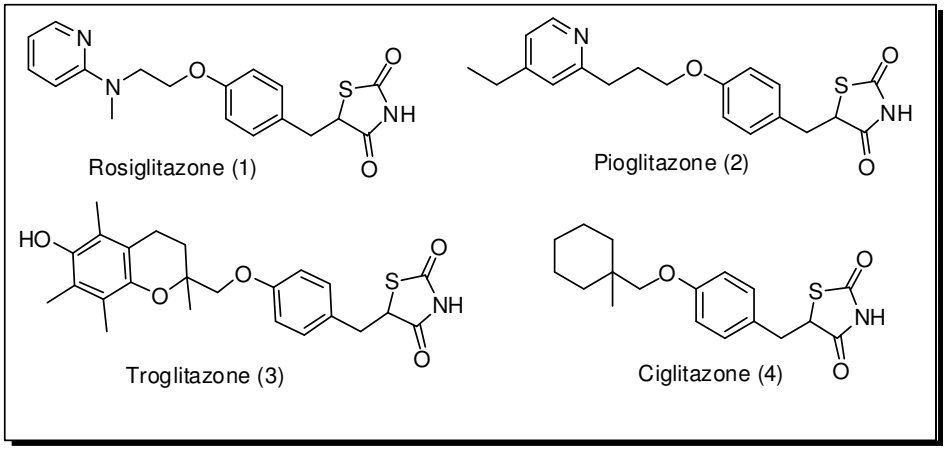


**Figure 2**
***Thiozolidinone analogs***

**Table 1**
***Oral hypoglycemic agents***

| S.No. | Class | Drug |
|---|---|---|
| 1 | (I)Insulin secretagogues:<br>Sulfonylureas (bind to the SUR1 subunits and block the ATP-sensitive $K^+$ Channel) | *1st generation*<br>Chlorpropamide<br>Acetohexamide<br>Tolazamide<br>Tolbutamide<br>*2nd generation*<br>Glipizide<br>Glyburide<br>Glimepiride |
| 2 | (II) Insulin sensitizers<br>Biguanides (activation AMP kinase) | Metformin |
| 3 | Thiazolidinediones<br>(PPARγ agonists) | Pioglitazone<br>Rosiglitazone |
| 4 | Alpha-glucosidase Inhibitors | Acarbose, Miglitol |
| 5 | Non-sulfonylureas<br>Meglitinides<br>(Block ATP sensitive $K^+$ Channel) | Repaglinide<br>(Prandin)<br>Nateglinide<br>(Starlix) |
| 6 | PPARα agonist | Fibrates/Rexinoids |
| 7 | Protein tyrosine kinase inhibitors | CLX 0300/0301/<br>0900/0901 |

Thiazolidinediones, considered as the second major class of "insulin sensitizers", were introduced in 1997. They interact with peroxisome proliferator-activated receptors (PPARγ), which results in increased glucose uptake in muscles as well as reduced glucose production (Figure 2). One of the drugs of this class, troglitazone was withdrawn due to hepatic toxicity but other agents of this class like pioglitazone and rosiglitazone did not show liver toxicity so these agents continued to be used widely[4].

### *4. PPARS AS A PROMISING TARGET FOR DM*

PPARs are considered as promising target for treatment of diabetes since evidences support that stimulus to PPARγ increases insulin resistance. Insulin-sensitizing drugs such as thiazolidinediones (TZDs) were found with high affinity toward PPARγ. In addition, these agents' binding affinity appears to intimately relate to their potency. There are some Non-TZD-related PPARγ agonists, i.e. oxyiminoacetic acid derivatives which also show strong anti-diabetic activity.

The PPARs are of 3 types: α, β, and gamma[5].

- α (alpha) NR1C1- It expresses mainly in kidney, liver, muscle, heart, and adipose tissue.
- β (beta) NR1C2- It expresses mainly in adipose tissue, brain, and skin.
- γ (gamma) NR1C3- This PPAR γ expresses in three different subtypes:
  - γ1 –It usually expresses in colon, heart, kidney, muscle, spleen and pancreas.
  - γ2 – It expresses in adipose tissue.
  - γ3 – It expresses in white adipose tissue, macrophages and large intestine.

These receptors, recognized in Xenopus frogs, provoke the proliferation of peroxisomes[6]. The first PPAR was discovered and classified as PPARα and is referred to as *peroxisome proliferators*, because it increases the number of peroxisomes in the liver tissue, apart from improving insulin sensitivity[7]. The fibrates agents discovered in the early 1980s turned out to be ligands of PPAR. Conformational changes of PPARs are brought in by the ligand or various co-activator or co-repressor proteins at LBD (Ligand Binding Domain) which stimulate or inhibit the functions of the receptor[8].

### *4.1 Structure of PPARs*

PPARs are belongs to nuclear receptors, and possess three main functional domains (Figure 3) with the following segments:[9,10]

1. N-terminal region -A/B
2. DBD (DNA binding domain) - C
3. flexible hinge region -D
4. LBD (ligand binding domain) -E
5. C-terminal region –F


**Figure 3**
***Structure of PPARs receptor[9,10].***

When the receptor is activated, the DBD which has 2 zinc finger motifs binds to DNA by hormone response elements (HRE). The LBD consists of one β-sheet and 13 α-helices[11]. Various natural or synthetic ligands bind at the LBD, and stimulate or inhibit the receptor.

### *4.2 Mechanisms of PPAR activation and regulation of target gene expression*

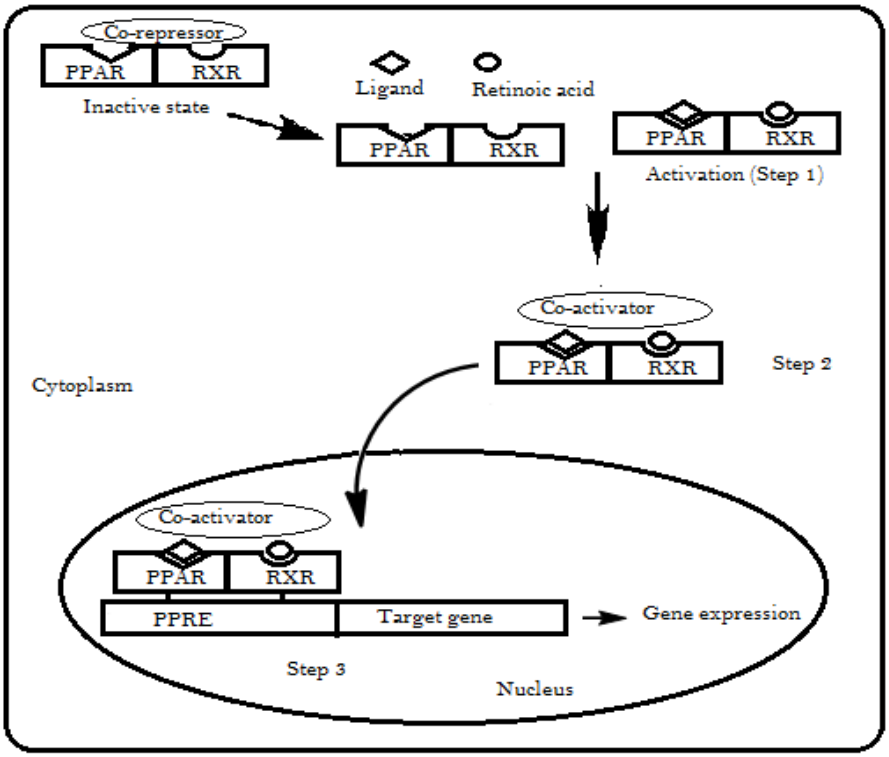


**Figure 4**
***PPAR activation and its transcriptional Mechanism.[13]***

PPARs activated by various ligands regulate the transcriptional activity as shown in Figure 4. Natural ligands or molecules like thiazolidinone bind to PPARγ, leading to activation and complexation with retinoid X receptor (RXR) on DNA. Further, it forms heterodimers and binds to DNA via peroxisome proliferative response elements (PPREs) [12]. One of the co-repressors such as SMRT (Silencing Mediator for Retinoid and Thyroid hormone receptor) usually involved in PPARγ-mediated gene transcription leads to down-regulation (Figure 4) [13]. Several

proteins[14,15] are identified and characterized as coactivators of PPARγ i.e. P300, CREB binding protein (CBP), PPARγ co-activator-1(PGC-1), and PPAR binding protein (PBP). Other co-activator recently reported by Zhu *et al*[16], is PPAR interacting protein (PRIP). Normally, nuclear receptors remain inactive with co-repressors, and their activation led by conformational changes, further facilitates required gene transcription[17]. Other than the cofactor, PPARγ can be downed by Mitogen-Activated Protein (MAP) kinase[18]. The mechanism involved is phosphorylation, particularly at Ser114, diminishes the PPARγ activity as well as adipocyte differentiation[19-23].

### *4.3 PPARs interactions with ligands*

Ligand Binding Domain (LBD) of PPARγ has a Y-shaped binding pocket and is twice in volume in comparison to other nuclear receptors. Agonists, such as rosiglitazone, bind in the form of "U-shaped" conformation and occupy about just 40% of the total volume of the pocket. Direct interactions between the thiazolidinedione head group of rosiglitazone and the AF2 helix of PPARγ lock the receptor in an activated conformation to which coactivators can bind Nolte *et al*.[24] identified the space by virtual atoms fitting and reported total unoccupied volume at approximately 1,300 A$^{o}$ LBD. The binding mode of BRL49653 is depicted in figure 5.

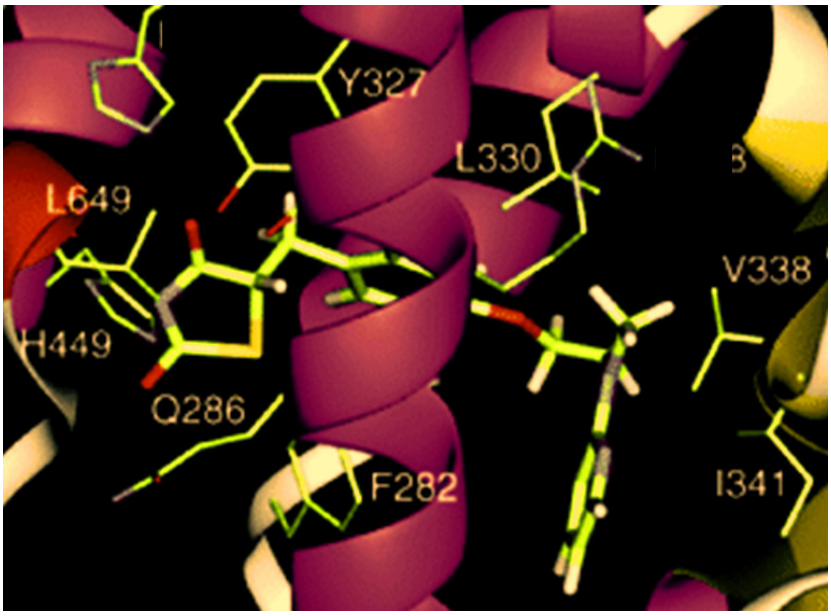


**Figure 5**
***Ternary complex of PPARγ LBD, and binding of BRL49653*[25]**

TZDs are known to have specificity toward PPARγ, where as other subtypes of receptors are not conserved; amino acid residue e.g. H323, Q286 are not found in PPARα or PPARδ respectively[25].

### *4.5 Correlation between Androgen receptor and PPARs*

Nonsteroidal antiandrogens showed PPAR agonists, due to involvement of androgen receptor in metabolic disorder like diabetes. This inspired us to carry out an extensive study of these types of compounds as PPAR agonists. In brief, androgen receptor[26] is classified as NR3A member, which regulates gene expression that is accountable for male pubertal and sexual changes or growth. Other than prostate cells AR is also found in pancreatic cells specifically at β -cell[27]. The AR expression decreased with the progress of diabetes in diabetic mice strongly suggesting the correlation of AR with proliferation of β-cell[28].

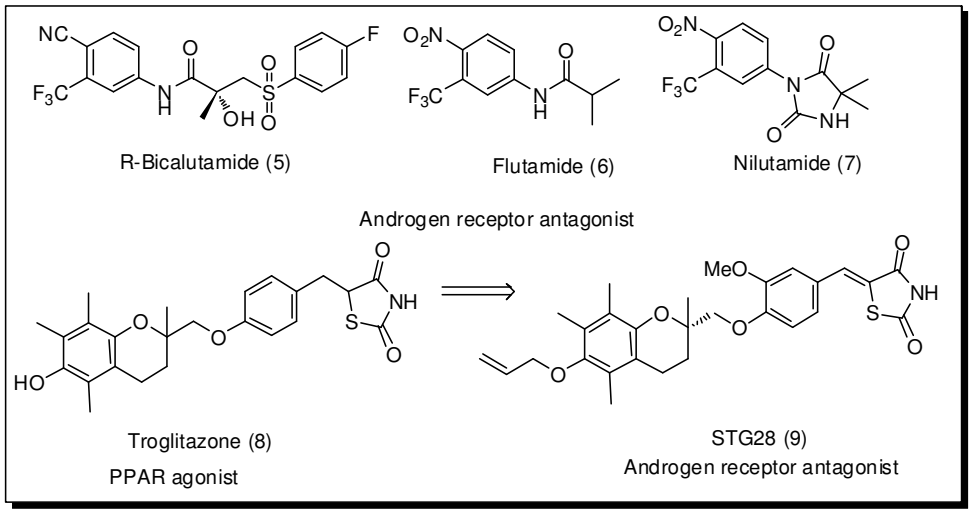


**Figure 6**
***Correlation of AR antagonist and PPAR agonist***

AR involved in male metabolism and its over expression affect the insulin sensitivity and adiposity in both humans and rodents[29,30]. AR blockers were found to improve metabolic abnormalities and dysadipocytokinemia[31]. It was observed that low expression of AR in white adipose tissue (WAT), increases the insulin sensitivity[32]. Another study[33] in A-AR$^{-/y}$ mice also proves that AR is involved in controlling energy balance. Yet another study revealed that androgen treatment prevents diabetes in non-obese diabetic mice,[34] whereas AR$^{-/y}$ mice study resulted in increased triglyceride content,[35] which is directly related to insulin resistance and obesity, and further increases the probability of cardiovascular disease[36]. It was reported that PPAR agonist such as troglitazone at high doses reduces the AR expression in prostate cancer cells i.e. LNCaP, and leads to the development of novel androgen receptor antagonist STG28 (Figure 6) [37]. Collett *et al*. have shown that PPARα, an androgen regulated gene in human prostate, is highly expressed in prostatic carcinoma[38].

***5. Dual activator of PPARα, γ receptor***

Mortality and morbidity associated with diabetes mellitus are due to its complications such as cardiovascular disorders. It is observed that PPARα activation involves in reduction of triglycerides and regulates energy homeostasis,[39] and also reduces the diabetic complications particularly cardiovascular disorders[40-42].

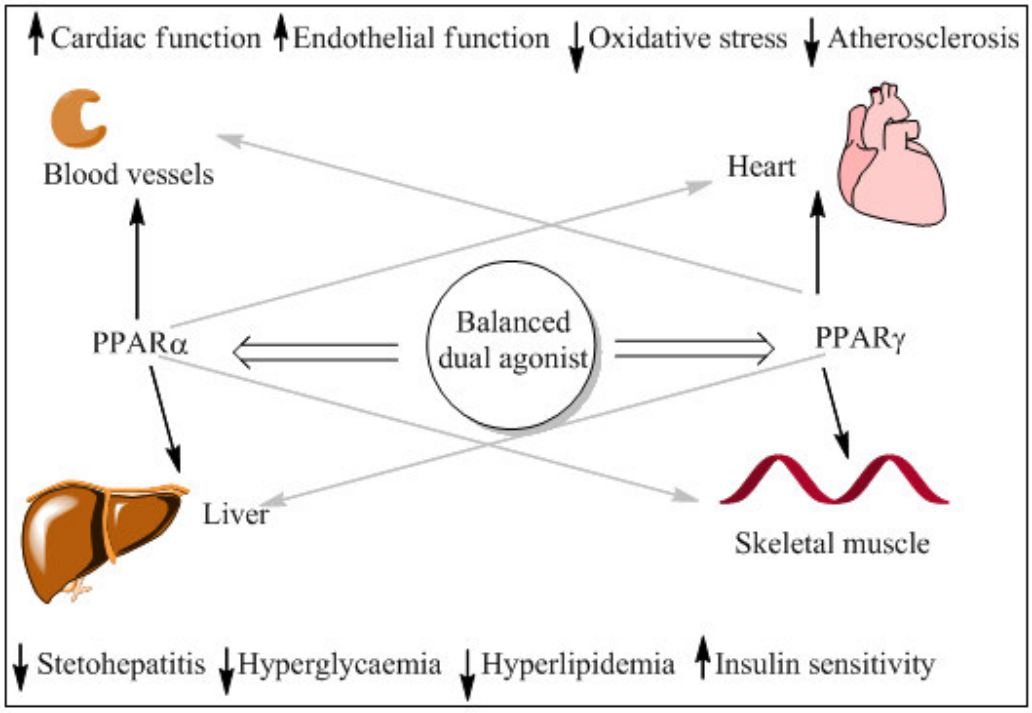


**Figure 7**
***PPARα/γ dual agonists association to regulate metabolic activity*[43-47]**

Activation of PPARγ by insulin sensitization enhances the glucose metabolism, whereas PPARδ activation improves the metabolism of fatty acids. The PPARα/γ dual agonists such as netoglitazone, naveglitazar, ragaglitazar, tesaglitazar, muraglitazar, imiglitazar, LY 929, MK 767, and LSN862,[43] are known to reduce triglycerides, and increase HDL levels which being cardioprotective, also improves insulin sensitivity (Figure 7) [44-48]. Fibric acid derivatives (such as bezafibrate) used first clinically as pan PPARα/γ/δ agonist, were found to have lipid-lowering effect[39]. Also PPARγ-induced weight gain was not observed in case of PPAR pan agonists. The PPARα/γ dual agonists, such as muraglitazar and tesaglitazar, found to be toxic, were terminated in phase III clinical trials[43-48]. PPAR dual agonist such as muraglitazar was found to decrease haemoglobin A1C as well as improve the lipid metabolism in a diabetic person[49]. But, it was discontinued recently due to its side effects such as heart failure and oedema[50]. Another congener such as tesaglitazar though found beneficial in case of dyslipidemia as well as in hyperglycemia[51], was also discontinued because of increased serum creatinine level, and decline in the rate of glomerular filtration[52]. The toxic effects caused by muraglitazar and tesaglitazar have raised several questions about safety concerns in the use of PARα/γ dual agonists. As discussed earlier a balanced affinity of ligands toward the PPARα/γ subtype receptor is required to increase effectiveness and minimise the side effects or toxicity. PPARα or PPARγ supra activation is the main cause of adverse effects like renal dysfunction, carcinogenesis, heart failure and fluid retention[53,54]. Muraglitazar has high affinity for PPARγ, whereas tesaglitazar is more specific for PPARα, consequently these agonists are associated with toxic or adverse effects (Figure 8).

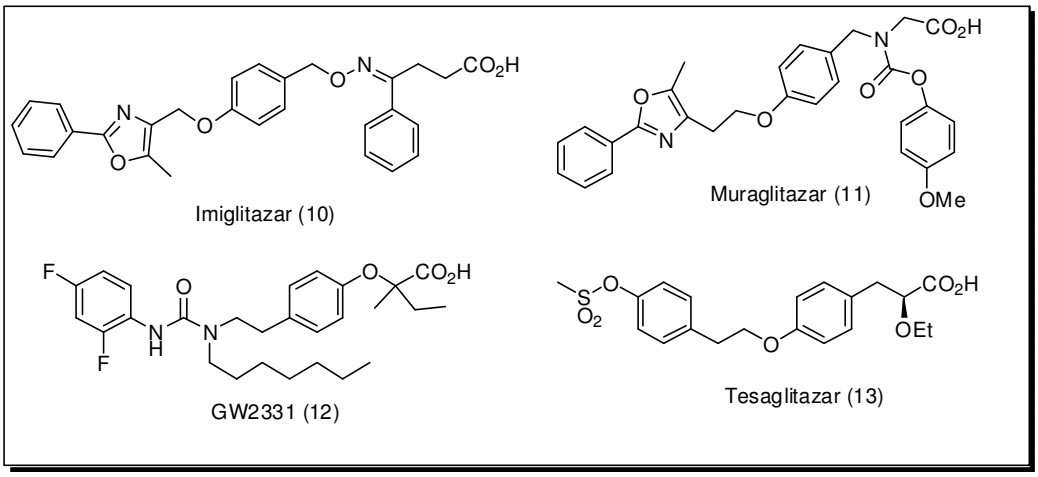


**Figure 8**
***PPAR dual agonist.***

A PPAR agonist[55] in its design normally contains a lipophilic heterocyclic tail and an acidic head connected with a spacer. A recently reported PPARα agonist Imiglitazar has been found to have hydrogen bonding with amino acid residues Tyr314, Tyr 464, and Ser280 as essential characteristics for PPARα agonist activity. Besides this, Imiglitazar has moderate PPARγ activity through interaction with Cys295 amino acid residue[56]. Chiral molecules exist as *R* and *S* isomers. Out of 666 drugs, there are more than 355 (53%) that have at least one chiral centre, whereas 181 drugs (27%) are used in their pure single enantiomer form and 174 (26%) in a racemic mixture[57]. In case of chiral drugs, stereochemistry plays an important role in biological activity[58] due to its interaction with chiral environment. A single enantiomeric form provides better therapeutic indication for altered in metabolism by a reduction in doses or variability to improve tolerability[59-61]. The influence of chiral centre, demonstrated in butanoic acid, a conformationally constrained analog of the well known PPARα/γ agonist GW2331, was found stereocontrolled (Figure 9) [62]. Introduction of the benzooxazole group as a lipophilic part, where the *R*-enantiomer, (*R*)-15, is able to activate both PPARα and PPARγ, shows higher potency on PPARα. The *S*-enantiomer, (*S*)-14, displays a lower efficacy toward PPARγ and behaves as a partial agonist of this receptor subtype. Though, the *S*-enantiomer carboxylate group participates in a hydrogen bonding network with His323, His449, and Tyr473 almost identical to that found for the *R*-enantiomer. However, the ligand ethyl substituent gives rise to repulsive interactions with the Gln286, backbone of helix 3.

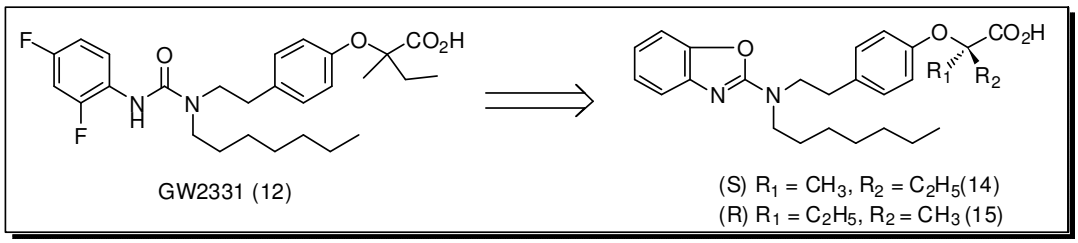


**Figure 9**
***Chiral centre effect on PPAR activity***

The Nateglinide's D-phenylalanine derivatives showed influence of stereochemistry on antihyperglycemic activity[63]. This demonstrated that *R*-enantiomer was essential for activity along with carboxylic acid moiety,[64] Similarly Repaglinide's *S*-enantiomer was found potent and exhibited its stereoselective effect[65]. Modified series of phenylalanine derivatives such as (*S*)-(19) and (*R*)-(19) showed good insulin-releasing effect in comparison to nateglinide, whereas (*S*)-(19) was found potent for in-vitro insulin-sensitizing effect[64]. New oxazole derivatives with oximinobutyric acid and glycine showed PPARα agonists containing polymethylene spacer instead of phenylene group. Further tetramethylene spacer of NS-220 modified to afford 1,3-dioxane-2-carboxylic acid derivative (21), was reported to be a selective PPARα as well as moderate dual agonist toward PPARα/γ. It suggests that polymethylene spacer is selective for PPARα agonism whereas phenylene spacer is good for dual PPARα/γ agonism[56]. Among the azetidinone acid derivatives, 3*S*,4*S* stereoisomer (22)[66] was reported to be the most potent stereoisomer to show stereochemical effect on PPARα and γ receptors. Among the altered lipophilic part of aryl tetrahydropyridine, (*S*)-(23) was recognized as a dual PPARα/γ agonist with an $EC_{50}$ of 1.73 M, PPARα agonism and 0.64 l M, γ agonism[67].

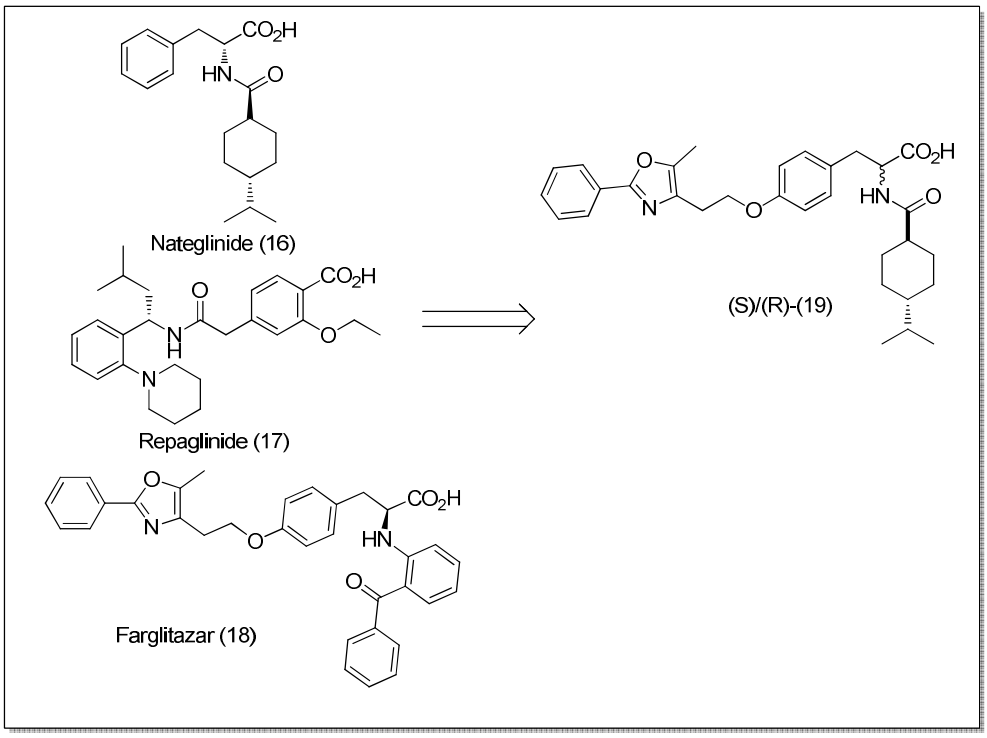


**Figure 10**
***Stereoelectronic effect on binding affinity of dual PPAR agonist***

Similar approach was adopted by Kasuga *et al* to generate a alkoxyphenyl)propanoic acid compound as a selective PPARδ agonist. Based on their findings, they developed a potent PPARα/δ dual agonist such as TIPP-401 (24) [68]. Thiamide derivative (*R*)-(25) also showed PPARα/γ dual agonist with good $EC_{50}$ = 0.136M in PPARγ and 0.377M in PPARα. The SAR of these derivatives captivatingly exhibited that their stereochemistry governs the PPARα/γ dual agonism (Figure 11) [69].The lipophilic group was changed in heterocycle carrying aryl-pyridyl and aryl-pyrimidinyl tail groups as indanylacetic acid derivatives (26), a

new class of PPARα/γ and PPARα/γ/δ agonists (27) (Figure 12) [70]. SAR studies of these derivatives (i.e. (*S*)-(28) and (*S*)-(29) compounds), revealed stereochemical effect that showed good oral efficacy as compared to rosiglitazone[71].

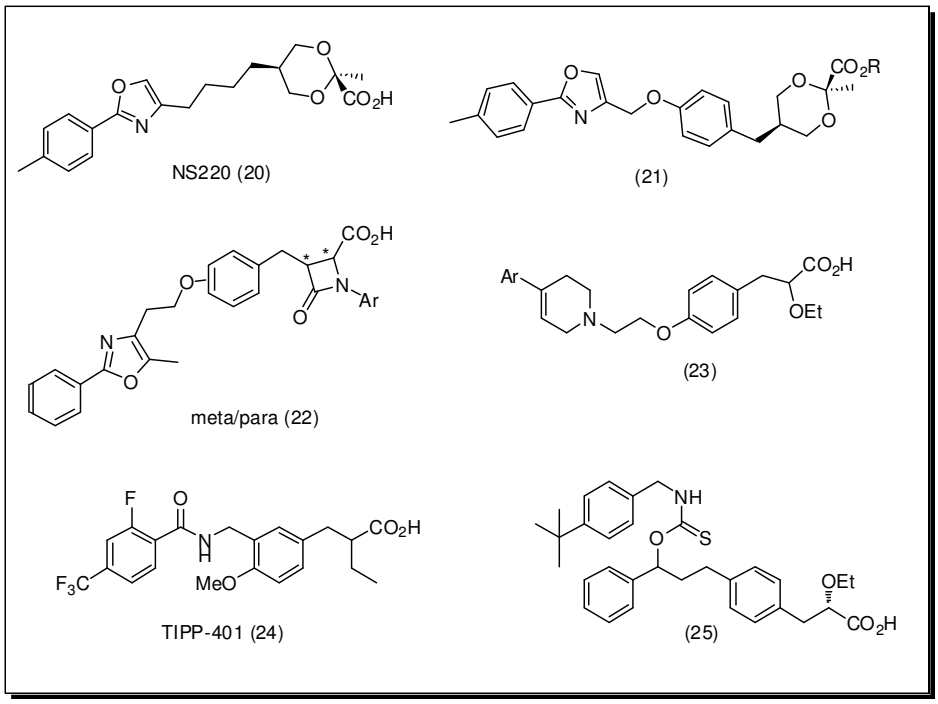


**Figure 11**
***Various chiral PPAR dual agonist***

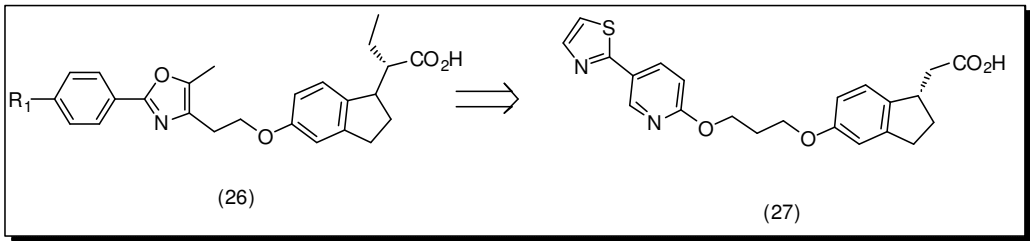


**Figure 12**
***Indanylacetic acid analogs***

Novel oximes and amides with thiazolidinedione moiety have shown anti-hyperglycemic activity. In these series, (*S*)-(31) compound was found to be a potent dual PPARα/γ agonist comparably more potent than the reference drug i.e. rosiglitazone. This suggest that (*S*)-(31) class of compounds are potent dual PPARα/γ agonists, whereas compound (30) showed lowering effect of glucose in plasma although with PPARα/γ weak agonism[72]. In a recent study Das *et al*. developed a new thieno-oxazine analog (32) which was found as antihyperglycemic and lipid modulating agent (Figure 13) [73]. This dual agonist of PPARα /γ showed better activity than standard drugs like pioglitazone and fenofibrate.

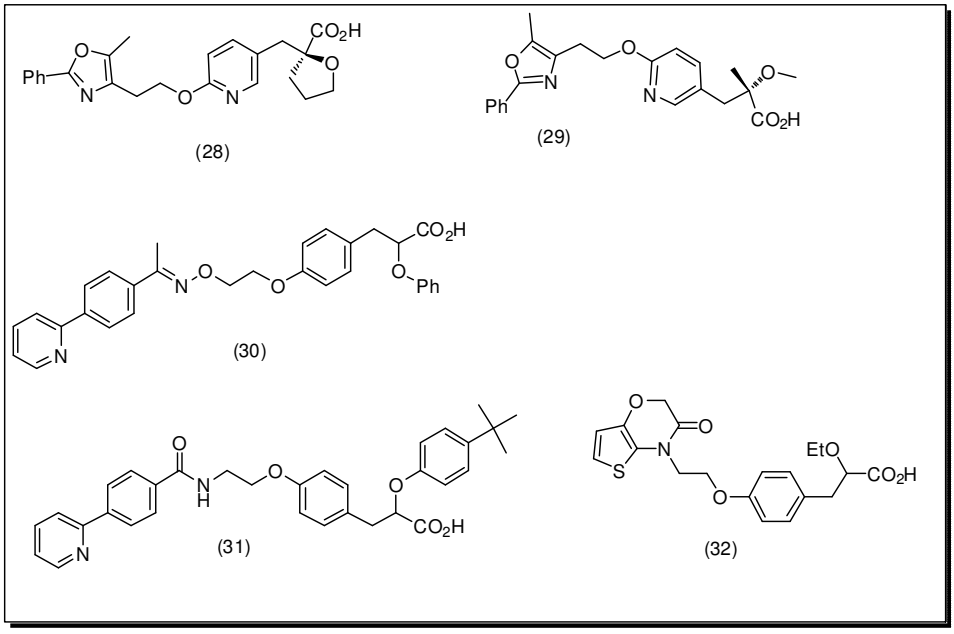


**Figure 13**
***Chiral dual PPAR agonist***

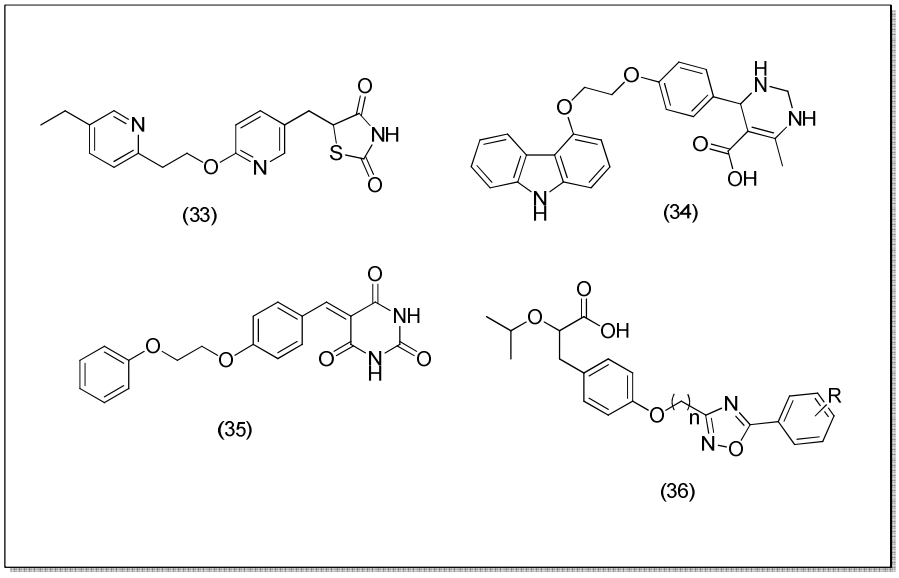


**Figure 14**
***Various heterocyclic compounds***

Molecular modeling studies carried out on glitazones containing pyridine ring (33) as a middle linker unit showed 1.6 fold PPARγ activation at 1 μM concentration[74]. Tetrahydropyrimidine carboxylic acid derivatives (34) substituted with 2,4-thiazolidinone were studied and found to fit best at the active site of PPARγ receptor[75]. Barbituric acid derivatives using virtual screening and molecular docking approach were designed, and evaluated by radio ligand binding studies on PPARγ with $IC_{50}$ of 0.1 μM (35) [76]. PPARα/γ/δ activators of oxadiazole series when subjected to Comparative Molecular Field Analysis (CoMFA) by P.V. Bharatam et al. showed the potential of

oxadizoles (36) as PPARα/γ/δ activators (Figure 14)[77].

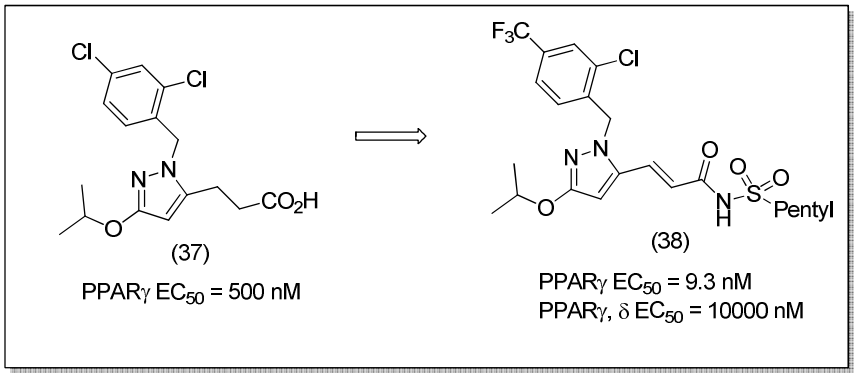


**Figure 15**
***Benzylpyrrole analogs***

In non-thiazolidinedione (TZD) class of compounds novel benzylpyrazole acylsulfonamides were discovered as non carboxylicacid PPARγ agonists (37, 38). Their further optimization led to the development of potent compound that was an antidiabetic agent having good metabolic stability (Figure 15) [78]. Studies on benzylpyrazole and pyridyloxybenzyl acylsufonamide (39, 40) and sufonyl anlogs derivatives from fibrates by Rikimaru et al. showed that their sufonamide analog were more potent on PPAR gamma receptor (Figure 16, 17)[79,80].

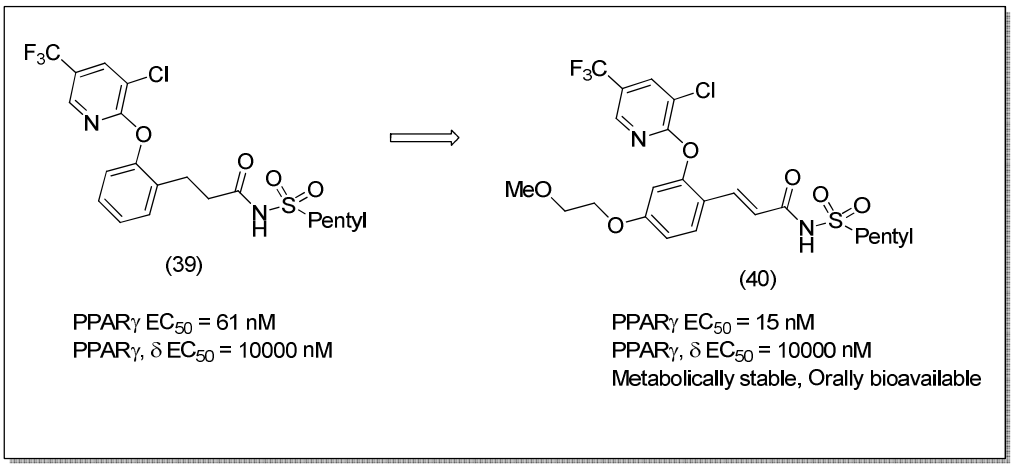


**Figure 16**
***Sulfonyl analogs***

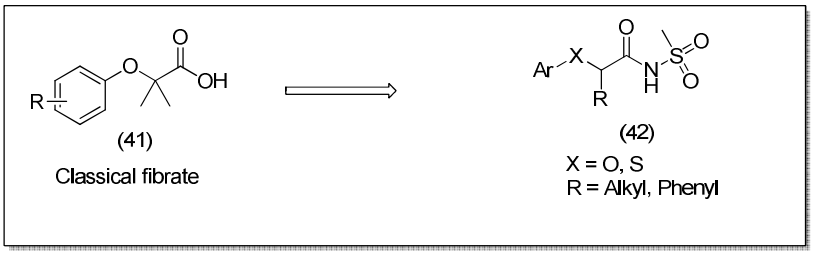


**Figure 17**
***Sulfonyl analogs of classical fibrate compound***

New class of classical fibrate analogs which were synthesized containing *N*-(methylsulfonyl)amides scaffold (42) showed good agonistic potency on PPARα (Figure 17)[81].

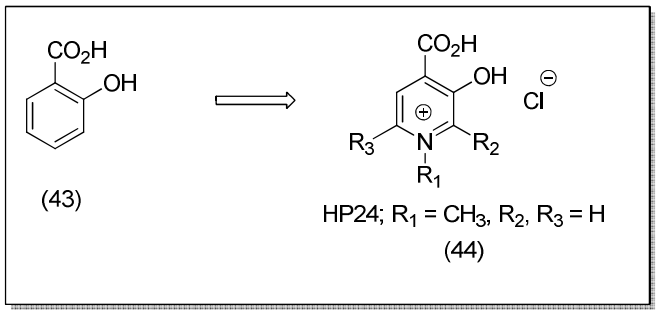


**Figure 18**
***3-Hydroxy-4-pyridinecarboxylic acids derivative***

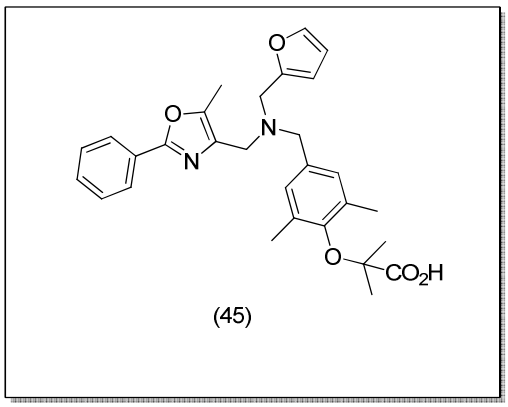


**Figure 19**
***Oxazole derivatives***

One of the potent compound HP 24 (44) of novel 3-Hydroxy-4-pyridinecarboxylic acids (HPs), showing good anti-inflammatory activity, was found to reduce COX-2 as well as NF-κB mediated protein expression (Figure 18) [82]. New zwitterionic compounds were developed with α/γ dual agonism activity among which compound (45) was observed to be a potent dual agonist to reduce glucose level without any weight gain (Figure 19) [83].

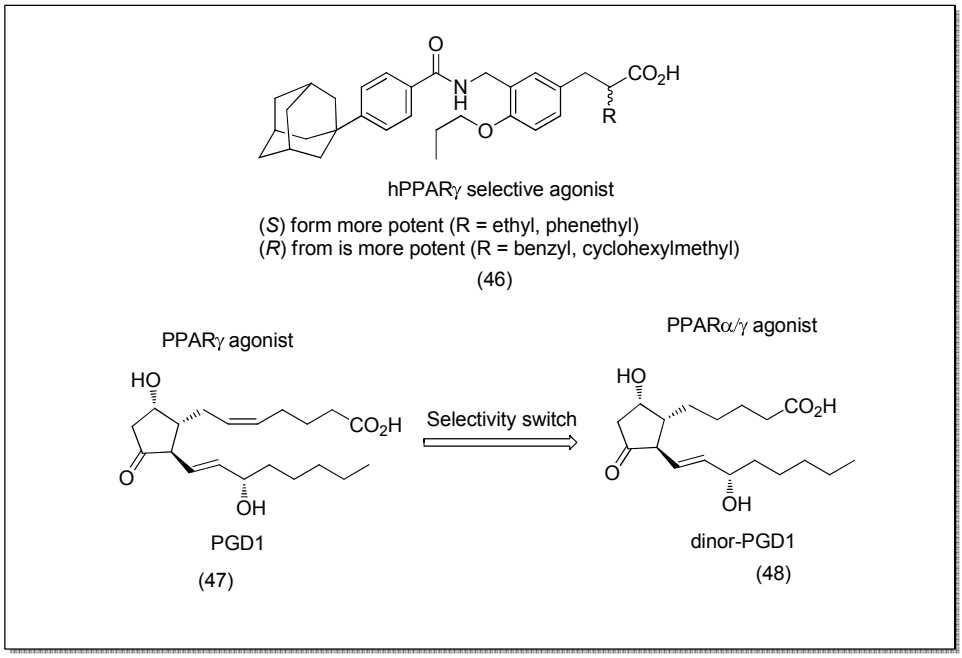


**Figure 20**
***Prostaglandins derivative***

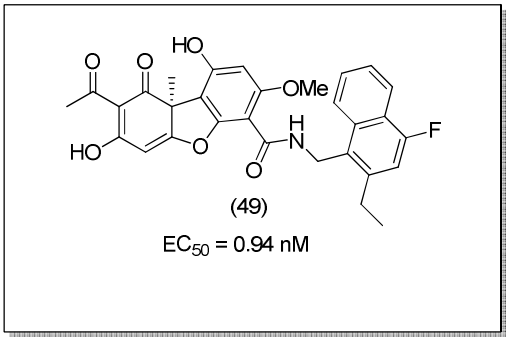


**Figure 21**
***Cercosporamide derivatives***

Various 2,3-dinorprostaglandin derivatives were synthesized and evaluated for PPARs agonism. Dinor-$PGD_1$ and 13-*epi*-dinor-$PGD_1$ were found potent dual agonists for PPARα/γ in comparison to arachidonic acid (Figure 20)[84,85].

A series of novel (–)-Cercosporamide derivatives (49) synthesized as PPARγ modulators showed that compound 49 was found the most potent PPARγ partial agonist (Figure 21) [86].

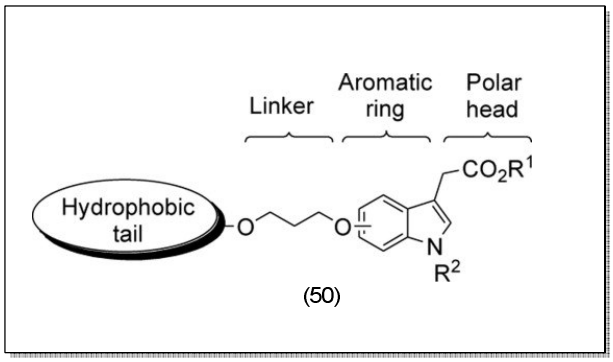


**Figure 22**
***Alkoxyindole-3-acetic acid analogs***

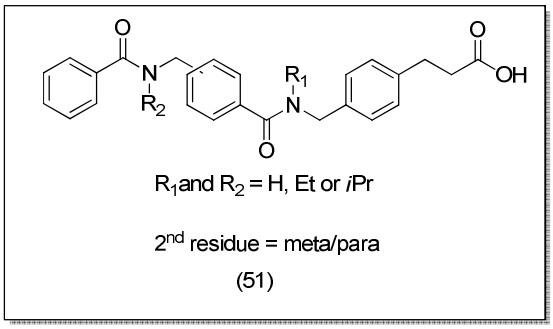


**Figure 23**
***Arylpeptoid derivatives***

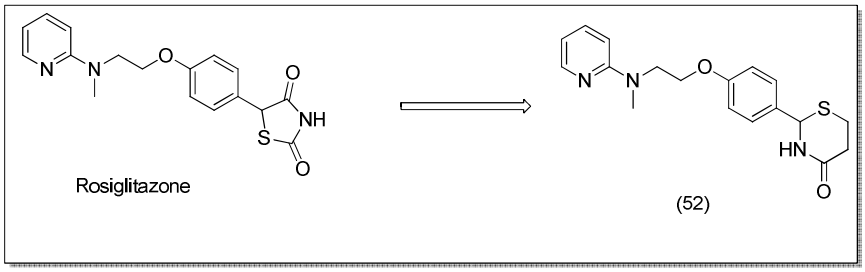


**Figure 24**
***Rosiglitazone analogs***

Various series of synthesized carbazole or phenoxazine having alkoxyindole acetic acid (50) (Figure 22)[87]and arylpeptoid 51 (Figure 23)[88] were reported for transactivation of PPARα/γ/δ. On the basis of rosiglitazone, novel thiazolidinone and thiazinanone analogs were designed and evaluated as potential antidyslipidemic and antihyperglycemic agents 52 (Figure 24)[89]. Flavone based novel antidiabetic compounds were reported for PPAR-γ agonist activity 53,54 (Figure 25)[90]. Novel benzimidazolone derivatives were also evaluated for PPARγ modulator as a central part of molecules, with increased selectivity for PPARγ 55 (Figure 26) [91]. Recently, some orally active carboxylic acid derivatives were reported for antiobesity and antidiabetic activity (Figure 27) [92].

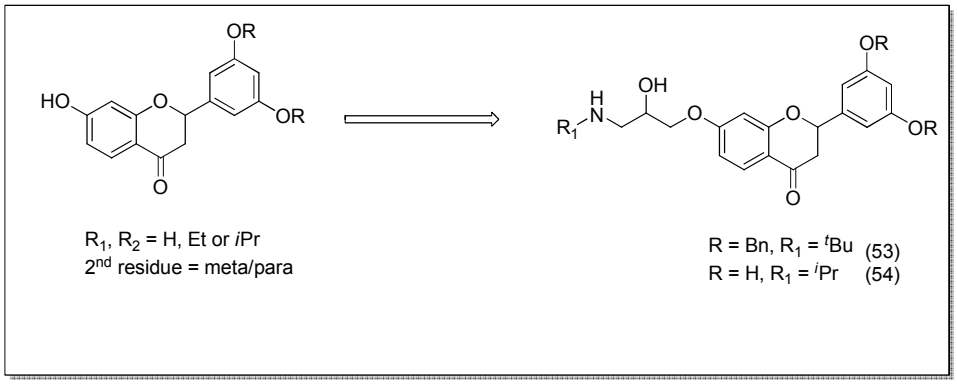


**Figure 25**
***Heterocyclic scaffolds***

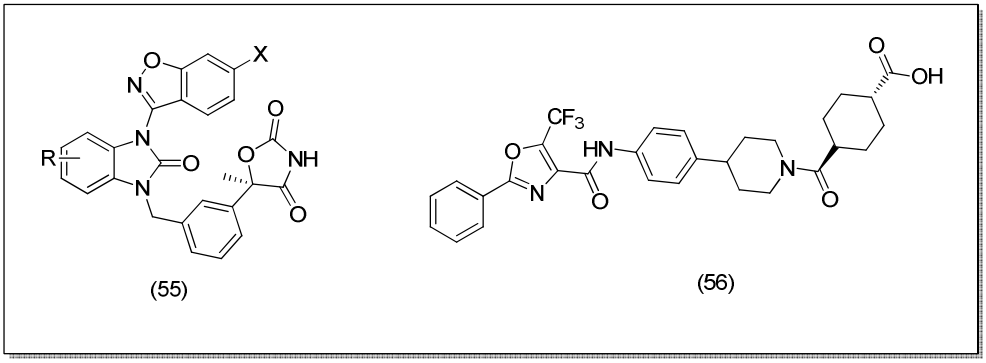


**Figure 26**
***Heterocyclic scaffolds***

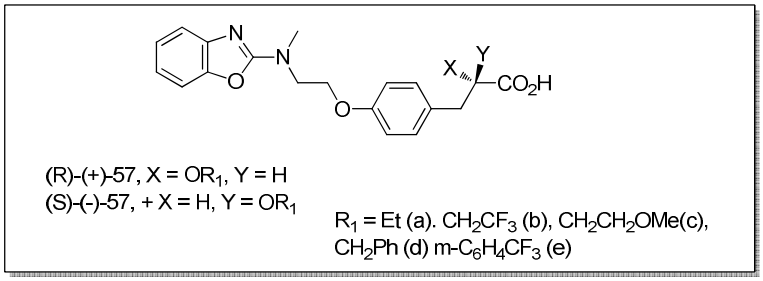


**Figure 27**
***Orally active carboxylic acid derivatives***

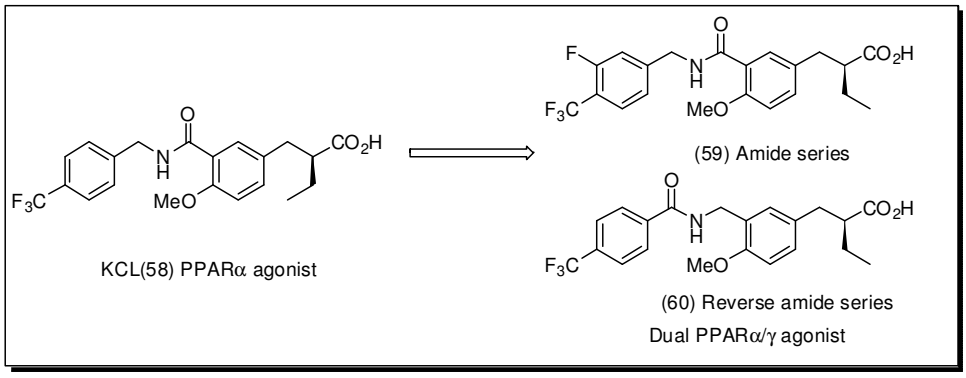


**Figure 28**
***Phenylpropanoic amide derivatives***

Compounds 57(a-e) were found to be potent antihypoglycemic agents with PPARγ as a molecular target and on their further biological evaluations, revealed that the (*S*)-enantiomers (57) evidently showed better potency in comparison to (*R*)-enantiomer, in vitro[93,94] as well as *in vivo* antihyperglycaemic activity (Figure 27) [95-97]. Various substituted derivatives of phenylpropanoic acid (59 and 60), synthesized by Kasuga *et al*.[98] were found effective human PPARα selective agonist (Figure 28).

## 6. CONCLUSION

A perusal of the literature shows the need of developing new antidiabetic agents. Drugs currently available are associated with various side effects like severe cardiac toxicity, weight gain, hepatotoxicity. So, there is a need of developing a balanced PPARα/γ dual activator agents. Recent reports, revealing that chirality greately influence the PPAR agonistic activity.

## ACKNOWLEDGEMENT

The author is grateful to SERB- Department of Science & Technology (DST) Govt. of India for research funding.

**CONFLICT OF INTEREST**
Conflict of interest declared none.

## 7. REFERENCES

1. Hilary K, Ronald EA and William HH, Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections, Dia Care, 21: 1414-1431 (1998).
2. International Diabetes Federation, IDF Diabetes Atlas, 6th Edn, Brussels, Belgium: International Diabetes Federation, (2013). Accessed on 12 June 2015. http://www.idf.org/diabetesatlas.
3. Peter A. Friedman, Endocrine pancreas and pharmacotherapy of diabetes mellitus and hypoglycemia. Goodman & Gilman's the Pharmacological basis of Therapeutics -11th Edn, MakGraw Hill, New York, 2006, pp. 1378-1412.
4. Reddy V S, Sahay RK, Bhadad SK, Agrawal JK and Agrawal NK, Newer oral antidiabetic agents, J Indian Acad Clin Med, 1: 245-251 (2000).
5. Berger J and Moller DE, The mechanisms of action of PPARs, Annu Rev Med, 53: 409-435 (2002).

6. Dreyer C, Krey G, Keller H, Givel F, Helftenbein G and Wahli W, Potential role for peroxisome proliferator activated receptor (PPAR) in preventing colon cancer, Cell, 68: 879-887 (1992).
7. Issemann I and Green S, Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators, Nature, 347: 645-650 (1990).
8. Yu S and Reddy JK, Transcription coactivators for peroxisome proliferator-activated receptors, Biochim Biophys Acta, 1771 (8): 936-951 (2007).
9. Willson TM and Wahlil W, Peroxisome proliferator-activated receptor agonists, Curr Opin Chem Biol, 1 (2): 235-241 (1997).
10. Kota1 BP, Huang THW and Roufogalis BD, An overview on biological mechanisms of PPARs, Pharmacol Res, 51(2): 85-94 (2005).
11. Zoete V, Grosdidier A and Michielin O, Peroxisome proliferator-activated receptor structures: ligand specificity, molecular switch and interactions with regulators, Biochim Biophys Acta, 1771(8): 915-925 (2007).
12. Osada T, Tsukamoto T, Takiguchi M, Mori M and Osumi T, Identification of an extended half-site motif required for the function of peroxisome proliferator-activated receptor alpha, Genes Cells, 2 (5): 315-327 (1997).
13. Lavinsky RM, Jepsen K, Heinzel T, Torchia J, Mullen TM, Schiff R, Del-Rio AL, Ricote M, Ngo S, Gemsch J, Hilsenbeck SG, Osborne CK, Glass CK, Rosenfeld MG and Rose DW, Diverse signaling pathways modulate nuclear receptor recruitment of N-CoR and SMRT complexes, Proc Natl Acad Sci, 95 (6): 2920-2925 (1998).
14. Glass CK, Rose DW and Rosenfeld MG, Nuclear receptor coactivators, Curr Opin Cell Biol, 9 (2): 222-232 (1997).
15. Esterbauer H, Oberkofler H, Krempler F and Patsch W, Human peroxisome proliferator activated receptor gamma coactivator 1 (PPARGC1) gene: cDNA sequence, genomic organization, chromosomal localization, and tissue expression, Genomics 62 (1): 98-102 (1999).
16. Zhu Y, Kan L, Qi C, Kanwar YS, Yeldandi AV, Rao MS and Reddy JK, Isolation and characterization of peroxisome proliferator-activated receptor (PPAR) interacting protein (PRIP) as a coactivator for PPAR, J Biol Chem, 275 (18): 13510-13516 (2000).
17. Pazin MJ and Kadonaga JT, What's up and down with histone deacetylation and transcription?, Cell, 89 (3): 325-328 (1997).
18. Shao D, Rangwala SM, Bailley ST, Krakow SL, Reginato MJ and Lazar MA, Interdomain communication regulating ligand binding by PPAR-gamma, Nature, 396: 377-380 (1998).
19. Hu E, Kim JB, Sarraf P and Spiegelman BM, Inhibition of adipogenesis through MAP kinase-mediated phosphorylation of PPARgamma, Science, 274: 2100 (1996).
20. Zhang B, Berger J, Zhou G, Elbrecht A, Biswas S, White- Carrington S, Szalkowski D and Muller DE, Insulin- and mitogen-activated protein kinase-mediated phosphorylation and activation of peroxisome proliferator-activated receptor-γ, J Biol Chem, 271 (50): 31771-31774 (1996).
21. Adams M, Reginato MJ, Shao D, Lazar MA and Chatterjee VK, Transcriptional activation by peroxisome proliferator-activated receptor gamma is inhibited by phosphorylation at a consensus mitogen-activated protein kinase site, J Biol Chem, 272 (8): 5128-5132 (1997).
22. Camp HS and Tafuri SR, Regulation of peroxisome proliferator-activated receptor gamma activity by mitogen-activated protein kinase, J Biol Chem, 272 (16): 10811-10816 (1997).
23. Balasubramanyam M and Mohan M, Current concepts of PPAR-g signaling in diabetes mellitus, Curr Science, 79 (10): 1440-1446 (2000).
24. Nolte RT, Wisely GB, Westin S, Cobb JE, Lambert MH, Kurokawa R, Rosenfeld MG, Willson TM, Glass CK and Milburn MV, Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma, Nature, 395 (6698): 137-143 (1998).
25. Xu HE, Stanley TB, Montana VG, Lambert MH, Shearer BG, Cobb JE, McKee DD, Galardi CM, Plunket KD, Nolte RT, Parks DJ, Moore JT, Kliewer SA, Willson TM and Stimmel JB, Structural basis for antagonist-mediated recruitment of nuclear co-

repressors by PPAR-alpha, Nature, 415 (6873): 813-817 (2002).
26. Balagopal P, Rooyackers OE, Adey DB, Ades PA and Nair KS, Effects of aging on in vivo synthesis of skeletal muscle myosin heavy-chain and sarcoplasmic protein in humans, Am J Physiol Endocrinol Met, 273: E790-E800 (1997).
27. Li RJ, Qiu SD, Wang HX, Tian H, Wang LR and Huo YW, Androgen receptor: a new player associated with apoptosis and proliferation of pancreatic beta-cell in type 1 diabetes mellitus, Apoptosis, 13 (8): 959-971 (2008).
28. Fan WQ, Yanase T, Nomura M, Okabe T, Goto K, Sato T, Kawano H, Kato S and Nawata H, Androgen receptor null male mice develop late-onset obesity caused by decreased energy expenditure and lipolytic activity but show normal insulin sensitivity with high adiponectin secretion, Diabetes, 54 (4): 1000-1008 (2005).
29. Shoupe D, and Lobo RA, The influence of androgens on insulin resistance, Fertil Steril, 41 (3): 385-388 (1984).
30. Toprak S, Yonem A, Cakir B, Guler S, Azal O, Ozata M, and Corakci A, Sensitivity to growth hormone – the perspective, Horm Res, 55 (2): 67 (2001).
31. Ibanez L, Valls C, Cabre S, and De-Zegher F, Flutamide-metformin plus ethinylestradiol-drospirenone for lipolysis and antiatherogenesis in young women with ovarian hyperandrogenism: the key role of early, low-dose flutamide, J Clin Endocrinol Metab, 89 (9): 4716-4720 (2004).
32. Kubota N, Terauchi Y, Miki H, Tamemoto H, Yamauchi T, Komeda K, Satoh S, Nakano R, Ishii C, Sugiyama T, Eto K, Tsubamoto Y, Okuno A, Murakami K, Sekihara H, Hasegawa G, Naito M, Toyoshima Y, Tanaka S, Shiota K, Kitamura T, Fujita T, Ezaki O, Aizawa S, and Kadowaki T, PPAR gamma mediates high-fat diet-induced adipocyte hypertrophy and insulin resistance, Mol Cell, 4 (4): 597-609 (1999).
33. Yu IC, Lin HY, Liu NC, Wang RS, Sparks JD, Yeh S and Chang C, Hyperleptinemia without obesity in male mice lacking androgen receptor in adipose tissue, Endocrinology, 149 (5): 2361-2368 (2008).
34. Fox HS, Androgen treatment prevents diabetes in nonobese diabetic mice, J Exp Med, 175 (5): 1409-1412 (1992).
35. Lin HY, Xu Q, Yeh, S, Wang RS, Sparks JD and Chang C, Insulin and leptin resistance With hyperleptinemia in mice lacking androgen receptor, Diabetes, 54 (6): 1717-1725 (2005).
36. Fernandez-Real JM and Ricart W, Insulin resistance and chronic cardiovascular inflammatory syndrome, Endocrinol Rev, 24 (3): 278-301 (2003).
37. Yang CC, Wang YC, Wei S, Lin LF, Chen CS, Lee CC, Lin CC and Chen CS, Peroxisome proliferator-activated receptor γ–independent suppression of androgen receptor expression by troglitazone mechanism and pharmacologic exploitation, Cancer Res, 67 (7): 3229-3238 (2007).
38. Collett GP, Betts AM, Johnson MI, Pulimood AB, Cook S, Neal DE and Robson CN, Peroxisome proliferator-activated receptor α is an androgen-responsive gene in human prostate and Is Highly expressed in prostatic adenocarcinoma, Clin Cancer Res, 6 (8): 3241-3248 (2000).
39. Tenenbaum A, Motro M and Fisman EZ, Dual and pan-peroxisome proliferator-activated receptors (PPAR) co-agonism: the bezafibrate lessons, Cardiovasc Diabetol, 4 (14): 1-5 (2005).
40. Israelian-Konaraki Z and Reaven PD, Proliferator-activated receptor-alpha and atherosclerosis: from basic mechanisms to clinical implications, Cardiol Rev, 13 (5): 240-246 (2005).
41. Tai ES, Collins D, Robins SJ, O'Connor JJ, Bloomfield HE and Ordovas JM, The L162V polymorphism at the peroxisome proliferator activated receptor alpha locus modulates the risk of cardiovascular events associated with insulin resistance and diabetes mellitus: the veterans affairs HDL intervention trial (VA-HIT). Atherosclerosis, 187 (1): 153-160 (2006).
42. Sheejav S, Reddym H, Joseph JC and Krishna Raj R, Continuing pharmacy education series-risk factors and complications of diabetes, Int J Pharma Bio Sciences, 1(3) 1-11 (2010).
43. Pourcet B, Fruchart JC, Staels B and Glineur C, Selective PPAR modulators, dual

and pan PPAR agonists: multimodal drugs for the treatment of Type 2 diabetes and atherosclerosis, Opin Emerg Drugs, 11 (3): 379-401 (2006).
44. Etgen GJ, Oldham BA, Johnson WT, Broderick CL, Montrose CR and Brozinick JT, A tailored therapy for the metabolic syndrome: The dual peroxisome proliferator-activated receptor-α/γ agonist LY465608 ameliorates insulin resistance and diabetic hyperglycemia while improving cardiovascular risk factors in preclinical models, Diabetes, 51 (4): 1083-1087 (2002).
45. Fievet C, Fruchart JC and Staels B, PPAR alpha and PPAR gamma dual agonists for the treatment of type 2 diabetes and the metabolic syndrome, Curr Opin Pharmacol, 6 (6): 606-614 (2006).
46. Humphries PS, Almaden JV, Barnum SJ, Carlson TJ, Do QQT and Fraser JD, Pyridine-2-propanoic acids: Discovery of dual PPARalpha/gamma agonists as antidiabetic agents. Bioorg Med Chem Lett, 16 (23): 6116-6123 (2006).
47. Gabriely I, Ma XH, Yang XM, Rossetti L and Barzilai N, Leptin resistance during aging is independent of fat mass, Diabetes, 51(4):1016-1021 (2002).
48. Mamnoor PK, Hegde P, Datla SR, Damarla RK, Rajagopalan R and Chakrabarti R, Antihypertensive effect of ragaglitazar: a novel PPARalpha and gamma dual activator, Pharmacol Res, 54 (20, 129-135 (2006).
49. Kendall MD, Rubin CJ, Mohideen P, Ledeine JM, Belder R and Gross J, Improvement of glycemic control, triglycerides, and HDL cholesterol levels with muraglitazar, a dual (α/γ) peroxisome proliferator–activated receptor activator, in patients with type 2 diabetes inadequately controlled with metformin monotherapy: A double-blind, randomized, pioglitazone-comparative study. Diabetes Care, 29 (5): 1016-1023 (2006).
50. Nissen SE, Wolski K and Topol EJ, Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. J Am Med Assoc, 294 (20): 2581-2586 (2005).
51. Cox SL, Muraglitazar: An investigational agent for the treatment of type 2 diabetes and associated dyslipidemia, Drugs Today, 4: 2139 (2006).
52. Conlon D, Goodbye glitazars?, Br J Diabetes Vasc Dis, 6: 135-137 (2006).
53. Cheng AYY and Fantus IG, Thiazolidinedione-induced heart failure, Ann Pharmacother, 38 (5): 817-820 (2004).
54. Lipscombe J, Lewis GF, Cattran D and Bargman JM, Deterioration in renal function associated with fibrate therapy, Clin Nephrol, 55(1), 39-44 (2001).
55. Balakumar P, Rose M, Ganti SS, Krishan P and Singh M, PPAR dual agonists: are they opening pandora's box?, Pharmacol Res, 56(2): 91-98 (2007).
56. Pingali H, Jain M, Shah S, Patil P, Makadia P, Zaware P, Sairam KVVM, Jamili J, Goel A, Patel M and Patel P, Modulation of PPAR receptor subtype selectivity of the ligands: aliphatic chain vs aromatic ring as a spacer between pharmacophore and the lipophilic moiety, Bioorg Med Chem Lett, 18 (24): 6471-6475 (2008).
57. Francotte E, Lindner W, Folkers G, Kubinyi H and Mannhold R, Ed. Chirality in drug research, Vol 33, Wiley-VCH publisher, 1-370, (2006).
58. McConathy J and Owens MJ, Primary care companion, J Clin Psychiatry, 5(2), 70-73 (2003).
59. Hulin B, Newton LS, Lewis DM, Genereux PE, Gibbs EM and Clark DA, Hypoglycemic activity of a series of alpha-alkylthio and alpha-alkoxy carboxylic acids related to ciglitazone, J Med Chem, 39(20), 3897-3907 (1996).
60. Buckle DR, Cantello BCC, Cawthorne MA, Coyle PJ, Dean DK, Faller A, Pinto IL, Rami HK, Smith DG and Smith SA, Non-thiazolidinedione antihyperglycemic agents. 2: alpha-Carbon substituted-beta-phenylpropanoic acids, Bioorg Med Chem Lett, 6 (17): 2127-2131 (1996).
61. Willson TM, Brown PJ, Sternbach DD and Henke BR, The PPARs: from orphan receptors to drug discovery, J Med Chem, 43 (4): 527-550 (2000).
62. Pochetti G, Godio C, Mitro N, Caruso D, Galmozzi A, Scurati S, Loiodice F, Fracchiolla G, Tortorella P, Laghezza A, Lavecchia A, Novellino E, Mazza F and Crestani M, Insights into the mechanism of

partial agonism: crystal structures of the peroxisome proliferator-activated receptor gamma ligand-binding domain in the complex with two enantiomeric ligands, J Biol Chem, 282 (23): 17314-17324 (2007).
63. Shinkai H, Nishikawa M, Sato Y, Toi K, Kumashiro I, Seto Y, Fukuma M, Dan K and Toyoshima S, N-(cyclohexylcarbonyl)-D-phenylalanines and related compounds. A new class of oral hypoglycemic agents, J Med Chem, 32 (7): 1436-1441 (1989).
64. Tang L, Yu J, Wu H, Fan H, Yang Y and Ji R, NSAIDs revisited: Putative molecular basis of their interactions with peroxisome proliferator-activated gamma receptor (PPARγ), Euro J Med Chem, 43 (9): 1918-1925 (2008).
65. Malaisse WJ, The anomeric malaise: a manifestation of B-cell glucotoxicity, Horm Metab Res, 23 (7): 307-311 (1991).
66. Wang W, Devasthale P, Farrelly D, Gu L, Harrity T, Cap M, Chu C, Kunselman L, Morgan N, Ponticiello R, Zebo R, Zhang L, Locke K, Lippy J, O'Malley K, Hosagrahara V, Zhang L, Kadiyala P, Chang C, Muckelbauer J, Doweyko AM, Zahler R, Ryono D, Hariharanb N and Chenga PTW, Discovery of azetidinone acids as conformationally-constrained dual PPARα/γ agonists, Bioorg Med Chem Lett, 18 (6): 1939-1944 (2008).
67. Kim E, Park CS, Han T, Bae M-H, Chong W, Lee CH, Shin YH, Ahn B-H, Kim MK, Shin CY, Son MH, Kim JK, Moon HS, Shim HJ, Kim EJ, Kim SH, Lim JI, Lee CH, Design, synthesis, and evaluation of novel aryl-tetrahydropyridine PPARalpha/gamma dual agonists, Bioorg Med Chem Lett, 18 (18): 4993-4996 (2008).
68. Kasuga J, Yamasaki D, Araya Y, Nakagawa A, Makishima M, Doi T, Hashimoto Y and Miyachi H, Design, synthesis, and evaluation of a novel series of alpha-substituted phenylpropanoic acid derivatives as human peroxisome proliferator-activated receptor (PPAR) alpha/delta dual agonists for the treatment of metabolic syndrome, Bioorg Med Chem, 14 (24): 8405-8414 (2006).
69. Kim N-J, Lee K-O, Koo B-W, Li F, Yoo J-K, Park H-J, Min K-H, Lim JI, Kim MK, Kimc J-K and Suh Y-G, Design, synthesis, and structure-activity relationship of carbamate-tethered aryl propanoic acids as novel PPARalpha/gamma dual agonists, Bioorg Med Chem Lett, 17 (13): 3595-3598 (2007).
70. Cantin L-D, Liang S, Ogutu H, Iwuagwu CI, Boakye K, Bullock WH, Burns M, Clark R, Claus T, delaCruz FE, Daly M, Ehrgott FJ, Johnson JS, Keiper C, Livingston JN, Schoenleber RW, Shapiro J, Town C, Yang L, Tsutsumic M and Ma X, Indanylacetic acid derivatives carrying aryl-pyridyl and aryl-pyrimidinyl tail groups—new classes of PPAR γ/δ and PPAR α/γ/δ agonists, Bioorg Med Chem Lett, 17 (4): 1056-1061 (2007).
71. Humphries PS, Bailey S, Almaden JV, Barnum SJ, Carlson TJ, Christie LC, Do Q-QT, Fraser JD, Hess M, Kellum J, Kim YH, McClellan GA, Ogilvie KM, Simmons BH, Skalitzky D, Sun S, Wilhitea D, Zehnder LR, Pyridine-3-propanoic acids: Discovery of dual PPARalpha/gamma agonists as antidiabetic agents, Bioorg Med Chem Lett, 16 (23): 6120-6123 (2006).
72. Takamura M, Sakurai M, Yamada E, Fujita S, Yachi M, Takagi T, Isobe A, Hagisawa Y, Fujiwarad T, Yanagisawa H, Synthesis and biological activity of novel α-substituted β-phenylpropionic acids having pyridin-2-ylphenyl moiety as antihyperglycemic agents, Bioorg Med Chem, 12 (9): 2419-2439 (2004).
73. Das SK, Reddy KA, Abbineni C, Iqbal J, Suresh J, Premkumarb M and Chakrabarti M, Novel thieno oxazine analogues as antihyperglycemic and lipid modulating agents, Bioorg Med Chem Lett, 13 (3): 399-403 (2003).
74. Ramachandran U, Mital A, Bharatam PV, Khanna S, Rao PR, Srinivasan K, Kumar R, Chawla, HP, Kaul CL, Raichur S and Chakrabarti R, Studies on some glitazones having pyridine as the linker unit, Bioorg Med Chem, 12 (4), 655-662 (2004).
75. Kumar R, Mittal A and Ramachandran U, Design and synthesis of 6-methyl-2-oxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid derivatives as PPARγ activators, Bioorg Med Chem Lett, 17 (16): 4613-4618 (2007).
76. Sundriyal S, Viswanad B, Bharathy E, Ramarao P, Chakraborti AK and Bharatam PV, New PPARγ ligands based on 2-hydroxy-1,4-naphthoquinone: Computer-

aided design, synthesis, and receptor-binding studies, Bioorg Med Chem Lett, 18 (11): 3192-3195 (2008).
77. Shah P, Mittal A and Bharatam PV, CoMFA analysis of dual/multiple PPAR activators, Eur J Med Chem, 43 (12): 2784-2791 (2008).
78. Rikimaru K, Wakabayashi T, Abe H, Imoto H, Maekawa T, Ujikawa O, Murase K, Matsuo T, Matsumoto M, Nomura C, Tsuge H, Arimura N, Kawakami K, Sakamoto J, Funami M, Mol CD, Snell GP, Bragstad KA, Sang BC and Dougan DR, A new class of non-thiazolidinedione, non-carboxylic-acid-based highly selective peroxisome proliferator-activated receptor (PPAR) γ agonists: Design and synthesis of benzylpyrazole acylsulfonamides, Bioorg Med Chem, 20 (2): 714-733 (2012).
79. Rikimaru K, Wakabayashi T, Abe H, Tawaraishi T, Imoto H, Yonemori J, Hirose H, Murase K, Matsuo T, Matsumoto M, Nomura C, Tsuge H, Arimura N, Kawakami K, Sakamoto J, Funami M, Mol CD, Snell GP, Bragstad KA and Sang B-C, Structure-activity relationships and key structural feature of pyridyloxybenzene-acylsulfonamides as new, potent, and selective peroxisome proliferator-activated receptor (PPAR) γ agonists, Bioorg Med Chem, 20 (10): 3332-3358 (2012).
80. Ammazzalorso A, D'Angelo A, Giancristofaro A, Filippis BD, Matteo MD, Fantacuzzi M, Giampietro L, Linciano P, Maccallini C, and Amoroso R, Design, synthesis and docking studies of new furobenzopyranones and pyranobenzopyranones as photoreagent towards DNA and as antimicrobial agents, Euro J Med Chem, 58: 317-322 (2012).
81. Brun P, Dean A, Marco VD, Surajit P, Castagliuolo I, Carta D and Ferlin MG, Peroxisome proliferator-activated receptor-γ mediates the anti-inflammatory effect of 3-hydroxy-4-pyridinecarboxylic acid derivatives: Synthesis and biological evaluation, Euro J Med Chem, 62: 486-497 (2013).
82. Shibata Y, Kagechika K, Yamaguchi M, Kubo H and Usui H, Design, synthesis and evaluation of novel zwitterionic compounds as PPARα/γ dual agonists. Bioorg Med Chem Lett, 22 (23): 7075-7079 (2012).
83. Ohashi M, Nakagome I, Kasuga J, Nobusada H, Matsuno K, Makishima M, Hirono, S, Hashimoto Y and Miyachi H, Design, synthesis and in vitro evaluation of a series of α-substituted phenylpropanoic acid PPARγ agonists to further investigate the stereochemistry-activity relationship, Bioorg Med Chem, 20 (21): 6375-6383 (2012).
84. Sato A, Dodo K, Makishima M, Hashimoto Y and Sodeoka M, Synthesis and evaluation of 2,3-dinorprostaglandins: Dinor-PGD1 and 13-epi-dinor-PGD1 are peroxisome proliferator-activated receptor α/γ dual agonists, Bioorg Med Chem Lett, 23 (10): 3013-3017 (2013).
85. Furukawa A, Arita T, Fukuzaki T, Mori M, Honda T, Satoh S, Matsui Y, Wakabayashi, K, Hayashi S, Nakamura K, Araki K, Kuroha M, Tanaka J, Wakimoto S, Suzuki O and Ohsumi J, Synthesis and biological evaluation of novel (-)-Cercosporamide derivatives as potent selective PPARγ modulators, Euro J Med Chem, 54: 522-533 (2012).
86. Gim HJ, Li H, Lee E, Ryu J-H and Jeon R, Design and synthesis of alkoxyindolyl-3-acetic acid analogs as peroxisome proliferator-activated receptor-γ/δ agonists, Bioorg Med Chem Lett, 23 (2): 513-517 (2013).
87. Kim T, Lee W, Jeong KH, Song JH, Park S-H, Choi P, Kim S-N, Lee S and Ham J, Total synthesis and dual PPARα/γ agonist effects of amorphastilbol and its synthetic derivatives, Bioorg Med Chem Lett, 22 (12): 4122-4126 (2012).
88. Raza S, Srivastava SP, Srivastava DS, Srivastava AK, Haq W and Katti SB, Thiazolidin-4-one and thiazinan-4-one derivatives analogous to rosiglitazone as potential antihyperglycemic and antidyslipidemic agents, Euro J Med Chem, 63: 611-620 (2013).
89. Hu Y, Yang Y, Yu Y, Wen G, Shang N, Zhuang W, Lu D, Zhou B, Liang B, Yue X, Li F, Du J and Bu X, Synthesis and identification of new flavonoids targeting liver X receptor β involved pathway as potential facilitators of Aβ clearance with

reduced lipid accumulation, J Med Chem, 56 (15): 6033-6053 (2013).

90. Verma AK, Singh H,Satyanarayana M, Srivastava SP, Tiwari P, Singh AB, Dwivedi AK, Singh SK, Srivastava M, Nath C, Raghubir R, Srivastava AK, and Pratap R, Flavone-based novel antidiabetic and antidyslipidemic agents, J Med Chem, 55 (10): 4551-4567 (2012).
91. Liu W, Lau F, Liu K, Wood HB, Zhou G, Chen Y, Li Y, Akiyama TE, Castriota G, Einstein M, Wang C, McCann ME, Doebber TW, Wu M, Chang CH, McNamara L, McKeever, B, Mosley RT, Berger JP, Meinke PT, Benzimidazolones: a new class of selective peroxisome proliferator-activated receptor γ (PPARγ) modulators, J Med Chem, 54 (24): 8541-8554 (2011).
92. Qian Y, Wertheimer SJ, Ahmad M, Cheung AWH, Firooznia F, Hamilton MM, Hayden S, Li S, Marcopulos N, McDermott L, Tan J, Yun W, Guo L, Pamidimukkala A, Chen Y, Huang KS, Ramsey GB, Whittard T, Conde-Knape K, Taub R, Rondinone CM, Tilley J and Bolin D, Discovery of orally active carboxylic acid derivatives of 2-phenyl-5-trifluoromethyloxazole-4-carboxamide as potent diacylglycerol acyltransferase-1 inhibitors for the potential treatment of obesity and diabetes, J Med Chem, 54 (7): 2433-2446 (2011).
93. Haigh D, Birrell HC, Cantello BCC, Eggleston DS, Haltiwanger RC, Hindley RM, Ramaswamy A and Stevens NC, Non-thiazolidinedione antihyperglycaemic agents. Part 5: Asymmetric aldol synthesis of (S)-(–)-2-oxy-3-arylpropanoic acids, Tetrahedron Asymm, 10 (7): 1353-1367 (1999).
94. Young PW, Buckle DR, Cantello BCC, Chapman H, Clapham JC, Coyle PJ, Haigh D, Hindley RM, Holder JC, Kallender H, Latter AL, Laurie KWW, Mossakowska D, Murphy GJ, Cox LR and Smith SA, Identification of high-affinity binding sites for the insulin sensitizer rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for peroxisomal proliferator-activated receptor gamma, J Pharmacol Exp Ther, 284 (2): 751-759 (1998).
95. Haigh D, Allen G, Birrell HC, Buckle DR, Cantello BCC, Eggleston DS, Haltiwanger RC, Holder JC, Lister CA, Pinto IL, Rami HK, Sime JT, Smith SA and Sweeney JD, Non-thiazolidinedione antihyperglycaemic agents. Part 3: The effects of stereochemistry on the potency of alpha-methoxy-beta-phenylpropanoic acids, Bioorg Med Chem, 7 (5): 821-830 (1999).
96. Hulin B, McCarthy PA and Gibbs EM, The glitazone family of antidiabetic agents. Current Pharmaceutical Design, 2: 85-102 (1996).
97. B Hulin. 3-Aryl -Z-hydroxypropionic acid derivatives and analogs as antihypertensives, International Patent Appl, WO91/19702, 1991.
98. Kasuga J-I, Yamasaki D, Araya Y, Nakagawa A, Makishima M, Doi T, Hashimotoa Y and Miyachia H, Design, synthesis, and evaluation of a novel series of alpha-substituted phenylpropanoic acid derivatives as human peroxisome proliferator-activated receptor (PPAR) alpha/delta dual agonists for the treatment of metabolic syndrome, Bioorg Med Chem, 14 (24): 8405-8414 (2006).