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Perspective

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Targeting Peroxisome Proliferator-Activated Receptors (PPARs): Development of Modulators

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INTRODUCTION

Metabolic syndrome (MS) remains one of the leading causes of mortality in Western societies and has become a major public health challenge worldwide.[1] The term metabolic syndrome refers to a cluster of risk factors of metabolic origin that promote development of cardiovascular diseases and type 2 diabetes melitus (T2DM). Metabolic syndrome includes such pathological factors as insulin resistance, hyperinsulinemia, abdominal obesity, impaired glucose tolerance, type 2 diabetes, microalbuminuria, a high level of triglycerides, a low level of HDL cholesterol, elevated blood pressure, and a proinflammatory and prothrombic state. The peroxisome proliferator-activated receptors (PPARs) were cloned in 1990 as orphan members of the nuclear receptor family which includes receptors for steroid, retinoid, and thyroid hormones and vitamin D.[2] PPARs are transcription factors activated by the binding of small lipophilic ligands. They induce or repress transcription of a large number of different genes, thereby influencing cellular functions. Among these functions, PPARs contribute to the regulation of glucose, lipid, and cholesterol metabolism, apparently making them ideal targets for the development of oral agents for treating metabolic syndrome.[3] Consequently, PPAR agonists have for many years represented a promising approach to treating type 2 diabetes and associated metabolic diseases, including obesity, hypertension, and dyslipidemia. There are three known subtypes of PPAR receptors, designated PPARα, -γ, and -β/δ. While the PPAR subtypes share a high level of sequence and structural homology, each PPAR subtype exhibits a unique tissue expression profile.[4]

This review covers the rapid progress that has been made in functional analysis of peroxisome proliferator-activated receptors (PPARs) and that has led to a greater understanding of these receptors, establishing them as molecular targets for development of drugs against metabolic diseases. Natural and synthetic ligands for the three subtypes, PPARα, PPARγ, and PPARβ/δ, are reported: agonists and antagonists, partial and selective PPAR modulators (SPPARMs), dual agonists, and PPAR$\alpha,\gamma,\beta/\delta$ pan-agonists. We conclude with a view of the future of PPAR ligand research and the emergence of new hybrid compounds of a multitarget drug type, advantageous in the treatment of chronic inflammation.

PPARα

PPARα is found in tissues with high rates of fatty acid catabolism and is highly expressed in brown adipose tissue, followed by liver, kidney, heart, and skeletal muscle. This receptor regulates lipid metabolism and modulates inflammation by its effect on genes which control reverse cholesterol transport as well as transport and degradation of free fatty acids through peroxisomal and β-oxidation pathways. PPARα is the molecular target mainly of hypolipidemic fibrates, including clofibrate and bezafibrate.[5] These compounds are representative of the fibrate class and operate by increasing clearance, decreasing synthesis of very low density lipoproteins (VLDLs) rich in triglycerides, and decreasing the serum level of apolipoprotein CIII (apoCIII), a known inhibitor of VLDL clearance. The rise in HDL cholesterol levels observed with fibrates stems in part from transcriptional induction of the major HDL apolipoproteins apoA-I and apoA-II. PPARα is also involved in antiatherosclerosis mechanisms. Agonists have been shown to down-regulate expression of VCAM-1, inhibit nuclear factor κB (NF-κB) and activator protein 1 (AP-1), and mediate the reduction in plasma levels in interleukin-6, fibrogen, and C-reactive protein. For the past 2 decades, PPARα agonists have been useful in the treatment of dyslipidemia associated with atherosclerosis. Indeed, fibrates have been shown, in secondary prevention studies, to slow progression of atherosclerosis and reduce the number of coronary events in patients with normal levels of LDL cholesterol and, more recently, in diabetic patients. PPARα receptor activation has also been shown to produce anti-inflammatory effects in vascular cells.[6]

PPARγ

PPARγ, the most widely investigated PPAR subtype, is expressed predominantly in adipose tissue but also, at lower levels, in heart, colon, kidney, spleen, intestine, skeletal muscle, liver, and macrophages. PPARγ is a key factor in adipogenesis and also plays an important role in insulin sensitivity, cell cycle regulation, and cell differentiation. PPARγ has been shown to be an important regulator of target genes involved in glucose and lipid metabolism and, more recently, in inflammation. PPARγ agonists have been most extensively studied for their

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ability to enhance the sensitivity of target tissues to the effects of insulin. Benefits of PPARγ activation are seen in the current clinical use of PPARγ-modulating agents as antidiabetic drugs. PPARγ agonists of the thiazolidine-2,4-diones (TZDs) class, which induce insulin sensitization and improve glycemic control, are currently being used in treatment of type 2 diabetes.[7] However, despite their efficacy, these drugs possess a number of deleterious target-related side effects, including significant weight gain, peripheral edema, increased risk of congestive heart failure, and an increased rate of bone fracture. Such major safety concerns have not only restrained clinical use of these drugs but also led to failed development of many PPARγ agonists.[8]

■ PPARβ/δ

The third subtype, PPARβ/δ, is ubiquitously expressed. Although cloned in the early 1990s like the others, PPARβ/δ remains the least understood PPAR subtype in part because of its ubiquitous expression. A growing body of evidence suggests that PPARβ/δ plays a role in the regulation of fatty acid catabolism, energy metabolism, and reverse cholesterol transport.[9] In addition, some potent and selective PPARβ/δ agonists have been shown to improve insulin resistance and reduce plasma glucose in animal models of type 2 diabetes.[10] Likewise, PPARβ/δ has been implicated in dyslipidemia, as well as in fertility and cancer.

■ STRUCTURAL FEATURES OF PPARS

All three PPAR subtypes share structural and functional organization similar to that of other nuclear receptors. Four major domains have been identified: the A/B, C, D, and E domains. The N-terminal A/B domain differs in both length and predicted amino acid sequence and contains activation function 1 (AF-1), whose action is independent of the presence of a ligand. The A/B domain is highly variable in sequence among the different nuclear receptors. This domain plays an important role in regulating PPAR activity through both phosphorylation and interdomain communication.[11] The C domain comprises about 70 amino acids and encodes the DNA binding domain (DBD). This domain is responsible for binding of the PPAR receptor to the peroxisome proliferator response element (PPRE) in the promoter region of target genes. It is a highly conserved domain containing two zinc fingers. The D hinge region is a flexible domain that connects the DBD with the ligand binding domain (LBD) and is a docking domain for cofactors. The E C-terminal region contains two important domains that are moderately conserved in sequence and highly conserved in structure among the various nuclear receptors. One is the LBD responsible for ligand specificity and activation of PPAR binding to the PPRE, resulting in modulation of gene expression. This region also has been found to play an important role in dimerization and nuclear localization. The other is represented by the ligand-dependent activation domain AF-2, which is located in C-terminal α-helix 12 and is critical for both ligand binding and recruitment of PPAR cofactors. This domain is variable in sequence among the different nuclear receptors. They share a common mode of action that involves heterodimerization with the nuclear 9-*cis*-retinoic acid receptor (RXR), and the complex is bound to DNA with a low level of association with coactivators. Upon binding of a small molecule agonist, the interaction with coactivators is strengthened, resulting from a conformational change and leading to gene transcription of proteins involved in the control of lipid and carbohydrate metabolism.[12] The PPARs can induce or repress transcription of a number of different genes, thereby influencing cellular functions via three distinct mechanisms: ligand-dependent transactivation, ligand-independent repression, and ligand-dependent transrepression. The prototypic activity of PPAR is to activate transcription in a ligand-dependent manner by binding directly to specific PPRE in target genes as heterodimers with RXR. Ligand-dependent transactivation is linked to the recruitment of coactivator complexes that modify chromatin structure and facilitate assembly of general transcriptional machinery at the promoter. In addition, PPARs repress transcription of direct target genes in the absence of ligands (ligand-independent repression). This activity has been linked to recruitment of corepressor complexes that function to antagonize the action of coactivator complexes and maintain genes in a repressed state in the absence of a ligand. PPARs can also negatively regulate gene expression in a ligand-dependent manner by inhibiting the activities of other transcription factors, such as NF-κB and AP-1 families (ligand-dependent transrepression). In contrast to transcriptional activation and repression, which usually involves the binding of PPAR to specific response elements in the promoter or enhancer regions of target genes, transrepression does not involve binding to typical receptor-specific response elements. Crystal structures of the LBD of human PPARα, PPARγ, and PPARβ/δ have been solved in complex with several ligands and have revealed a common three-dimensional fold structure among LBDs, consisting of an antiparallel α-helical sandwich of 12 helices (helix 1 to helix 12) and a small three-stranded antiparallel β-sheet in the core of the LBD, forming a hydrophobic ligand binding cavity.[13] This structure reveals a large binding pocket, which may explain the diversity of ligands for PPARs. The central cavity spans the domain between the AF-2 helix within C-terminal α-helix 12 and the three-stranded antiparallel β-sheet. The three PPAR subtypes have a common large Y-shaped binding site (Figure 1). The

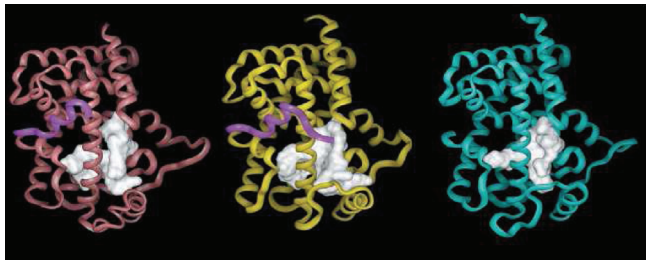

Figure 1. Tridimensional structure of ligand binding domain (LBD) for each subtype of PPAR.

ligands for PPARα or PPARγ should be able to adopt a U-shaped conformation and an L-shaped conformation for PPARβ/δ.[14] PPAR ligands stabilize a specific conformation of the AF2 helix and provide a suitable interface for binding a coactivator. Interestingly, despite a common general structure of the LBD, ligand binding to PPARs shows both species and isotype specificities. As previously shown, PPARs are central to the regulation of energy homeostasis, with each subtype controlling particular aspects. As a result, agents that activate individual PPARs could have different clinical effects.[15] Screening for PPAR ligands has led to identification of natural and synthetic agonists that are able to activate them. This review enumerates the different natural and synthetic ligands of PPARs

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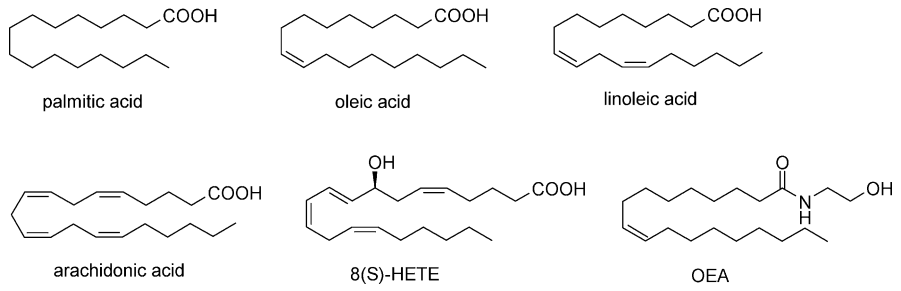

Figure 2. Natural PPARα ligands.

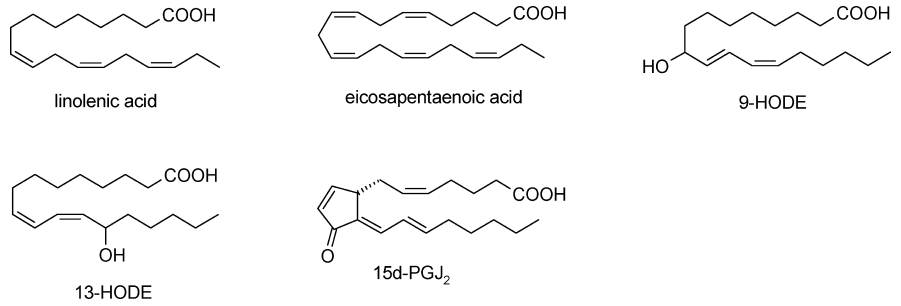

Figure 3. Natural PPARγ ligands.

described in the literature. Some of the major achievements continue to warrant our attention.

1. Natural Ligands. *1.1. PPARα.* Some saturated or unsaturated fatty acids, and eicosanoids such as palmitic acid, oleic acid, linoleic acid, and arachidonic acid, have been identified as endogenous activators of PPARα (Figure 2). In particular, PPARα was described as being the only subtype to bind a wide range of saturated fatty acids with affinities in the micromolar range. While total fatty acid levels in serum reached these concentrations, it was not known whether the free concentrations of fatty acids in cells were high enough to activate the receptor. This prompted several investigators to search for high-affinity natural ligands among the known eicosanoid metabolites of polyunsaturated fatty acids. The lipoxygenase metabolite 8(*S*)-hydroxy-5,9,11,14-eicosatetraenoic acid (8(*S*)-HETE) was identified as a higher affinity PPARα ligand, although it was not found at sufficiently high concentrations in the right tissues to enable its characterization as a natural ligand. Since no single high-affinity natural ligand has been identified, Willson and co-workers suggested that one physiological role of PPARα may be to sense the total flux of fatty acids in metabolically active tissues. More recently, *N*-(2-hydroxyethyl)oleamide (oleoylethanolamide, OEA),[16] a naturally occurring lipid chemically related to the endocannabinoid anandamide, was reported to exert its action through PPARα activation.

1.2. PPARγ. A number of natural ligands have been described for PPARγ, primarily including fatty acids and their metabolites, eicosanoid derivatives (Figure 3). However, these ligands have relatively low affinities and activate the receptor at micromolar concentrations ($K_D \approx 2-50\ \mu M$) superior to their physiological levels. PPARγ has a clear preference for polyunsaturated acids, unlike PPARα. The essential fatty acids linoleic acid, linolenic acid, arachidonic acid, and eicosapentaenoic acid (EPA) have been shown to bind to PPARγ, as well as the 15-lipoxygenase metabolites of linoleic acid, 9-hydroxy-10,12-octadecadienoic acid (9-HODE), and 13-hydroxy-9,11-octadecadienoic acid (13-HODE).[17] The J-series of prostaglandins derived from PGD_2 have also been identified as PPARγ ligands. The terminal metabolite 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) activates PPARγ at low micromolar concentrations and also induces adipocyte differentiation.[18] This prostaglandin has become the most widely used naturally occurring PPARγ ligand.

1.3. PPARβ/δ. PPARβ/δ is also activated by unsaturated and saturated long-chain fatty acids (LCFA), EPA, arachidonic acid, and a number of eicosanoids, HODE (hydroxyoctadecadienoic acid), and prostacyclin (PGI_2). The semisynthetic prostacyclin carbaprostacyclin was reported to be the most potent PPARβ/δ natural ligand (Figure 4).[19]

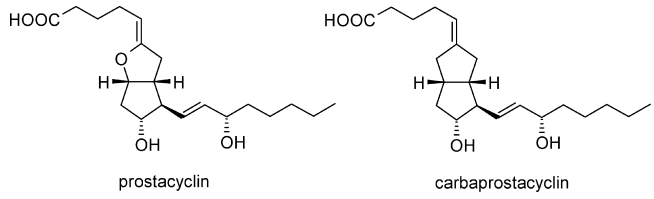

Figure 4. Natural PPARβ/δ ligands.

2. Synthetic Ligands. Many synthetic PPAR ligands have been reported in the literature since the discovery of PPARs. Data from a number of crystallographic studies exploring these compounds reveal a fairly clear view of the agonist binding mode in the LBD. Nearly all the compounds conformed to a three-module structure, with a binder group involved in a series of hydrogen bonds in front of the AF-2, a linker mainly arranged around central helix 3 and an effector end occupying the large cavity of the binding site (Figure 5).[20]

2.1. PPARα. 2.1.1 PPARα Agonists. 2.1.1.1. Fibrates. PPARα is the predominant target for fibrates, a class of drugs well-established in the therapy of dyslipidemia and hypertriglyceridemia (Figure 6). The hypolipidemic fibrate drugs are currently used in clinical practice for treatment of dyslipidemia (in particular, low HDL cholesterol and elevated

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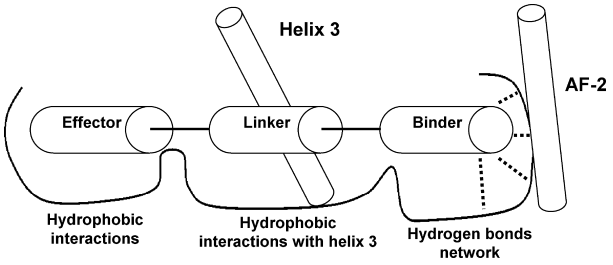

Figure 5. Agonist binding mode.

triglyceride levels) and for reducing cardiovascular risk.[21] In 1962, Thorp and Waring showed that clofibrate (**1**), the ethyl ester of α-parachlorophenoxyisobutyric acid, among a series of α-aryloxyisobutyric acid derivatives, was most effective at decreasing the concentration of cholesterol and other lipids in rat plasma and liver.[22] In 1965, **1** became the first PPARα agonist (EC_{50} = 55 μM) to be used in clinical therapy in the treatment of dyslipidemia. However, it was withdrawn from the market because of severe adverse effects, as it was shown to increase mortality among treated patients. In an attempt to improve the pharmacological profile of clofibrate, some analogues were synthesized and biologically evaluated. These compounds were referred to as "second generation fibrates" and include fenofibrate (**2**), ciprofibrate (**3**), bezafibrate (**4**), and the dimethylphenoxypentanoic acid derivative gemfibrozil (**5**). These compounds increased the synthesis of lipoprotein lipase, thereby increasing clearance of triglycerides; however, they showed only modest selectivity over the other PPAR subtypes. Furthermore, the structures of these compounds were relatively small compared to the wide pocket they occupied, fostering the development of a newer generation of fibrate analogues. Attempts to identify more potent compounds led to the synthesis of a series of ureidofibrates that were active at lower doses in rodent models of hyperlipidemia. The first reported examples of selective PPARα agonists were ureido-based fibric acids **6** (GW9578) and **7** (GW7647)[23] with their respective EC_{50} values for human PPARα being 6 and 50 nM, respectively. α,α-Dimethylcarboxylic acids **6** and **7** showed 20-fold and 200-fold selectivity, respectively, compared to PPARγ and PPARβ/δ and possessed potent lipid-lowering activities in a cholesterol/cholic acid fed rat assay compared to fenofibrate. Researchers at Lilly also reported their phenoxyphenylpropanoic acid **8** (LY518674) to be a potent PPARα agonist with 200-fold binding selectivity compared to PPARγ and PPARβ/δ receptors.[24] In order to develop PPARα agonists more potent and selective than the fibrate class, Sierra et al.[25] modified their selective PPARβ/δ agonist (GW501516) (structure not disclosed) to incorporate the 2-aryl-2-methylpropionic acid group of fibrates, which led to compound **9** (GW590735), shown to be a potent and selective PPARα agonist with EC_{50} = 4 nM on PPARα and at least 500-fold selectivity versus others subtypes. This compound offered the potential for significantly improving therapeutic benefits compared to the fibrates in dyslipidemia and hypertriglyceridemia. Meyer et al. reported another PPARα agonist, **10** (K111),[26] which differed from the classical fibrate class by the long chain alkyl moiety, α-dichlorododecanoic acid. Compound **10** was an insulin sensitizer with PPARα selectivity compared to PPARγ and PPARβ/δ. This compound led to significantly decreased body weight and improved hyperinsulinemia, insulin sensitivity, hypertriglyceridemia, and HDL cholesterol levels, without adipogenesis or significant effects upon fasting glucose, 24 h urine glucose excretion, systolic and diastolic blood pressure, plasma fibrinogen, total cholesterol, and chemistry and hematology profiles. These benefits were similar to the health-improving effects of caloric restriction,

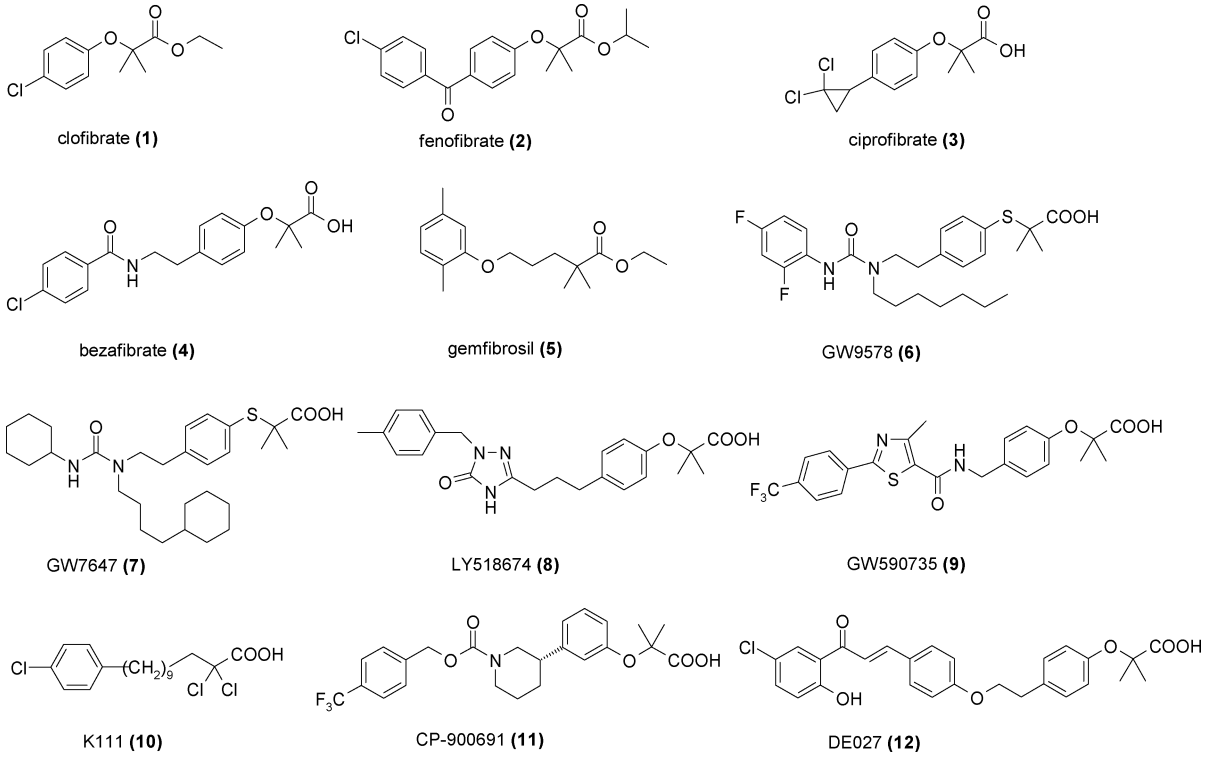

Figure 6. Fibrates synthetic PPARα agonist ligands.

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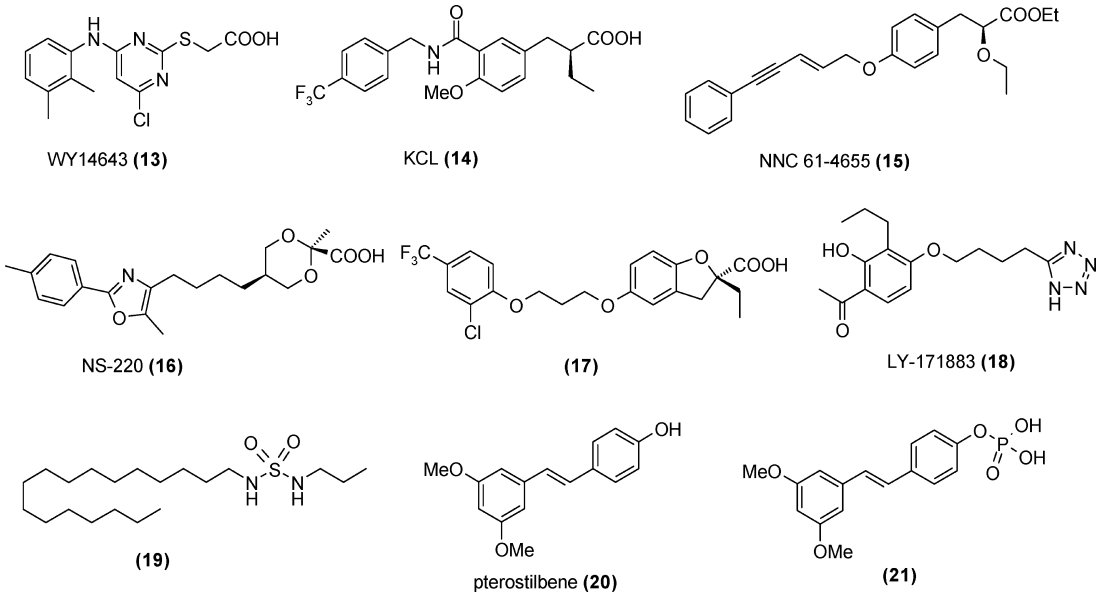

Figure 7. Non-fibrates synthetic PPARα agonist ligands.

providing preliminary evidence that **10** has excellent potential as a calorie-restricting mimetic agent. The results also showed that it is a potent antidiabetic and hypolipidemic drug in non-human primates. More recently, **11** (CP-900691), with a phenylpiperidine carbamate moiety, has been reported to be a highly selective PPARα agonist in T2DM monkeys, with favorable effects upon dyslipidemia as well as upon glycemic control, body weight, and inflammation.[27] Indeed, treatment of diabetic monkeys with **11** has been shown to increase HDL cholesterol and apoA1, reduce plasma triglycerides and apoB, improve the lipoprotein index, decrease body weight and CRP, and increase adiponectin. Li et al. reported hybrid compounds obtained by a combination of the classical fibrate "headgroup", a linker with the appropriate length, and a chalcone[28] known for over a century to have advantageous biological activities, including antioxidant, anti-inflammatory, anticancer, and anti-infective properties. Compound **12** (DE027) was described as being the most prominent, with EC_{50} = 60 nM. This compound was identified using a virtual screening approach based on the crystal structure of PPARα. Compound **12** has provided a promising novel family of chalcones with a potential hypolipidemic effect.

2.1.1.2. Non-Fibrates. Using a cell-based transactivation assay, **13** (WY14643), a non-fibrate selective PPARα agonist with a thioether moiety and a pyrimidine linker part, was identified as being a micromolar activator of murine PPARα (Figure 7). The Kyorin group reported a highly potent human PPARα-selective agonist, **14** (KCL). This compound is a non-fibrate phenylpropanoic acid derivative that is a potent human PPARα agonist in vitro, possessing selectivity for PPARα compared to the other subtypes.[29] Human PPARα selectivity of **14** is mainly due to a specific interaction between the hydrophobic tail part of **14** (the 4-trifluoromethyl group) and the key amino acid Ile272 located on the helix 3 region of human PPARα LBD. Compound **14** activates human and rat PPARα with EC_{50} of 0.06 and 5.2 μM, respectively. Thus, the transactivation activity of KCL for PPARα is approximately 100-fold less potent in rats than in humans. Compound **15** (NNC 61-4655),[30] a phenylpropargyl derivative, is a nonselective but PPARα-preferring potent PPAR agonist with excellent pharmacokinetic properties; it has been shown to have more efficacious in vivo effects in male db/db mice than PPARγ selective agonists such as rosiglitazone and pioglitazone. Kuwabara et al. reported a highly potent PPARα agonist, **16** (NS-220),[31] a dioxanecarboxylic acid derivative that presents PPARα agonist activity 1000 times more potent than fibrates, suggesting that the dioxanecarboxylic acid moiety is responsible for its high potency and selectivity for the PPARα subtype. This compound led to amelioration of metabolic disorders in type 2 diabetic mice. A series of 2,3-dihydrobenzofuran-2-carboxylic acids have been described that led to development of a novel class of PPARα agonists,[32] represented by compound **17**, which displays the best selectivity among PPARα selective agonists reported to date. Indeed, in animal models, it displays very high potency (EC_{50} < 10 nM) and subtype selectivity (>1000-fold), as well as highly potent and effective hypolipidemic activity. It is believed that the inherent selectivity of this class of compounds is primarily due to conformational constraints rendered by the structurally unique 2,3-dihydrobenzofurane ring. In male Syrian hamsters, 24 h drug exposure to **17** and fenofibrate administered in a series was measured following the final dose of each compound. It was found that **17** required only about $^{1}/_{500}$ of the exposure to fenofibrate to achieve comparable lipid-lowering efficacy, suggesting that the in vivo efficacy of these two compounds is closely correlated with their potency as PPARα agonists in vitro. Researchers at Lilly also reported a tetrazole ring binder, **18** (LY-171883), a leukotriene D_4 antagonist that induces peroxisome proliferation in rodent liver.[33] Like many peroxisome-proliferating agents, it causes transient lipid accumulation along with other changes in hepatic lipid metabolism. Study of the effect of **18** on lipid metabolism revealed that it increased triglycerides in liver, associated with a 3-fold increase in fatty acid synthetase. Some sulfamide-derived analogues of OEA with potent selective binding affinity for PPARα have been reported and have led to an *N*-octadecyl-*N*′-propylsulfamide (**19**). This compound has been shown to induce satiety, reduce food intake in rats, reduce body weight, and act as a lipid-lowering agent.[34] On the basis of the structure of another famous natural compound, resveratrol, which showed a beneficial effect at lowering the risk of cardiovascular

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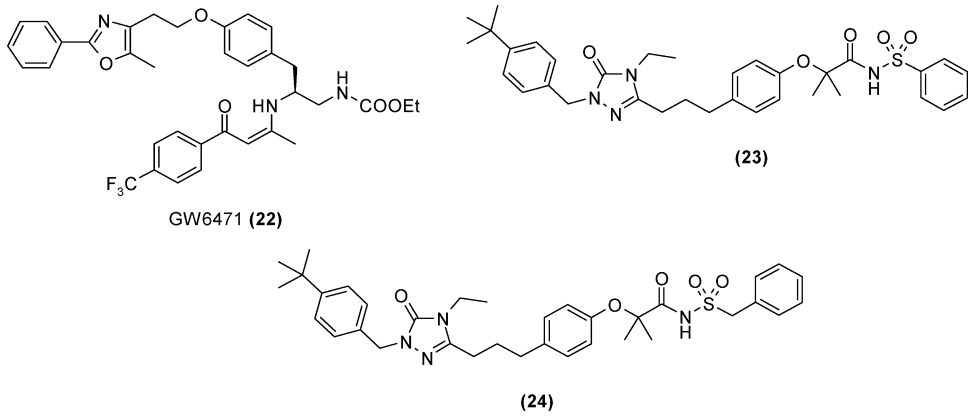

Figure 8. PPARα antagonist ligands.

diseases in animal models, pterostilbene (**20**) and its phosphate derivative (**21**)[35] have been reported, with the trans conformation being more active than cis analogues. Compound **21** is the most active compound in this series, with decreased cholesterol levels in animal models and higher potency than ciprofibrate.

2.1.2. PPARα Antagonists. Few PPARα antagonists have yet been reported (Figure 8). The L-tyrosine-based antagonist **22** (GW6471) was described as being a functional antagonist in cell-based transfection assays.[36] Cocrystal studies on PPARα have shown that this compound binds in a configuration similar to those of other tyrosine-based agonists. However, the ethyl carbamate headgroup of **22** displaced the AF-2 helix from an active conformation, creating a larger pocket for cofactor binding. Cofactor recruitment assays have shown that **22** recruits corepressor motifs, thereby maintaining the receptor in an inactive conformation. A series of thiazolone-based PPARα antagonists have also been described. Derived from carboxylic acid agonists in a triazolone series, the *N*-acylsulfamides A (**23**) and B (**24**) were identified as compounds with potent PPARα binding affinities that failed to activate the receptor in cell-based transfection assays.[37] These compounds were found to antagonize the activity of the PPARα full agonist GW2331 (structure not disclosed).

2.2. PPARγ. *2.2.1. PPARγ Agonists. 2.2.1.1. Glitazones.* Following the discovery of PPARγ, the first class of synthetic ligands to specifically bind it consisted of thiazolidine-2,4-diones (TZDs) or glitazones (Figure 9). TZDs, introduced on the market in the past 10 years, constitute the first class of insulin sensitizers. Their antidiabetic action occurs through improvement in hyperglycemia and hyperinsulinemia and lowering of insulin resistance.

Since the pioneering discovery by scientists at the Takeda Pharmaceuticals Company of ciglitazone (**25**),[38] which effectively reduces insulin resistance by potentiating insulin action in genetically diabetic and/or obese animals, several new TZDs have been developed. Troglitazone (**26**)[39] was derived from **25** by replacing the lipophilic tail (methylcyclohexyl methyl ether moiety) with a vitamin E residue. Pioglitazone (**27**)[40] and rosiglitazone (**28**)[41] were developed by modifications based on the metabolites of **25**. These compounds possess a pyridyl tail group. Some modifications were made with physical cyclization of the linker; indeed, rigidification of the ethoxy in a chromane structure led to englitazone (**29**).[42] This had the effect, however, of increasing the complexity of the compound because of the introduction of a chiral center, probably dooming an otherwise interesting possibility. It is noteworthy, however, that **29**, which lacks a large effector module, was shown to have less potency than **27** and **28**. Three of these TZDs have been marketed: **26**, withdrawn from clinical use in 1997 because of its severe hepatotoxicity; **27** and **28**, currently used as third-intention drugs in treatment of type 2 diabetes. The hepatotoxicity of **26** did not seem to apply to the other glitazones.[43] SAR studies of this family have shown the effectiveness of the methylene moiety as a linker between benzene and the TZD ring. Moreover, the 4-oxylbenzyl group appears to be essential for enabling the compound to exert favorable hypoglycemic and hypolipidemic activities. However, replacement of the thiazolidine-2,4-dione ring by an oxazolidine-2,4-dione ring or a 1-oxa-2,4-diazolidine-3,5-dione ring led to a decrease in activity, while other heterocycles, such as rhodamine, hydantoin, thiohydantoin, and 2-thioxo-5-thiazolidinedione, resulted in complete loss of activity. Nevertheless, because of their ability to induce gene expression in adipocytes and to enhance adipocyte differentiation, TZDs induced weight gain in often already obese patients as a mechanism-related class effect. In addition, other undesirable side effects[44] such as fluid retention, hemodilution, potent cardiac hypertrophy, liver toxicity, and an increased risk of cardiovascular-related death reported in preclinical and clinical studies emphasize the need for safer insulin sensitizers to treat metabolic syndrome and associated complications. Thus, there has been considerable interest in designing novel PPARγ-modulating drugs that retain efficacious insulin-sensitizing properties while minimizing potential adverse side effects, leading to conventional chemistry-led pharmacomodulation studies to improve the glitazones. Indeed, in order to synthesize novel TZDs with better safety and efficacy, a second generation of glitazones has been developed, focusing most intensively on the tail part. The two glitazones that are still marketed share a common trait: their effector module is fairly small compared to the large pocket in which it is bound. In fact, the binder part is common to the entire class and the linker has also been well conserved, having been modified only in the most recent glitazones. Indeed, it was the tail group that bestowed upon each of the glitazones their originality in chemical terms but also their specific biological activity. This module is the most probable candidate for explaining differences in affinity and potency between very similar glitazones, thus entitling it to the status of effector module of the compound. While maintaining a TZD moiety as the binder group, several attempts were made to modify the linker module as well as the effector. The effector module of **28**, the *N*-methyl-2-pyridyl moiety, was first

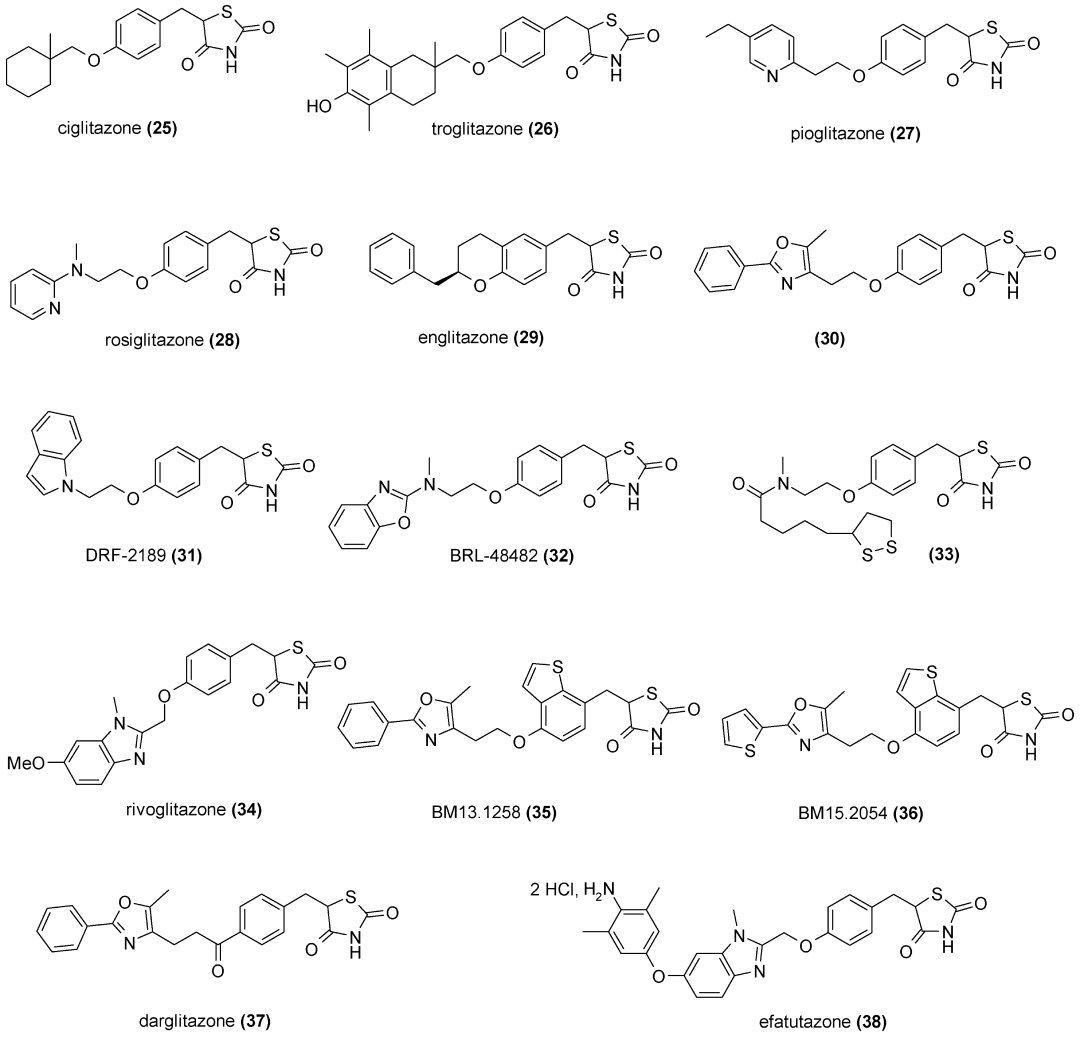

Figure 9. Glitazones synthetic PPARγ agonist ligands.

modified with different heterocycles. Replacement by a 4-oxazolyl moiety led to **30**,[45] which exhibited potent hypoglycemic and hypolipidemic activities and displayed the same biological profile as **25**. Compound **31** (DRF-2189), an indole-based tail group, was also reported to be analogous to **28**. Pharmacological studies showed equal potency for **31** and **28**. The plane shape of indole appears to be important for its activity. As a potential backup for **28**, **32** (BRL-48482) was developed in the same family, differing from its predecessors by its slightly larger effector module, a bicyclic benzoxazole. More drastic modifications in the effector module were also carried out: for example, its replacement by a dithiolane,[46] leading to compound **33**. An in silico docking study of this compound was carried out to elucidate its satisfactory activity; it showed a supplementary hydrogen bond with Ser-432 at its effector amide carboxyl, reinforcing hydrophobic contacts formed by the dithiolane cycle. When compared with biological data available for the compounds, docking results led to the hypothesis that the position of the effector in the pocket, either above the plane of the linker (in the upper arm of the Y-shaped pocket) or below it (in the lower arm), was a key to the affinity and probably functional activity of the ligands. Compound **33** was developed as a derivative of potent antioxidant vitamin α-lipoic acid and has been shown to be a potent PPARγ agonist, with improved insulin sensitivity and reduced triglyceride levels in Zucker rats. These new compounds may prove to be efficacious in the treatment not only of type 2 diabetes but also of atherosclerosis and prevention of vascular restenosis and inflammatory skin diseases. Rivoglitazone (**34**) presents a benzimidazolyl tail.[47] It was reported to be approximately 3 times more active than **28** in a cell-based PPARγ transfection assay but had little effect on PPARα and PPARδ activity in luciferase reporter assays. In vivo, it was found to be more potent than **28**, which can be explained not only by enhanced in vitro activity but also by a longer half-life. Daiichi Sankyo reported that a phase 3 clinical trial was discontinued in May 2009, but the drug was being reused in phase 2 to treat xerophthalmia. **35** (BM13.1258) and **36** (BM15.2054) possess a benzothiophene ring as a linker. They are potent PPARγ activators in transient assays in vitro. Considerable evidence indicates that the therapeutic effects of TZD are mediated via activation of PPARγ, resulting in insulin sensitization and improved glucose metabolism. The results of that study did not challenge this hypothesis but suggested that **35** and **36** may, in addition, affect muscle glucose metabolism via other biochemical pathways.[48] That conclusion was supported by the absence of a correlation between chronic oral effects of **35** and **36** on glycogenic and glycolytic fluxes and by acute insulin-dependent catabolic stimulation of glucose metabolism in vitro. Maintenance of the 4-oxazolyl moiety as

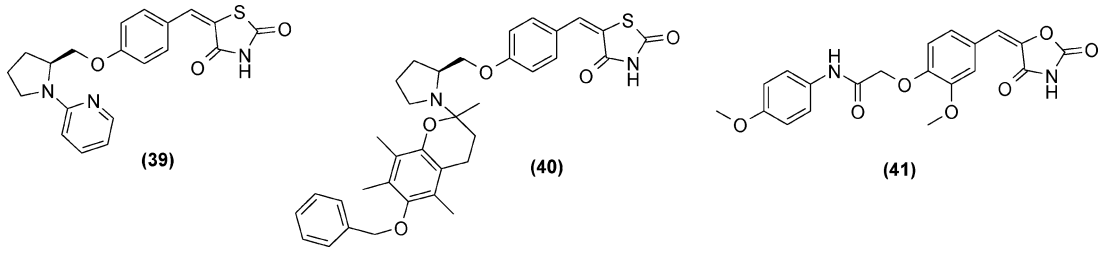

Figure 10. Glitazones analogues synthetic PPARγ agonist ligands.

the effector module and modification of the 4-ethoxybenzyl linker with a phenone moiety led to darglitazone (**37**), which showed better oral potency than **27** or **28**. However, that compound caused dramatic effects upon white and brown adipose tissue and unexpected morbidity/mortality in rats and monkeys.[49] Efatutazone (**38**) very potently activates PPARγ-mediated transcription, more than 40-fold that of **28**, and demonstrated high selectivity for PPARγ within the PPAR family. To date, several reports have shown preclinical antitumor activity for PPARγ agonists in certain models, including carcinogenesis and xenograft models. However, pilot clinical trials in cancer patients using PPARγ agonists have been inconclusive. The antitumor activity of efatutazone has been investigated and was demonstrated in vitro and in vivo.[50] Compound **38**, developed by the Daiichi Sankyo Company, is currently in phase 2 of clinical trials for colorectal cancer indications, either alone or in combination with conventional chemotherapy.

A series of antidiabetic unsaturated TZDs have also been reported in order to develop agonists without a stereogenic center at C-5 of TZD and have led to compounds **39** and **40** (Figure 10).[51] Surprisingly, these compounds show little or no in vitro activity toward PPARγ but more effective euglycemic and in vivo triglyceride-lowering activities than **26**. These observations raise the possibility that some TZDs mediate their antidiabetic activity via mechanisms other than PPARγ, although activation of PPAR by metabolites of these drugs cannot be ruled out. Furthermore, these unsaturated compounds have a better pharmacological profile than their saturated analogues. More recently, a new series of glitazones with a different scaffold and promising levels of glucose uptake activity have been described. The highest activity was shown for compound **41**,[52] which possesses a 1,3-oxazolidin-2,4-dione headgroup connected to the linker part, with a double bond and an anisidine tail part. This compound displays satisfactory antihyperglycemic activity in the presence of insulin.

However, the TZD ligands contain a stereogenic center at C-5 of their headgroup, and one drawback of this class of compounds is the rapid racemization of the resident chiral center under physiological conditions, leading to development of the TZDs as racemates. By use of a PPARγ binding assay, it has been shown that only the (*S*)-enantiomers of the TZDs bind to the receptor with high affinity.[53] In fact, the antidiabetic activity of **28** in humans is only due to the (*S*)-(−)-enantiomer. This suggests that only 50% of the drug substance in the currently approved TZDs binds to the target receptor while 50% of the drug substance is inactive but can be converted to the active enantiomer if not first metabolized.

2.2.1.2. Non-Glitazones. To overcome this problem, several groups have identified acyclic head groups that are less prone to racemization. The acidic functionality of the TZD ring is considered essential for its binding to PPARγ, so some PPARγ agonists have been developed as bioisosteres of the TZD ring, conserving acidic properties by replacement of this ring with acyclic structures such as carboxylated hydroxyureas, α-heteroatom- or α-carbon-substituted carboxylic acids, and 1,3-dicarbonyl compounds.

The first acyclic non-carboxylic acid derivative was compound **42**, a carboxylated hydroxyurea able to normalize the blood glucose level in an in vivo study (Figure 11).[54] The α-heteroatom-substituted-β-phenylpropionic acid series (Figure 11) was based on replacement of the TZD moiety of insulin sensitizer **32** by α-heteroatom-substituted-β-phenylpropionic acids and maintenance of the 4-oxazolyl effector module. These compounds, typified by α-ethoxy acid **43** (SB-213068), have been shown to be potent PPARγ agonists. In contrast to the TZDs, α-benzyloxy acids do not undergo racemization in vivo. Within this series, the (*S*)-enantiomers were shown to have higher binding affinity for PPARγ and were more potent than their (*R*) counterparts in adipocyte differentiation assays.[55] Compound **43** is one of the most potent antihyperglycemic agents yet reported. It was assumed that the role of acidic TZD was played by carboxylic acid in these compounds and that an appropriate substituent at the α-position could alter the chemical environment around the carboxylic acid in such a way that the entire group would mimic the TZD ring. Some benzofuran non-TZD derivatives have also been described,[56] based on incorporation of oxygen into a benzofurane ring, as described above for englitazone but without creating a stereocenter. These modifications led to compounds **44** and **45** which possess α-alkoxy and α-thioether carboxylic acid groups, respectively. For both compounds, the effect of stereochemistry at the α-position of the carboxylic acid group was examined, and it was shown that the activity resided entirely within the (*S*)-enantiomers. These two compounds were shown to stimulate glucose uptake at low nanomolar concentrations in adipocyte cell lines. Some acetic acid derivatives bearing a benzoxazinone core have been synthesized[57] and have led to compounds **46** and **47**. Substitution on the amide of the benzoxazinone ring by lipophilic aliphatic chains enhanced receptor activation while generally maintaining bioavailability and resistance to oxidative metabolism. It should be noted that these compounds have an (*R*) absolute configuration, and show potent efficacy in vivo in a db/db mouse model of type 2 diabetes. An aminomethyl cinnamate (AMC) series of PPARγ agonists is represented by compound **48**, which possesses a large linear effector module, a biphenyl-4-oxazolyl moiety. The α-heteroatom of the linker was moved to the ortho position of the aromatic ring, eliminating the epimerizable stereocenter and producing highly selective PPARγ compounds.[58] With this large linear effector moiety, further investigation led to the discovery of tetrahydroisoquinolines (THQs) represented by compound **49**, a non-TZD.[59] This compound exhibits potent PPARγ affinity for the isolated receptor and in cellular assays while showing good selectivity

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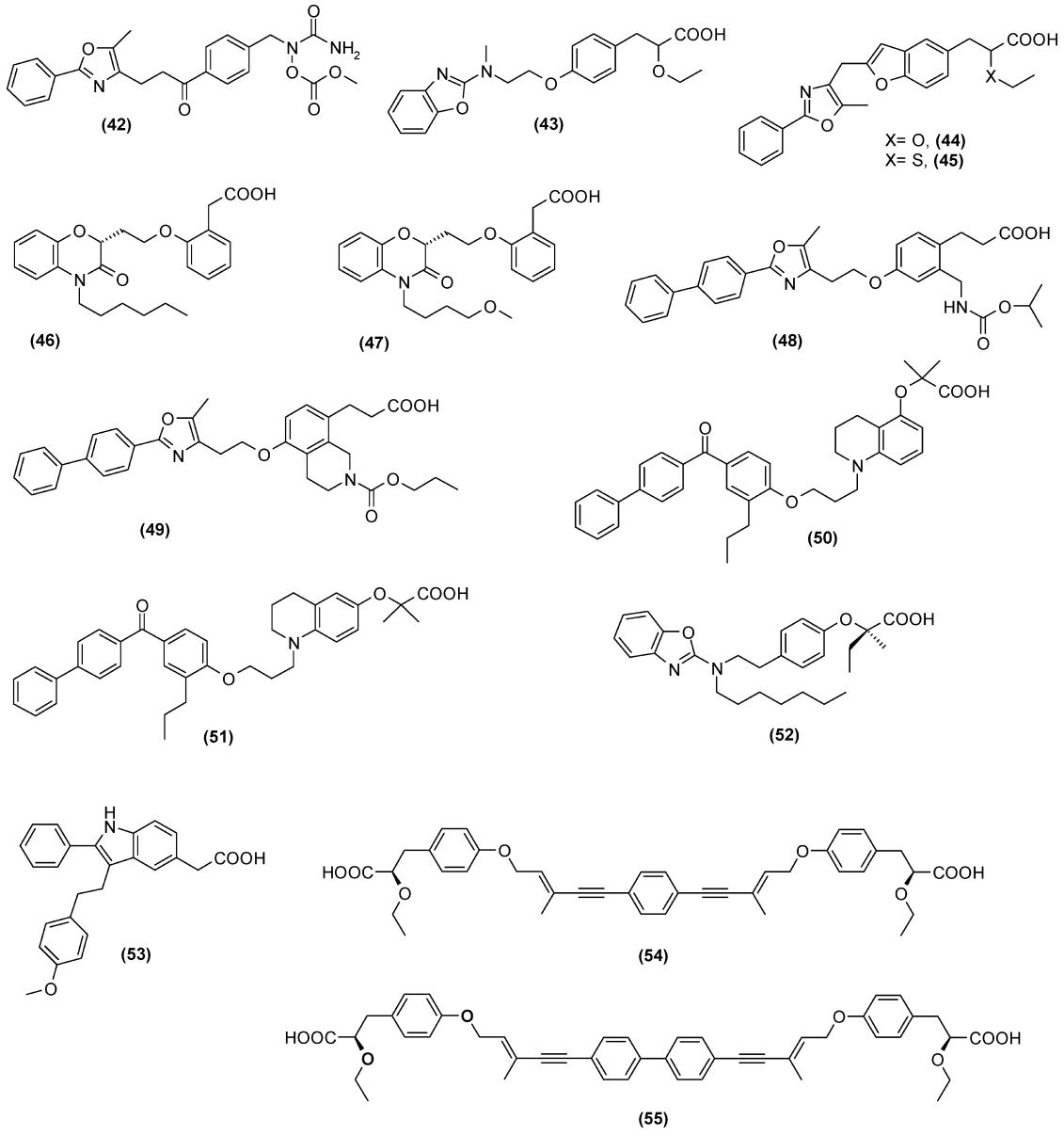

Figure 11. Non-glitazones synthetic PPARγ agonist ligands.

against PPARα. Compound **49** has an excellent in vivo profile in db/db and ZDF models of type 2 diabetes and also possesses desirable pharmacokinetic properties. Lin et al. recently reported new fibrate derivatives[60] **50** and **51** with potent selective PPARγ agonist activities. These compounds were synthesized based on structural modification of a previously described indole fibrate derivative dual PPARα/γ agonist in which indole was replaced by a tetrahydroquinoline core. X-ray cocrystal analyses revealed that selective PPARγ agonist activity is conferred by the tail part building block 4-phenylbenzophenone. Cell-based reporter assays of two enantiomeric fibrate-like derivatives showed that (*R*)-enantiomer **52** is a full agonist of PPARγ whereas the (*S*)-enantiomer is a less potent partial agonist.[61] Analysis of the crystal structures of the PPARγ ligand binding domain, complexed with the (*R*)- and the (*S*)-enantiomers, respectively, showed that the differing degree of stabilization of helix 12 induced by the ligand determined its behavior as a full or partial agonist. Other structurally diverse PPARγ agonists have been described in the literature. Henke et al. reported selective PPARγ agonists in a series of indole-5-carboxylic acids represented by **53** (GW0207).[62] This compound had in vitro potency toward PPARγ similar to or better than that of the three currently marketed thiazolidinedione antidiabetic agents, along with an excellent pharmacokinetic profile in rats. Sauerberg et al. studied the concept of dimeric ligands in the design of new PPAR agonists.[63] A dimeric ligand with a common group **54** or a full dimeric ligand **55** gave PPARγ agonists with retained or increased potency compared to **28**. The dimeric agonists altered the PPAR subtype profile compared to their monomeric counterparts, suggesting that the dimeric design concept can be used to fine-tune the subtype selectivity of PPAR agonists.

An alternative to α-heteroatom-substituted β-phenylpropanoic acids was found in the development of L-tyrosine analogues (Figure 12). Farglitazar (**56**) was the first example of the binding mode of the second large class of PPARγ agonists, the glitazars. Compared with **28**, **56** was primarily characterized by its large binder module, an *N*-(2-benzoylphenyl)-L-tyrosine

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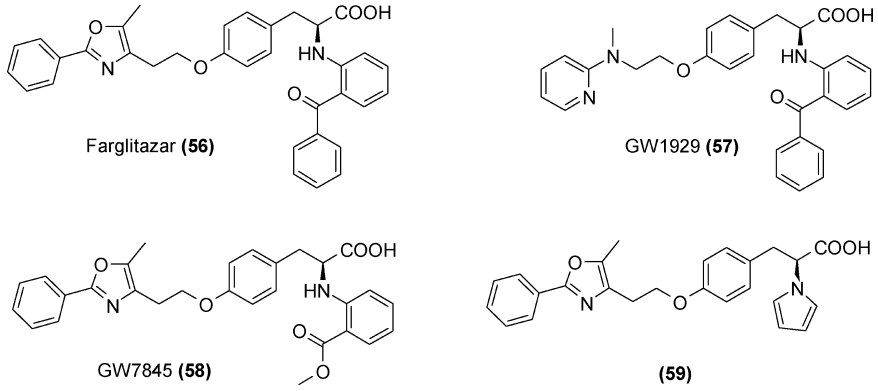

Figure 12. L-Tyrosine analogues synthetic PPARγ agonist ligands.

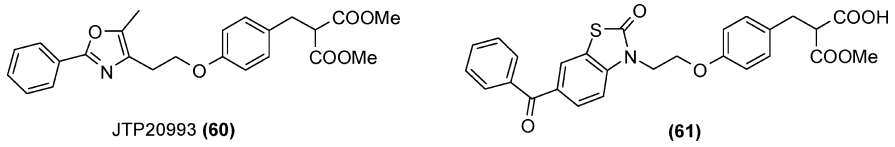

Figure 13. 1,3-Dicarbonyl analogues synthetic PPARγ agonist ligands.

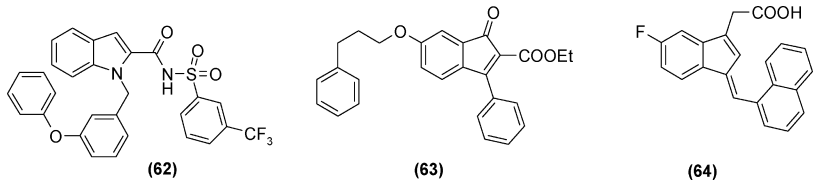

Figure 14. Other synthetic PPARγ agonist ligands.

rather than a TZD. It nevertheless shared the same binding mode, forming hydrogen bonds with both His-323 and -449, Ser-289, and Tyr-473 with its acid moiety. TZD and carboxylic acid moieties of **28** and **56**, respectively, were imperative for AF-2 helix interaction. Although these compounds have an asymmetric center, the (*S*)-enantiomers have been shown to possess greater binding affinity and functional activity at PPARγ than the corresponding (*R*)-enantiomers and are conveniently synthesized from naturally occurring L-tyrosine.[64] Unlike the TZDs, these tyrosine-based compounds do not undergo racemization in vivo. The X-ray crystal structure of **56** bound to PPARγ showed that the benzophenone group was inserted into a lipophilic pocket while the tyrosine nitrogen and the benzophenone carbonyl formed an intramolecular hydrogen bond. This intramolecular hydrogen bond reduces the basicity and polarity of the tyrosine amino group. Compound **56** leads to potent reduction in glucose activity, reduction of triglycerides, and a rise in HDL cholesterol in diabetic patients. The positive lipid effects of **56** may be due to residual PPARα activity in the compound. However, it failed to pass phase 3 of clinical trials because of the emergence of adverse effects such as peripheral edema. Other tyrosine-based PPARγ agonists have been developed, exemplified by **57** (GW1929) and **58** (GW7845).[65] This series also contains some of the most potent PPARγ agonists reported to date, with a number of analogues having subnanomolar activity toward human PPARγ. In addition, these compounds showed >1000-fold selectivity for PPARγ over the PPARα and PPARβ/δ subtypes in cell-based transactivation assays. Compound **57** demonstrated antihyperglycemic activity equipotent to that of troglitazone at >100-fold lower plasma concentrations in ZDF rats,[66] which paralleled their differences in PPARγ binding and activation. Still other L-tyrosine analogues were developed, with alternative N-subsituents that added a small lipophilic substituent while mimicking some of the effects of the intramolecular hydrogen bond present in the benzophenone analogue, leading to pyrrole derivative **59**.[67] This compound incorporates a pyrrole as a low molecular weight N-substituent, and its low basicity may be the key to its potent PPARγ activity. Unfortunately, as for the TZD class and despite excellent potency, several compounds from the L-tyrosine analogue class present unwanted therapeutic profiles marked by fluid retention, weight gain, and potential cardiac hypertrophy.

Replacement of the TZD ring by a noncyclic 1,3-dicarboxyl moiety led to compounds **60** and **61**[68] based on replacement of the 2-phenyloxazole of **60** by a 2-(3*H*)-benzothiazolone (Figure 13). These compounds show interesting insulin-sensitizing and hypoglycemic activities, with levels of glucose and triglyceride correction comparable to those of **28** in ob/ob mouse studies.

Several compounds have been described as PPARγ agonists without belonging to the classical three-module structure ligands previously described (Figure 14). Thus, some *N*-sulfonyl-2-indolecarboxamide compounds derived from indole-derived PPARγ binding agents were reported[69] and led to identification of **62**. Several of these compounds were found to stimulate osteoblast differentiation in a cell-based assay, thus suggesting potential applications in treatment of osteoporosis. Some indenone derivatives, possessing a simple structure containing neither TZD nor the carboxylic acid moiety, were synthesized and led to the discovery of compound **63**,[70] which displays the most active agonistic activity in this series and a new binding mode in the X-ray cocrystal structure. In contrast

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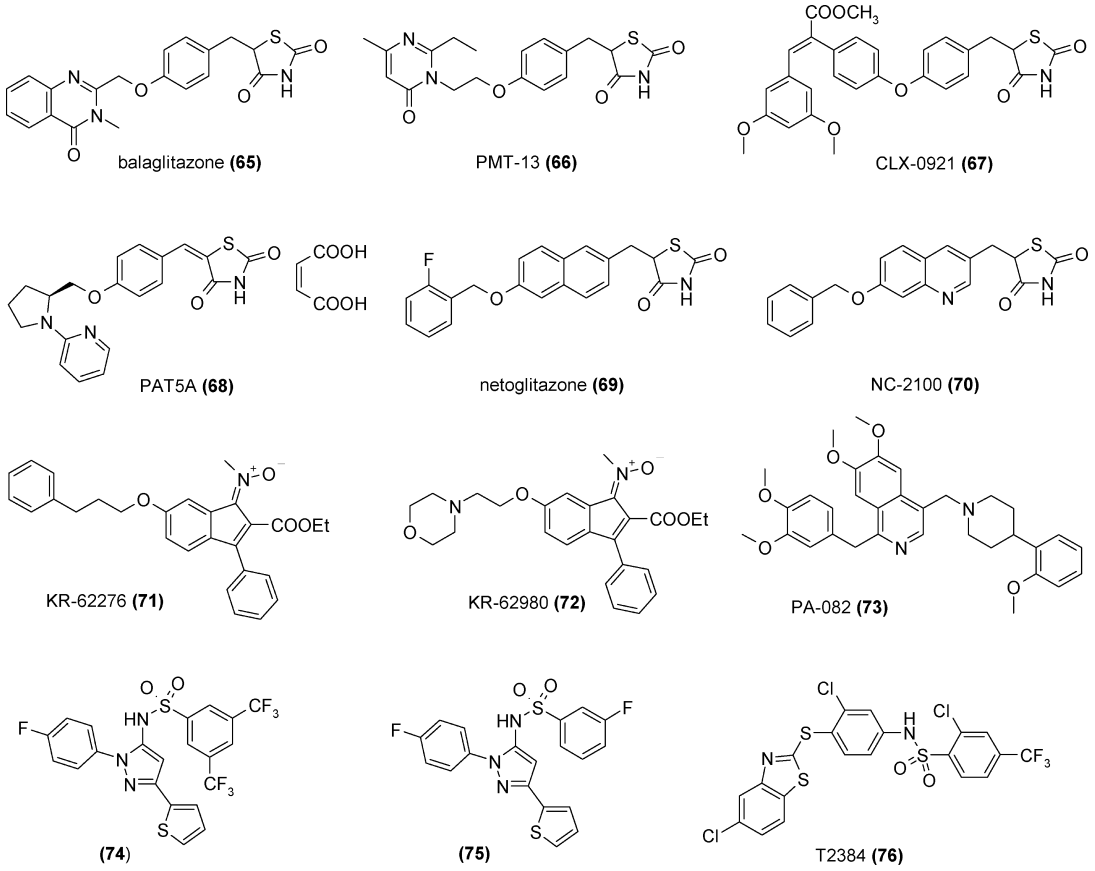

Figure 15. PPARγ partial agonist ligands.

to **28**, the indenone moiety of **63** occupies the base part of the PPARγ LBD pocket and the phenylpropyl group stretches deeply into the upper part of the cavity. The indenones seem to be a novel and interesting chemical class that might be further optimized for treatment of type 2 diabetes. Derivatives of the nonsteroidal anti-inflammatory drug (NSAID) sulindac sulfide were recently described as potential selective agonists of PPARγ, without the COX inhibitory activity of the parent NSAID; they have led to compound **64**,[71] equipotent to **28**. Compound **64** induces expression of a liver fatty acid binding protein (L-FABP) and an adipocyte fatty acid binding protein (aP2), two established PPARγ target genes. Taken together, these compounds represent potential leads in the development of novel PPARγ agonists.

While the clinical benefits of PPARγ agonists in treating metabolic disorders have been clearly demonstrated, the current generation of glitazone drugs has been associated with undesirable side effects. Thus, there has been significant interest in the design of novel PPARγ-modulating drugs. A moderate reduction in PPARγ activity has been shown to prevent insulin resistance and obesity induced by a high-fat (HF) diet. Therefore, appropriate functional modulating of PPARγ activity could be a logical approach to protection against obesity and related diseases such as type 2 diabetes. For this reason, efforts are being made to identify partial agonists and/or selective PPAR modulators (SPPARMs) and antagonists for PPARγ in an attempt to combine their antidiabetic and antiobesity effects. Genetic and pharmacologic studies suggested that moderate activation of PPARγ can lead to better therapeutic outcome than activation of the receptor with a high-affinity, potent full agonist.[72] These lessons have been translated into the identification and exploration of PPAR partial agonists and selective PPAR modulators (SPPARMs).

2.2.2. PPARγ Partial Agonists. Partials agonists are defined as weak activators of PPARγ that elicit the same activation pattern and show linked dose−response curves but with lower maximal activity compared to full agonists (Figure 15). They might induce alternative receptor conformation and thus recruit different coactivators, resulting in distinct transcriptional effects compared to classical glitazones. Balaglitazone (**65**) is a TZD with a quinazoline-3-one tail moiety that has shown PPARγ partial agonist activity.[73] Studies have shown that treatment with **65** leads to significant improvement in glycemic control and the HDL-C level, with minimum side effects. The first phase 3 study to determine the efficacy and safety of **65** was announced by Dr. Reddy's Laboratories, Ltd., and Rheoscience in January 2010. Those studies indicated that in addition to robust glucose-lowering ability, use of **65** led to lower body fluid accumulation, lower fat accumulation, less heart enlargement, and no reduction in bone formation, indicating that balaglitazone may be able to displace the balance between desirable and undesirable side effects and thus shows a better safety profile than full agonists of PPARγ. Compound **66** (PMT-13) was developed around a pyrimidinone derivative of thiazolidinedione[74] and showed PPARγ transactivation similar to that of **28**, without any activity against PPARα and PPARδ. In both in vivo and in vitro studies, **66** showed better efficacy than the reference thiazolidinediones and no treatment-related adverse effects. The compound has also shown satisfactory systemic exposure in rats after oral administration. Compound **67** (CLX-0921), derived from a natural product and possessing a polyphenol-based structure, is another second-generation

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glitazone that has given encouraging findings in early clinical testing.[75] Compound **66** is a weak activator of PPARγ compared to **28**. Despite this difference, the drug maintains potent glucose-lowering activity in vivo and, in contrast to **28**, increases glycogen synthesis in liver cells, possibly providing an added mechanism for lowering glucose levels in diabetic animals. Another interesting compound in this category is **68** (PAT5A), a malic acid salt of unsaturated TZD that has a *N*-(2-pyridyl)pyrolidine tail group and selectively modulates PPARγ activity. In contrast to **28**, **68** inhibits cholesterol and fatty acid biosynthesis, suggesting that it possesses a unique receptor-independent non-PPAR-related property. As expected, administration of **68** in a rodent model of type 2 diabetes (db/db mice) resulted in a dose-dependent reduction in plasma glucose similar to that seen with **28** but with lower drug-induced weight gain.[76] To eliminate the chiral center of **29**, a full PPARγ agonist, derivatives have been developed. The chromane cycle central linker was replaced with a naphthalene moiety, and a methyleneoxy group was added to maintain linker flexibility, leading to the TZDs netoglitazone (**69**)[77] and **70** (NC-2100).[78] In cell-based reporter assays, these structurally related glitazones appeared to be weakly binding full agonists. Both **69** and **70** promote adipocyte differentiation in cell culture. They possess in vivo activities in obese insulin-resistant mice comparable to **28** despite their weak agonistic profiles. Furthermore, in mice, **69** produces less weight gain than other glitazones with comparable levels of glycemic control. Interestingly, **69** appears to function as a full or partial PPARγ agonist depending on the cell type and the response element used in the transactivation assay. More recently, **71** (KR-62776) and **72** (KR-62980) indenone derivatives have been developed as PPARγ-specific full agonists and display PPARγ partial agonist activities. These indenone compounds have been shown to inhibit adipocyte differentiation via activation of ERK; consequently, they do not induce weight gain in animal tests.[79] X-ray crystallography also confirmed that **71** and **72** utilize a different part of the PPARγ binding pocket than **28**. The headgroup of **28** stretches deeply into the left stem of the cavity; the indenone moiety of **71** and **72** occupies the basal part, while the side chain stretches deeply into the upper part of the cavity. Compound **73** (PA-082),[80] a non-TZD isoquinoline derivative, is a prototype of a novel class of partial PPARγ ligands that preferentially recruit PGC1α. PGC1α is a key regulator of energy expenditure and is down-regulated in diabetics. Selective recruitment of PGC1α to favorable PPARγ-target genes provides a possible molecular mechanism whereby partial PPARγ agonists dissociate TG accumulation from insulin signaling. X-ray diffraction of the cocrystal of **73** with the LBD of PPARγ has shown that it does not have a direct interaction with helix 12. The ligand is bound in an extended S-shaped conformation in the same part of the binding pocket as that described for a partial agonist by other published structures. Lu et al., through structure-based virtual screening, identified compound **74** and its analogue **75**, two pyrozol-5-ylbenzenesulfonamides, as new PPARγ partial agonists.[81] These compounds specifically bind to PPARγ compared to the other two subtypes and exhibit high potency and specificity in vitro and glucose-lowering efficacy in vivo. Structural biology studies have revealed that these compounds adopt a distinct binding mode and have no H-bonding interactions with PPARγ. This absence of an H-bonding interaction with the protein provides the structural basis for their partial agonism. Another benzenesulfonamide derivative, **76** (T2384), is a conformationally flexible PPARγ partial ligand that lowers plasma glucose and insulin levels in vivo, as seen with **28**.[82] However, **76** treatment does not increase body weight and has been shown to induce weight loss at higher tested doses. X-ray crystallography studies revealed that **76** was able to adopt two distinct binding modes, which we have termed "U" and "S", interacting with the ligand binding pocket of PPARγ primarily via hydrophobic contacts distinct from full agonists.

2.2.3. Selective PPARγ Modulators (SPPARMs). Chemically different ligands for nuclear receptors were able to induce a distinct agonistic and antagonistic response depending on the cellular context and specific target genes. They have thus been named "selective PPAR modulators" (SPPARMs).[83] This model proposed that different PPAR ligands bound to the ligand binding domain of the receptor and, depending on their chemical structure, induced distinct conformational changes in the receptor, resulting in differential interactions with cofactors and corepressors, themselves differing in type and concentration in different cellular contexts. The net result was that the subtle differences in transcriptional activation of target genes occurred between two different ligands. As such, distinct ligands specific to a common nuclear receptor could induce different biological responses depending, for example, on the cell type. A selective modulator was distinct from partial agonists in that dose−response relationships for various activities were uncoupled from each other. Thus, the pharmacologic definition of a selective modulator was a ligand that, compared with a full agonist, differentially induced specific receptor effects. An ideal SPPARM would be a potent, highly efficacious inducer of insulin sensitization with low potency and/or low maximal activity in terms of effects on adipose generation, loss of bone mineral density, fluid retention, and congestive heart failure.[84] The development of SPPARMs was therefore an exciting area of research and opened up important therapeutic perspectives.

The concept of SPPARγM was validated with the identification of Fmoc-L-leucine (**77**)[85] as a PPARγ ligand that exerted strong insulin-sensitizing effects but exhibited reduced adipogenic activity compared to current TZDs (Figure 16). These specific effects resulted from differential recruitment of coactivators. As seen above, partial agonists possessed a chemical structure derived from TZDs, like the previously described **65**, **66**, **67**, and **68**. However, the highest number of SPPARγM agonists possessed a different scaffold characterized by the absence of a TZD ring. Metaglidasen (**78**), a non-TZD, is also a selective PPARγ partial agonist that structurally, mechanistically, and preclinically differs from the TZDs.[86] Compound **78** is a single (−)-enantiomer of halofenate, which was previously clinically tested as a hypolipidemic agent. Compound **78** is a prodrug ester that was rapidly and completely modified in vivo by nonspecific serum esterases to the mature free acid form, which is the circulating form of the drug. Phase 2a clinical trial data indicated that **78** significantly lowers plasma glucose levels in the absence of side effects such as weight gain and edema, which are observed with currently used pharmacological agents. During this development program, Metabolex Inc. discovered that **78** was an effective uricosuric agent with unique properties and repurposed the drug to treat gout with excellent safety and tolerability, demonstrated in over 870 patients. Acton et al. have reported a series of indole derivatives as new SPPARγMs, which arose from structural modifications of two full PPARγ agonists previously identified by screening. These compounds improve pharmacokinetics

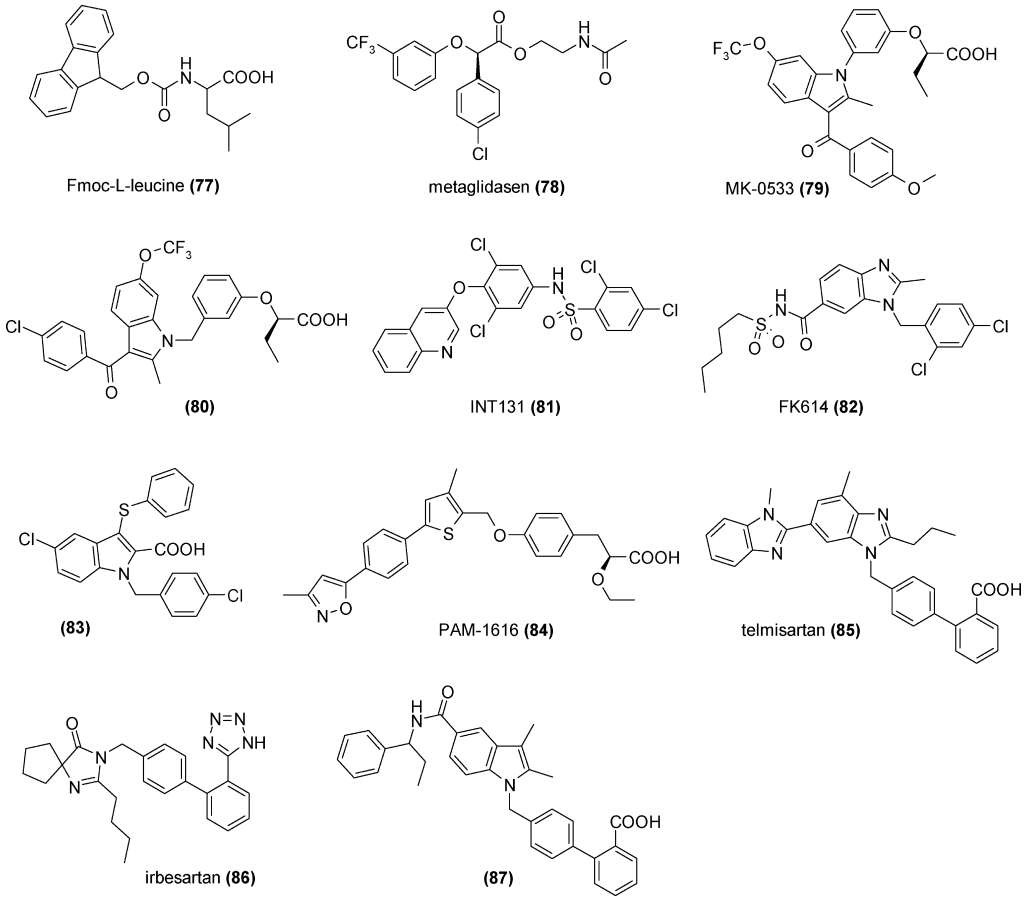

Figure 16. Selective PPARγ modulators (SPPARγMs).

compared to the original screening leads while also displaying robust antidiabetic activity in rodent diabetes models in comparison with a PPARγ full agonist. Compound **79** (MK-0533), the lead in this series, selectively induces genes important for sensitivity to insulin through mild PPARγ activation.[87] Some of these selective effects, rather than being caused by selective cofactor recruitment, result from partial activation of the receptor due to a general decrease in the affinity for cofactors. **79** displays no cardiac hypertrophy, attenuates increases in brown adipose tissue, minimizes increases in plasma volume, and causes no increase in extracellular fluid volume in vivo. Further investigation of **79** is warranted to determine whether the improvement in mechanism-based side effects observed in preclinical species will occur in humans. The same research group has also reported a series of 3-acylindole-1-benzylcarboxylic acids as new PPARγ modulators that display additional moderate intrinsic PPARα agonistic activity.[88] Compound **80** was identified and demonstrates potent efficacy in lowering both glucose and lipids in multiple animal models, with significantly attenuated side effects associated with PPARγ full agonists. The moderate PPARα activity of **80** not only contributed to managing lipid profiles but also appeared to potentiate its PPARγ efficacy by lowering glucose levels in preclinical diabetic animal models. These unique biological properties of compound **80** make it an attractive candidate as a novel therapeutic agent for treatment of T2DM and dyslipidemia. Compound **81** (INT131) developed by InteKrin Therapeutics, Inc., is a potent non-TZD selective SPPARγM currently in phase 2b of clinical trials for treatment of type 2 diabetes mellitus.[89] Compound **81** was specifically and carefully designed, using preclinical models, to exhibit a biological profile of strong efficacy with minimum side effects compared to PPARγ full agonists. Compound **81** binds to PPARγ in the same binding pocket as the TZDs but occupies a unique space in the pocket and contacts the receptor at distinct points from the TZDs. Importantly, the interaction with the activation helix of PPARγ by **81** and by TZDs differs. The net result of differential binding by the two types of ligands is an alternative conformational change in PPARγ, leading to distinct patterns of association with cofactors and thus, ultimately, to unique patterns of gene transcription. In chronic nonclinical studies, achievement of the targeted product profile has been validated for safety both in rodents and in non-human primates. In animal disease models, **81** achieved a high level of efficacy for desirable antidiabetic actions but had low or no activity in terms of other receptor-mediated side effects such as edema and adipogenesis. The strategy of InteKrin Therapeutics, Inc., was to develop **81** through phase-3-ready. The benzimidazole derivative **82** (FK614) represents a structurally novel class of PPARγ agonist that improves insulin sensitivity in animal models of type 2 diabetes.[90] Compound **82** behaves as a SPPARM, with differential effects on activation of PPARγ at each stage of adipocyte differentiation. Indeed, **82** appears to contribute to insulin sensitization by differentiating adipocytes, but it might only weakly contribute to adipocyte hypertrophy, itself leading to insulin resistance in mature adipocytes. The indole derivative **83** was identified and characterized as a novel non-TZD SPPARγM.[91] Compared to classical PPARγ full agonists, a differential gene expression profile was demonstrated

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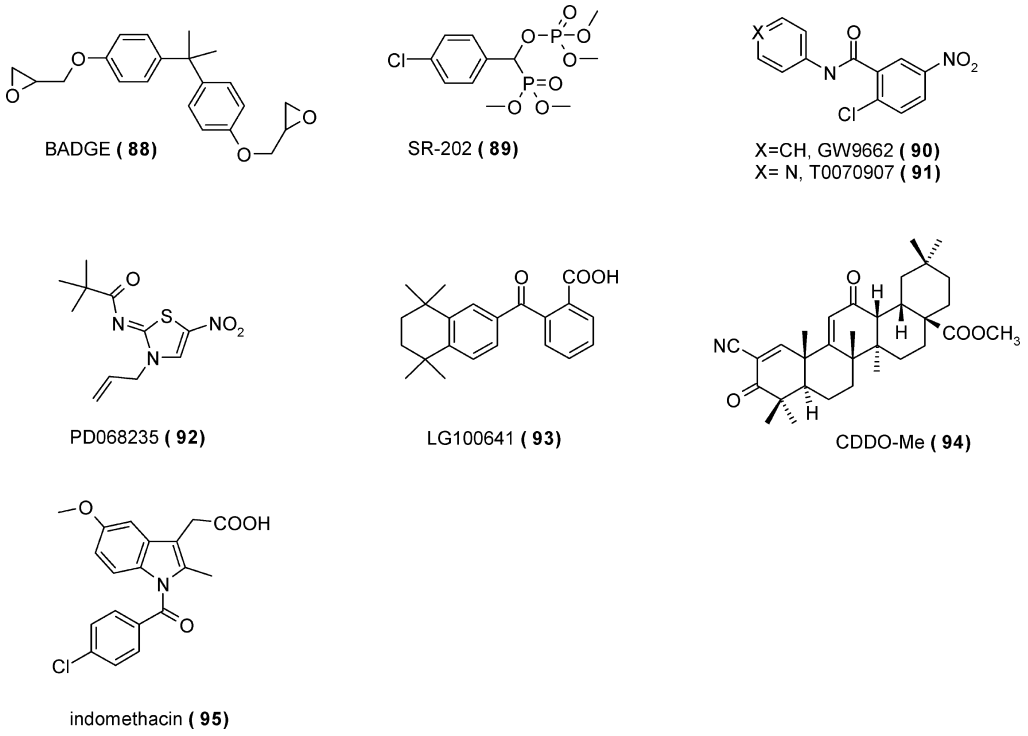

Figure 17. PPARγ antagonist ligands.

in vitro and in vivo along with potential antiobesity effects that were evident in HF fed mice. Importantly, compound **83** also retains beneficial in vivo metabolic effects without provoking cardiac toxicity. These findings established that compound **83** could produce altered receptor conformational stability leading to distinctive gene expression profiles, reduced adipogenic cellular effects and potentially improved in vivo biological responses. The Dong-A Research Center has characterized the pharmacological and safety profiles of **84** (PAM-1616) as a selective PPARγ modulator.[92] **84** significantly improves hyperglycemia in db/db mice with few side effects when orally administered. Intriguingly, **84** was seen to increase the gene expression of an inducible glucose transporter (GLUT4) while it partially induced that of a fatty acid carrier, aP2 in 3T3-L1 adipocytes, and also showed partial recruitment of an adipogenic cofactor, TRAP220, in comparison to **28**. Compound **84** increases expression of fluid-retention-inducing genes such as serum/glucocorticoid-regulated kinase (SGK)-1 to a lesser extent than **28**. These results suggest that **84** may be one of the earliest reported compounds to reduce edema in vitro and in vivo and might constitute a promising approach to developing new drugs for treatment of type 2 diabetes. Two angiotensin receptor blockers (ARBs), telmisartan (**85**) and irbesartan (**86**), which have been widely used for treatment of hypertension, were also recently described as being PPARγ modulators.[93] In accordance with the non-TZD partial agonist, the two ARBs induced distinctive conformation receptor changes after binding and demonstrated a specific cofactor recruitment profile compared with the glitazones which translated into a different gene expression pattern. Despite these preclinical data suggesting PPARγ modulator activity, **85** in humans has not demonstrated any benefits resulting from PPARγ-related effects, probably because of the fact that typical plasma concentrations of **85** are 10-fold lower than its PPARγ EC_{50}. Starting from the structure of **85**, a new series of potent and selective PPARγ modulators have been identified.[94] The most potent modulator, compound **87**, displays a novel binding mode in the PPARγ ligand binding domain and demonstrates similar effects on glucose and triglycerides in comparison to **57**, with fewer side effects, as assessed by in vivo experiments in Zucker fa/fa rats. Although some SPPARγMs have been under clinical development, until now none of them have been marketed. The concept of SPPARM is nonetheless applicable to PPARα and PPARδ. As such, gemfibrozil was shown to behave as a SPPARαM.[95]

2.2.4. PPARγ Antagonists. PPARγ antagonists appear to have effects similar to those of PPARγ agonists in rodents, that is, generation of small adipocytes and attenuated secretion of adipokines that interfere with insulin signaling. Consequently, not only PPARγ agonists but also PPARγ antagonists could be of potential clinical use, as such compounds would increase insulin sensitivity while preventing adipogenesis and obesity; thus, in contrast to TZD, they would not induce weight gain.[96] A moderate reduction in PPARγ activation with a PPARγ antagonist was shown to decrease triglyceride (TG) content in white adipose tissue, skeletal muscle, and liver. These inhibitors were shown to ameliorate high-fat-diet-induced obesity and insulin resistance.

The first compound described was bisphenol A diglycidyl ether **88** (BADGE),[97] a synthetic substance used in production of polycarbonates and industrial plastics (Figure 17). Competition radioligand binding studies showed this compound to be a ligand for PPARγ with micromolar affinity. Functional studies have indicated that **88** is a pure antagonist for this receptor. This compound has no apparent capacity to activate the transcriptional activity of PPARγ; however, **88** could antagonize the ability of agonist ligands such as **28** to activate the transcriptional and adipogenic action of this receptor. Phosphonophosphate **89** (SR-202) was identified as a new synthetic PPARγ antagonist that inhibited both TZD-stimulated

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recruitment of coactivator SRC-1 and TZD-induced transcriptional activity of the receptor. In vivo, **89** prevents high-fat-diet-induced insulin resistance, improves the lipid profile, and reduces adiposity in diabetic ob/ob mice. Because it has both antiobesity and antidiabetic effects, **89** may be a trigger for new compounds for use in treatment of obesity and type 2 diabetes.[98] Compounds **90** (GW9662) and **91** (T0070907),[99] a structurally related ligand, were identified in cell-based assays as potent selective PPARγ antagonists at micromolar concentrations. These compounds bind covalently to a cysteine located on helix 3 of the PPARγ LBD. Despite the fact that this cysteine residue is conserved in all three PPAR subtypes, these compounds display higher affinity for PPARγ than for PPARα and PPARβ/δ. Compound **90** antagonizes PPARγ activation in multiple cell types, including adipocytes, macrophages, and hepatic cells. Compound **90** was also described as inhibiting growth of breast tumor cells and promoting the anticancer effects of the PPARγ agonist **28** independently of PPARγ activation. Consistent with its role as an antagonist of PPARγ, **91** blocks agonist-induced recruitment of coactivator-derived peptides to PPARγ and promotes recruitment of the transcriptional nuclear receptor corepressor (N-CoR) to PPARγ. Compound **92** (PD 068235)[100] has also been reported to be a PPARγ antagonist that inhibits transcriptional activity and cofactor association induced by **28**. In addition, high micromolar concentrations of **92** block adipogenesis induced by either **28** or insulin. Compound **93** (LG100641) has been identified as a novel PPARγ ligand that does not activate PPARγ but selectively and competitively blocks thiazolidinedione-induced PPARγ activation and adipocyte conversion, though it stimulates insulin-mediated glucose uptake in adipocytes. It also antagonizes target gene activation and repression in agonist-treated 3T3-L1 adipocytes.[101] Structurally, **93** is very different from thiazolidinediones but similar to RXR selective ligands and has shown very weak binding to RXRs. Compound **93** has been described as a compound that might prevent obesity without inducing insulin resistance in peripheral tissues, but in vivo studies are necessary to further explore this hypothesis. The PPARγ antagonist ligand **94** (CDDO-Me) is a synthetic triterpenoid that was reported to ameliorate diabetes in high-fat-diet-fed type 2 diabetic mice. Oral **94** administration reduces total body fat, plasma triglyceride, and free fatty acid levels. It also improves glucose tolerance and insulin tolerance tests. Its potent glucose-lowering activity results from enhanced insulin action.[102] Compound **94** is considered to be a potential antidiabetic agent when used at low concentrations. At higher concentrations, the compound inhibits cancer cell growth and proliferation in a wide variety of cell lines, including ovarian, cervical, breast, liver, leukemia, and lung cancer. Compound **94** is currently in phase 1/2 clinical trials for cancer treatment.[103]

Indomethacin (**95**), an alternative inhibitor of cyclooxygenase (COX) activity belonging to the NSAIDs, has been described as inhibiting PPARγ activation in a COX-independent manner.[104] These results have implications not only for the cardiovascular system but also for processes underlying other chronic proliferative and inflammatory conditions for which NSAIDs have been regularly used and for which PPARγ ligands hold promise as novel antiinflammatory agents.

2.3. PPARβ/δ. *2.3.1. PPARβ/δ Agonists.* The human PPARβ/δ receptor was cloned in the early 1990s, and many research groups have tried to prepare selective ligands to study biological functions and possible applications to human therapy. But PPARβ/δ initially received the least attention of the three subtypes of PPAR because of its ubiquitous expression and the unavailability of selective ligands. However, recently reported synthetic PPARβ/δ agonists are helping to reveal its role as a powerful regulator of fatty acid catabolism and energy homeostasis, retarding weight gain and improving insulin resistance, thus demonstrating its potential therapeutic value in diabetes and obesity. The role played by PPARβ/δ in control of lipid metabolism and obesity is currently under investigation.[105] PPARβ/δ has also been shown to prevent tumorigenesis, especially in colon cancer. Several pharmalogical agonists of PPARβ/δ have been identified (Figure 18).

Compound **96** (L-165041) was reported to be a potent PPARβ/δ agonist that displayed >100-fold selectivity for both mouse and human PPARβ/δ receptors over other subtypes.[106] In vivo, **96** raises plasma cholesterol levels in insulin-resistant db/db mice at 30 mg kg^{-1} day^{-1} but does not significantly affect either glucose or triglycerides at the same in vivo exposure because of its weak activity toward PPARγ. Compound **96** has also been described as having neuroprotective properties in models of cerebral infarction and Parkinson's disease.[107] GlaxoSmithKline has used combinatorial chemistry and structure-based drug design to develop the potent subtype-selective PPARδ agonists **97** (GW501516) and **98** (GW0742). These compounds were shown to increase HDL-cholesterol, decrease LDL-cholesterol, triglycerides, and fasting plasma insulin, and lower the levels of small dense LDL in insulin-resistant obese rhesus monkeys. In addition, administration of **97** for 3 or 4 weeks in wild-type mice prevented fatty-acid-induced insulin resistance and inflammation in skeletal muscle cells. These effects of **97** may provide a potential therapeutic strategy for preventing lipid-induced insulin resistance.[108] The Novartis Research Foundation has reported identification of Y-shaped 1,3,5-substituted aryl systems from computer-aided drug design as potent and selective PPARβ/δ activators.[109] Compound **99** has been shown to be a potent and efficacious PPARβ/δ agonist but does not show cross-activity with other PPAR subtypes up to 10 μM. This compound is considered a useful tool for studying the biological effects of selective PPARβ/δ activation. The same authors also identified a novel series of trisubstituted isoxazoles as PPAR activators via a high-throughput screen. A series of structural optimizations led to improved efficacy and excellent functional receptor selectivity for PPARβ/δ, as was the case for **100** (LC1765), which regulated expression of genes involved in energy homeostasis and provided good in vivo pharmacokinetics properties in mice.[110] This compound did not seem to require a flexible linker between functional head and hydrophobic tail, a unique feature distinct from most reported PPAR modulators. In addition, a cocrystal structure of **100** with the PPARβ/δ ligand binding domain revealed formation and occupancy of a new hydrophobic cavity. In their constant effort to identify novel structures with PPARβ/δ agonistic activity, the Novartis Research Fundation, through the discovery, synthesis, and optimization of new compounds from high-throughput screening, succeeded in isolating **101**, which contains a bisaryl-substituted thiazole.[111] This compound exhibits good to excellent pharmacokinetic properties and demonstrates in vivo regulation of genes involved in energy homeostasis in relevant metabolic tissues. Compound **101** is currently undergoing additional evaluation to further elucidate the role of PPARβ/δ in glucose and lipid metabolism and to

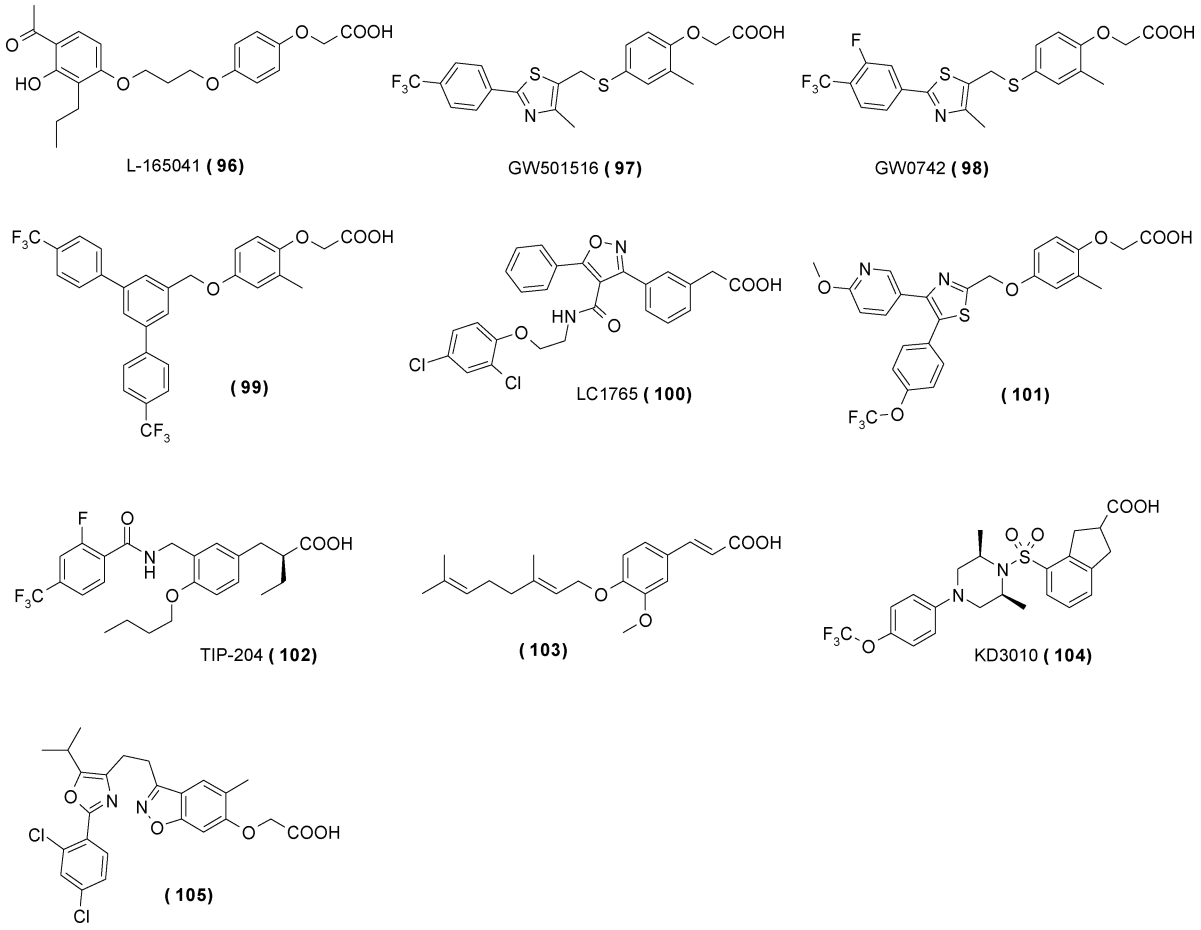

Figure 18. PPARβ/δ agonist ligands.

assess the potential of developing this series for diseases associated with metabolic syndrome. A series of 3-(4-alkoxyphenyl)propanoic acid derivatives have been described as PPARβ/δ agonists. SAR studies have shown the importance of the chain length of the alkoxy group at the 4-position, and (*S*)-enantiomer *n*-butoxy compound **102** (TIP-204) exhibits extremely potent PPARβ/δ transactivation activity; moreover, the X-ray crystal structure of the complex of **102** and the human PPARβ/δ ligand binding domain has also been elucidated.[112] Compound **102** regulates expression of genes involved in lipid and glucose homeostasis and should be useful not only as a chemical tool for studying PPARβ/δ function but also as a candidate drug for treatment of metabolic syndrome. Natural propenoic acid derivatives have been described as new PPARβ/δ agonists[113] and have been studied for their capacity to inhibit cell proliferation in a human epithelial carcinoma cell line. Results from this study demonstrated that 4′-geranyloxyferulic acid **103** could activate PPARβ/δ and inhibit cell proliferation of a human skin cancer cell line, suggesting that the biological effects of 4′-geranyloxyferulic acid may be mediated in part by activating this PPAR subtype. Future studies are necessary to demonstrate a definitive role for PPARβ/δ in mediating the chemopreventive effects of 4′-geranyloxyferulic acid. Metabolex Inc. and Ortho-McNeil, Inc., are co-developing MBX-8025 (structure not disclosed), a selective PPARβ/δ agonist for metabolic diseases, including type 2 diabetes.[114] Metabolex has recently completed a thorough phase 2 proof-of-concept study showing that MBX-8025 effectively addresses each of the lipid abnormalities associated with mixed dyslipidemia. In addition, MBX-8025 addresses other aspects of metabolic disorders including improvement in insulin sensitivity, trends toward decreased waist circumference and body fat, anti-inflammatory activity, and improved surrogate markers of liver health. Compound MBX-8025 appears to be a very attractive new candidate for dyslipidemia and metabolic syndrome. Compound **104** (KD3010), developed by Kalypsys Inc., is a highly selective potent PPARβ/δ agonist, affecting multiple facets of obesity and metabolic syndrome. It was phase-2-ready in 2009, with potential in diabetes mellitus and nonalcoholic steatohepatitis (NASH).[115] Kalypsis demonstrated that **104** exhibits antihyperglycemic, insulin-sensitizing and lipid-lowering effects in leptin-resistant db/db mice. In that mouse model, **104** also attenuates key side effects of **28**, such as weight gain and impaired liver function. Activation of PPARβ/δ by **104** significantly improves insulin-sensitizating effects of suboptimal doses of **28**, thus demonstrating a rosiglitazone-sparing effect. Recently, a benzisoxazole derivative **105** was synthesized as a novel PPARβ/δ selective agonist.[116] Compound **105** exhibits potent human PPARβ/δ transactivation activity and high β/δ selectivity. PPARβ/δ agonists have been reported to have an oligodendrocyte differentiation-stimulating effect. Compound **105** was reported to stimulate differentiation of primary oligodendrocyte precursor cells in vitro, indicating that it may be an effective drug in the treatment of demyelinating disorders such as multiple sclerosis.

2.3.2. PPARβ/δ Partial Agonists. The 3,3-bis-(4-bromophenyl)alylsulfanyl derivative **106** was recently reported to be a selective partial PPARβ/δ agonist but with full agonist activity

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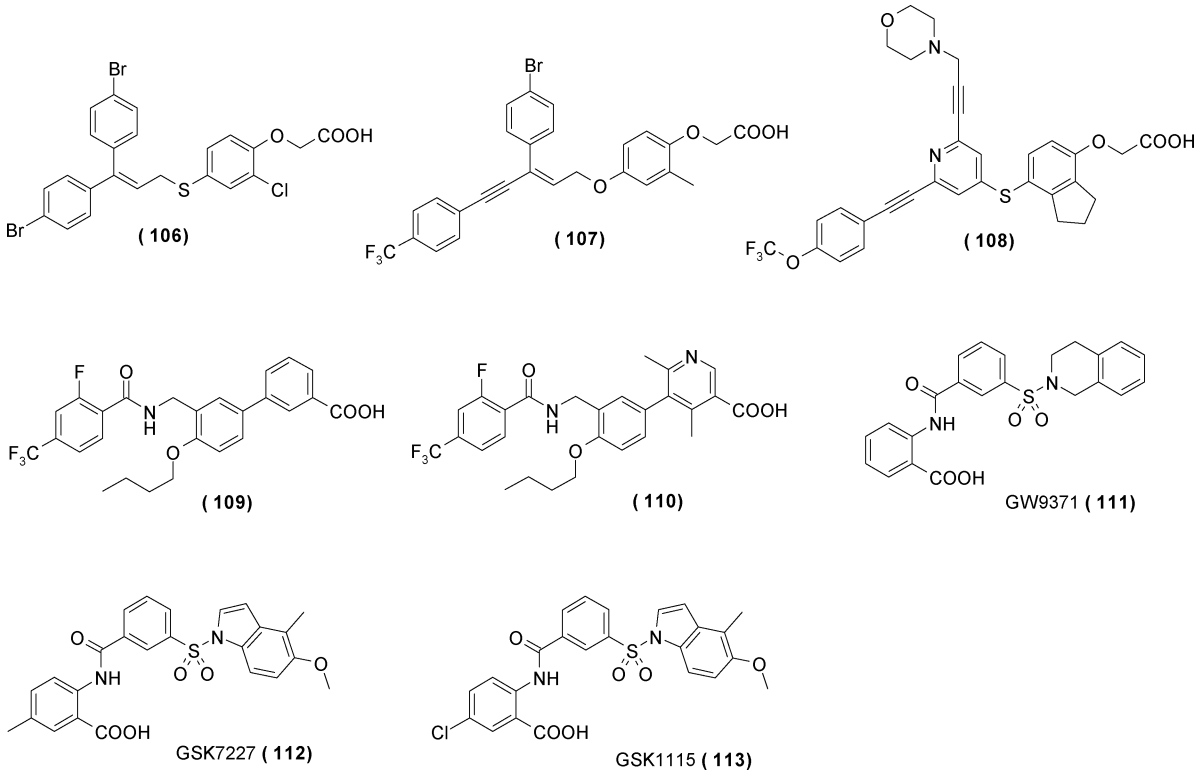

Figure 19. PPARβ/δ partial agonist ligands.

in terms of FFA oxidation in muscle cells both in vitro and in vivo (Figure 19).[117] In addition, **106** displays satisfactory oral pharmacokinetic properties in rats and corrects plasma lipid parameters and improved insulin sensitivity, suggesting that **106** has the potential to become a novel treatment for dyslipidemia. Havranek et al. suggested the possibility of replacing the arylalylsulfanyl tail group of **106** with a conformationally restricted phenylalkynylallyl, obtaining compound **107**.[118] These structural modifications result in higher PPARβ/δ potency and selectivity. A selective partial PPARβ/δ agonist was designed by introducing a bulky substituent close to the carboxylic acid, a cyclopentyl ring instead of methyl, without direct interactions with the AF-2 helix.[119] X-ray crystallographic data of compound **108** confirmed the impaired interaction with the AF-2 domain, explaining partial PPARβ/δ efficacy. On the basis of the X-ray crystal structure of the complex of **102** and the human PPARβ/δ ligand binding domain, biphenylcarboxylic acid **109** was designed and synthesized as a PPARβ/δ-selective partial agonist but possessed weak aqueous solubility.[120] To improve the aqueous solubility of **109**, substituents were introduced at the 2-position of the biaryl moiety, focusing on disruption of molecular planarity and symmetry and reducing lipophilicity. The 2-substituted pyridyl analogue **110** showed weaker PPARβ/δ partial agonistic activity but was at least 2700 times more soluble than **109**. Anthranilic acid **111** (GW9371) was identified as a novel class of PPARδ partial agonists through high throughput screening.[121] The design and synthesis of SAR analogues led to disubstituted derivatives **112** (GSK7227) and **113** (GSK1115), which represent the most potent and selective PPARβ/δ compounds in this series. These compounds induce expression, but with reduced efficacy compared to the full agonist, of two important PPARδ-regulated genes in human skeletal muscle cells: CPT1, a key regulator of fatty acid β-oxidation in skeletal muscle cells, and PDK4, which plays a key role in skeletal muscle metabolism by contributing to regulation of glucose metabolism.

2.3.3. PPARδ Antagonists. While compound **109** showed partial PPARβ/δ agonist activity, its 4-biphenylcarboxylic acid regioisomer **114** exhibited very weak PPARβ/δ agonistic activity and could be considered as an antagonist ligand (Figure 20).[122] A repressive effect on representative PPARβ/δ-responsive genes indicated that **114** is an effective PPARβ/δ antagonist and can repress these PPARβ/δ-regulated genes at the cellular level. One of the first PPARβ/δ small molecule antagonist ligands, **115** (GSK0660), was identified, via a high-throughput ligand displacement screen, as being a potent binder of PPARβ/δ with no activity in a standard cell-based agonist assay.[123] Compound **115** is a valuable tool for elucidation of PPARβ/δ signaling pathways in vitro, since the absence of in vivo bioavailability has limited use of this ligand for cellular systems. Another PPARβ/δ antagonist ligand identified from the high-throughput screen of the GSK compound collection was characterized by the pyridinylsulfone derivative **116** (GSK3787), with good pharmacokinetic properties.[124] Compound **116** has been described as an irreversible antagonist of human and mouse PPARβ/δ that covalently modifies Cys249 within the ligand binding pocket. In an effort to probe the role of PPARβ/δ in modulation of colon cancer, **116** was tested in a panel of colorectal cancer cell lines and noncolorectal cell lines but showed no measurable effect on inhibition of cell proliferation. However, these preliminary experimental results were based on a single tool compound, and more detailed studies are required to fully understand the potential role of PPARβ/δ inhibition in the etiology of cancer. A virtual screening approach based on combined use of pharmacophore modeling, 3D shape and electrostatic similarity screening was used to discover novel scaffolds for PPAR ligands.[125]

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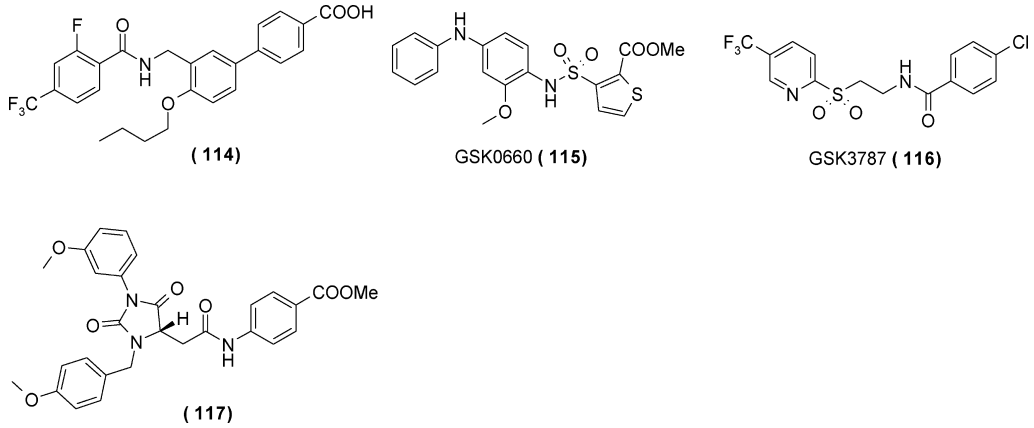

Figure 20. PPARβ/δ antagonist ligands.

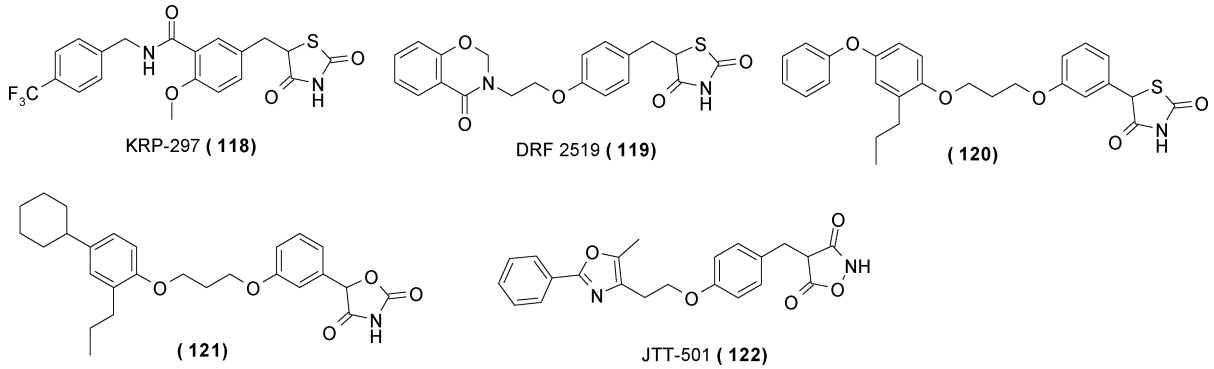

Figure 21. Dual PPARα/γ agonists TZDs analogues.

It was observed that compound **117** was able to repress the basal activity of PPARβ/δ and to reduce transcriptional activity induced by positive control **96** in the PPARβ/δ by about half at 1 μM.

2.4. Dual PPAR Agonists. Potent agonists with mixed receptor selectivity toward PPARα and PPARγ, also called dual PPARα/γ agonists, were thought to have significant potential as novel antidiabetic agents. In recent years, dual PPARδ/γ, PPAR α/δ, and pan-PPAR $\alpha/\delta/\gamma$ agonists have also emerged.

2.4.1. Dual PPARα/γ Agonists. Given the importance of controlling both glucose and lipid levels in type 2 diabetes, the concept of identifying ligands that bind to and activate both PPARα and PPARγ represents a logical continuation in the field of PPAR research. PPARγ agonists are associated with improved insulin sensitivity and glucose tolerance but at the cost of increased weight gain and other side effects, including liver dysfunction and bone loss. The fibrates have shown specific efficacy in reducing angiographic progression of coronary heart disease in type 2 diabetes mellitus, and this effect is most likely related to correction of atherogenic dyslipidemia. In addition to their beneficial effects upon lipid metabolism, there were reports in the literature that fibrates reduced body weight gain in rodents without affecting food intake,[126] leading to the hope that activation of PPARα would mitigate the weight gain induced by PPARγ activation seen in humans. The hypothesis that PPARα/γ dual agonism could provide additive and possibly synergistic pharmacology has resulted in an intensive effort by the pharmaceutical industry to develop and evaluate these agents. Dual activation of PPARα and PPARγ could, in theory, also limit the occurrence of side effects associated with TZD therapy. Thus, combined PPARα/γ activation has emerged as an interesting concept and spawned the development of various coagonists. A number of PPARα/γ dual agonists have been reported in this class of compounds and have shown robust insulin-sensitizing and hypolipidemic activities in clinical trials.

2.4.1.1. TZD Derivatives. The Kyorin Pharmaceutical Compagny modified the linker module of classical glitazone in an SAR study centered around a previous hit (Figure 21). They achieved an interesting result with **118** (KRP-297), which showed similar affinity for PPARγ and PPARα. In vivo, **118** was reported to improve abnormal lipid metabolism in liver and to elicit hypoglycemic, hypoinsulinemic, and hypolipidemic effects in obese rats.[127] However, further development of **118** was terminated in 2003 because of findings of a rare malignant tumor in mice.

Another modification consisted of including nitrogen in a lactone cycle, leading to **119** (DRF-2519).[128] This benzoxazinone analogue of TZD more satisfactorily improved hyperglycemia, hyperinsulinemia, abnormal lipid metabolism, and hypertension than PPARα or PPARγ selective ligands. Indeed, in vivo studies showed that **119** possessed better efficacy than both **28** and **118**. **119** might be beneficial for a whole range of complications associated with type 2 diabetes. A series of 5-arylthiazolidine-2,4-diones were identified as belonging to a class of dual PPARα/γ agonists. Changing the point of attachment of the thiazolidine-2,4-dione ring on the phenyl ring from a para- to a meta-orientation with respect to the three-carbon methylene tether, as was the case for compound **120**, transformed PPARγ selective agonists into dual PPARα/γ agonists. This compound has shown better efficacy than **28** in the db/db mouse model of type 2 diabetes and presents satisfactory pharmacokinetic parameters. Bioisosteric replacement

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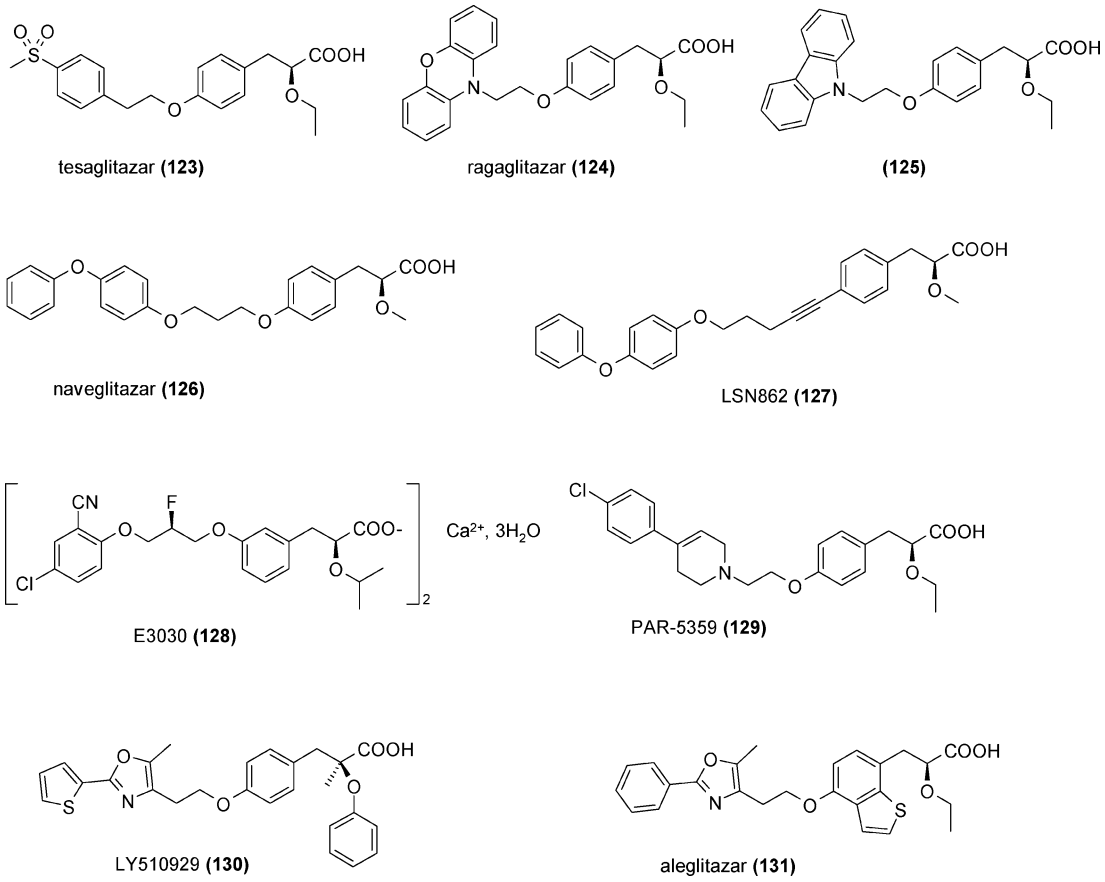

Figure 22. Dual PPARα/γ agonists α-alkoxy/aryloxy-β-phenylpropionic acid derivatives.

of the corresponding TZD ring with an oxazolidine-2,4-dione and structural modification of the aryloxy substituent with a cyclohexylphenyl tail group led to compound **121**.[129] This compound was found to be equal in both binding affinity and functional potency to the corresponding TZD analogue **120**. Compound **122** (JTT-501), an isoxazolidine-3,5-dione, is less potent than its parent **30**, a TZD with a phenyl oxazolidine tail group. However, the side effects profile is improved. It was found that **122** is a PPARγ agonist with some PPARα activity. This compound has been reported to activate PPARα at concentrations approximately 10-fold higher than those required for activation of PPARγ. Its activity is probably mediated through a malonic amide metabolite by hydrolysis of the binder heterocyclic ring.[130] Compound **122** improves hyperglycemia, hyperinsulinemia, and hypertriglyceridemia and enhances insulin-stimulated glucose oxidation in adipose tissues in non-insulin-dependent diabetes mellitus models. In particular, the triglyceride-lowering activity of **122** is a unique characteristic compared to thiazolidinedione counterparts.

2.4.1.2. α-Alkoxy/aryloxy-β-phenylpropionic Acid Derivatives. The first alkoxypropionic acid to display dual PPARα/γ agonist activities was described in 2001 and called tesaglitazar (**123**), developed by AstraZeneca (Figure 22). The crystal structures of PPARα and PPARγ in complex with **123** revealed a conserved hydrogen bonding network involving a Tyr in the AF2 helix that had to be formed in order to stabilize LBD in the active conformation throughout the entire PPAR family. Compound **123** monotherapy was reported to improve markers of glycemic control and atherogenic dyslipidemia at doses of 0.5 and 1 mg daily in subjects with manifestations of insulin resistance or type 2 diabetes.[131] A phase 3 program was conducted to examine the effects of **123** when given to patients with type 2 diabetes. However, in 2006, its development was discontinued in phase 3 of clinical trials after the emergence of several adverse effects, elevated serum creatinine and associated decreases in the glomerular filtration rate.[132] Scientists at Dr. Reddy's Research Foundation also came out with a series of α-ethoxy-β-phenylpropionic acid derivatives exemplified by ragaglitazar (**124**), which contains a phenoxazine group as the lipophilic tail portion of the molecule.[133] Compound **124**, by virtue of its dual PPARα- and PPARγ-activating property, acted on both the liver and adipose tissue and thereby shows greater improvement not only of hyperglycemia and hyperinsulinemia but also of abnormal lipid metabolism than marketed PPARα- or PPARγ-selective agonists. Despite demonstrating advantages in preclinical models, **124** was suspended from clinical studies because of development of bladder tumors in rodents.[134] To further understand the SAR generated in this series of **124** derivatives, additional tricyclic analogues were designed and synthesized and led to carbazole **125**,[135] which has a better dual PPARα/PPARγ activity profile than **124**.

Naveglitazar (**126**) was a γ-dominant PPAR α/γ dual agonist. This compound showed significant reduction in mean fasting serum glucose levels and triglyceride levels. It was selected for clinical evaluation in the treatment of type 2 diabetes. Cardiac effects in rats treated with **126** were similar to those reported for other PPARγ agonists and α/γ dual agonists. Furthermore, treatment of rats with **126** was associated with an increased incidence of sarcomas in males and urothelial tumors in

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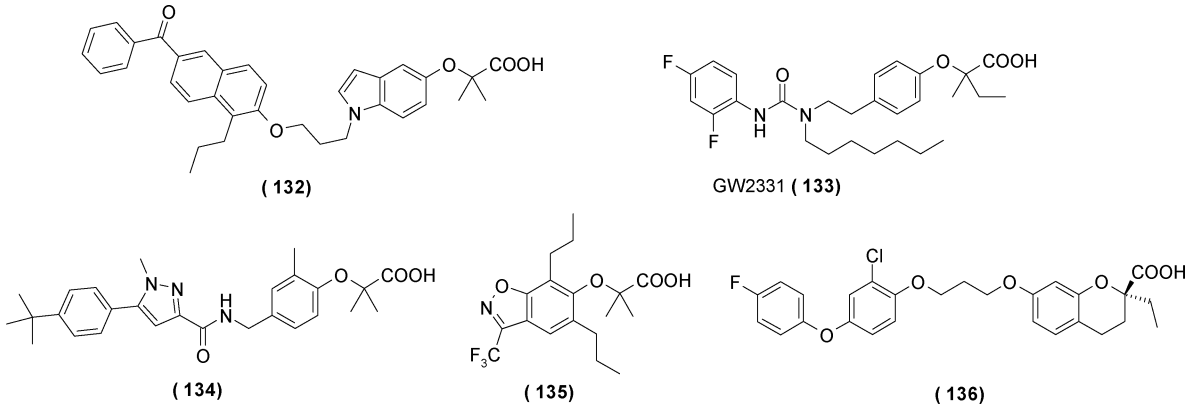

Figure 23. Dual PPARα/γ fibrate derivatives.

females, thus leading to discontinuation of this compound in clinical studies.[136] Modification of the linker of **126**, by replacing the oxygen directly bound to the central aryl ring with an alkyne moiety, provided compound **127** (LSN862). The alkyne linker did not affect the PPARα/γ selectivity profile and was still flexible enough to be adapted to both receptors. This compound was reported to be a high-affinity PPARγ partial agonist with relatively weaker but still significant PPARα agonist activity.[137] Compound **128** (E3030), a calcium salt of α-isopropyloxy-β-phenylpropionic acid, was reported to be a potent dual activator of PPARα and PPARγ in animal models. Experimental results suggested that this compound had potential for use in treatment of various types of metabolic dysfunction in type 2 diabetes, including dyslipidemia, hyperglycemia, hyperinsulinemia, and impaired glucose disposal.[138] The Dong-A Pharmaceutical Company characterized the pharmacological profile of **129** (PAR-5359), reported to be a well-balanced coagonist of PPARα and PPARγ and which demonstrated excellent antihyperglycemic and hypolipidemic activities. However, the pharmaceutical group decided not to enter into clinical development of **129** because of failure to guarantee a sufficient safety margin based on long-term toxicological studies.[139] Compound **130** (LY510929), an α-aryloxy-α-methylhydrocinnamic acid, possessed potent dual PPARα/γ activity.[140] In vivo studies showed that this compound improved insulin sensitivity and potently reversed diabetic hyperglycemia while significantly improving overall lipid homeostasis. Clinical trials were stopped because of severe side effects. Treatment with suprapharmacologic doses of **130** caused dose-dependent increases in heart weight in male and female rats, characterized by increased left ventricular lumen volume and wall thickness. Aleglitazar (**131**), a dual PPARα/γ agonist developed by Hoffman-La-Roche, is currently in phase 3 of clinical trials. A phase 2 trial showed that therapy with this agent reduced hyperglycemia and favorably modified levels of HDL-C and triglycerides, with an acceptable safety profile. Compound **131** is currently being studied in large-scale clinical trials to assess whether it reduces the risk of major cardiovascular end points (death, myocardial infarction, or stroke) among patients with diabetes and coronary artery disease. If ongoing studies confirm the theoretical benefits and safety of dual PPARα/γ agonism, **131** may become the first therapy demonstrated to reduce macrovascular complications in patients with diabetes.[141]

2.4.1.3. Fibrate Derivatives. A series of fibrates endowed with dual agonism of PPARα and -γ have also been reported. Some fibrate analogues, clofibric acid and fenofibric acid, the active metabolites of clofibrate and fenofibrate, were shown to be dual PPARα/γ activators with 10-fold selectivity for PPARα. Thus, successful studies were carried out to derive potent dual PPARα/γ agonists from PPARα selective fibrates (Figure 23).

In an indole-based series of PPAR agonists, Mahindroo et al. reported a new fibrate derivative, **132**, a dual PPARα/γ agonist. In this compound, the fibrate acid group is attached to the 5-position of indole and the N-terminal is attached via a three-carbon linker to the tail part hydrophobic naphthophenone moiety. In research on new PPARα selective agonists, some ureidofibrates have been described. One of them, **133** (GW2331), binds to both PPARα and PPARγ with high affinity in the nanomolar range. Starting from a selective PPARα agonist, pyrazole **134** has been generated with equipotent PPARα/γ dual activities.[142] Compound **134** demonstrates in vivo activity toward Zucker fatty rats and has also been tested in a rat 7-day toxicological study. No safety issues have been raised that would preclude further development. The 2-aryloxy-2-methylpropionic acid derivative **135** was identified as a PPARα/γ dual agonist with relative PPARα selectivity and has demonstrated potent efficacy in lowering both glucose and lipids in animal models without causing body weight gain. The PPARα activity of **135** appears to have played a significant role in lowering glucose levels in db/db mice.[143] A series of novel antidiabetics based on a (2*R*)-chromane-2-carboxylic acid, considered to be restricted fibrate analogues, have been developed and have led to compound **136**.[144] It has shown antihyperglycemic activity comparable to **28** in db/db mouse type 2 diabetes. In addition, the lipid-lowering activities of **136** were demonstrated in a Syrian hamster and a dog model. Unlike the currently marketed glitazone class, **136** is a single enantiomer invulnerable to racemization. It was recently demonstrated that **136** induces growth arrest and apoptosis in both imatinib-sensitive and -resistant chronic myeloid leukemia (CML) cell lines. These data suggest that PPARα/γ dual ligands could represent novel therapy for CML even when the cells are refractory to imatinib.[145]

2.4.1.4. L-Tyrosine Derivatives. Compound **137** (GW409544) contains a vinylogous amide substituent and possesses three fewer carbon atoms than the benzophenone found in **56** (Figure 24). Aside from this difference, the chemical structures of the compounds are identical. In contrast with **56**, **137** is a potent activator of both PPARα and PPARγ, with a <10-fold difference between its PPARα and PPARγ activities. Because of the larger steric size of Tyr-314 in PPARα compared with His-323 in PPARγ, **137** occupies a position in

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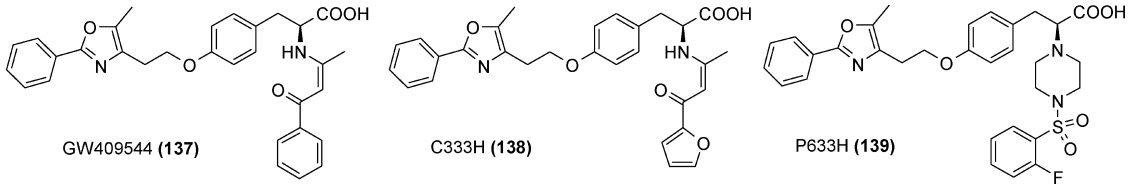

Figure 24. Dual PPARα/γ agonists tyrosine analogues.

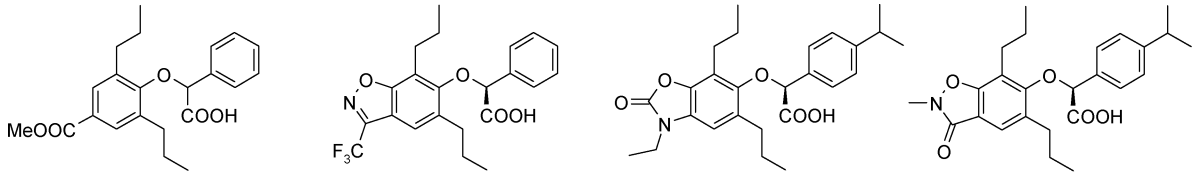

Figure 25. Dual PPARα/γ agonists *O*-arylmandelic acid analogues.

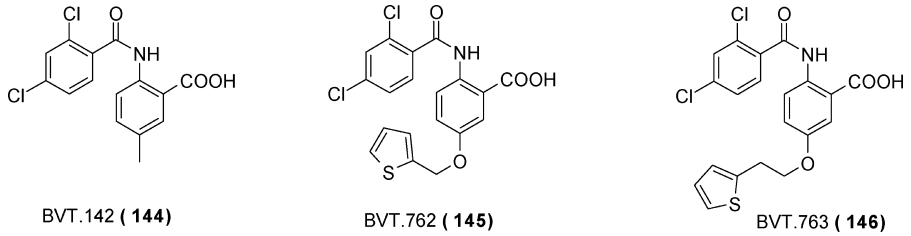

Figure 26. Dual PPARα/γ agonists 2-BABAs.

which it binds deeper into the PPARα ligand binding pocket than **56** in the PPARγ pocket. Thus, the potent dual PPARα/γ agonist activity of **137**, in which three carbon atoms are removed from farglitazar, is the result of re-engineering of the ligand to accommodate the larger size of the Tyr-314 residue in PPARα. Replacement of phenyl in the benzophenone of **56** with a furan ring led to **138** (C333H), reported to be a more potent agonist of PPARα than **2**; indeed, it was found to have a PPARγ activation effect similar to that of **28**. It not only controls glucose and lipid metabolism but also promotes preadipocyte differentiation and improves insulin resistance. Further studies should be carried out to develop **138** as a novel therapy for metabolic disease.[146] A series of compounds containing the piperazine ring, represented by **139** (P633H), have been designed on the basis of previously described compounds **56** and **137**. Preliminary studies in mice showed that **139** is well-tolerated in mice, with favorable pharmacokinetics and excellent oral bioavailability. Thus, **139** displays satisfactory druglike characteristics.[147] Although **139** was reported to be a high-potency PPARα/γ dual agonist with good functional activity in vitro, it produces opposing antidiabetic effects, promoting hepatic gluconeogenesis while increasing blood glucose levels in diabetic mice.

2.4.1.5. O-Arylmandelic Acid Derivatives. The only mandelic acid PPAR agonist **140** was discovered to be a PPAR ligand with micromolar PPARγ affinity but nanomolar affinity for PPARα (Figure 25). The novel structural features of **140**, coupled with its advantageous in vitro biological profile, prompted Merck Research Laboratories to embark on further investigation and led to trifluoromethylbenzisoxazole mandelic derivative (*S*)-**141**.[148] This compound is an effective antidiabetic dual PPARα/γ agonist with reduced PPARγ mechanism-based side effects. SAR developments, X-ray crystallography studies, and various in vivo evaluations of a new series of *S*-aryloxyphenylacetic acids culminated in the discovery of benzoxazolone **142** and benzisoxazolone **143**.[149] These compounds are characterized by their balanced binding affinity for both PPARα and PPARγ receptors, along with "super"-agonist activity in a PPARα-GAL4 transactivation assay and weak or partial agonist activity toward PPARγ. Most notably, they demonstrate excellent antihyperglycemic efficacy in the db/*db* mouse and hypolipidemic activity in hamster and dog models, without provoking typical PPARγ-mediated toxicity in a rat tolerability model.

2.4.1.6. 2-BABA. 2-BABA, or the 5-substituted 2-benzoylaminobenzoic acids family, has been described, via identification of **144** (BVT.142), as a new class of PPARα/γ modulators (Figure 26). Variations at the 5-position with a 2-thienylmethoxy and 2-(3-thienyl)ethoxy led to more potent compounds **145** (BVT.762) and **146** (BVT.763), respectively. X-ray crystallographic data showed that these compounds utilize a novel binding epitope not involving classical agonist characteristic interactions of thiazolidinediones. Compound **145** occupies a region in proximity to helix 3, and its carboxylic acid group interacts with the backbone nitrogen of Ser-342. 2-BABA derivatives act by binding at the entrance of the ligand pocket and activate the receptor without direct interaction with helix 12.[150]

2.4.1.7. Other Synthetic PPARα/γ Agonist Ligands. Another study of pure pharmacochemistry was rewarded by the discovery of muraglitazar (**147**), with a large binder module similar to that of **56** (Figure 27). Contrary to the preceding compounds, **147** does not bear a chiral center in its binder module, therefore considerably simplifying its synthesis. In early clinical studies, **147** demonstrated a significant glucose-lowering reduction in triglycerides and an increase in HDL-C in patients with type 2 diabetes.[151] The drug completed phase 3 clinical trials. However, in 2006, its further development was discontinued. Meta-analysis of phase 2 and phase 3 clinical trials revealed that it was associated with a greater incidence of myocardial infarction,

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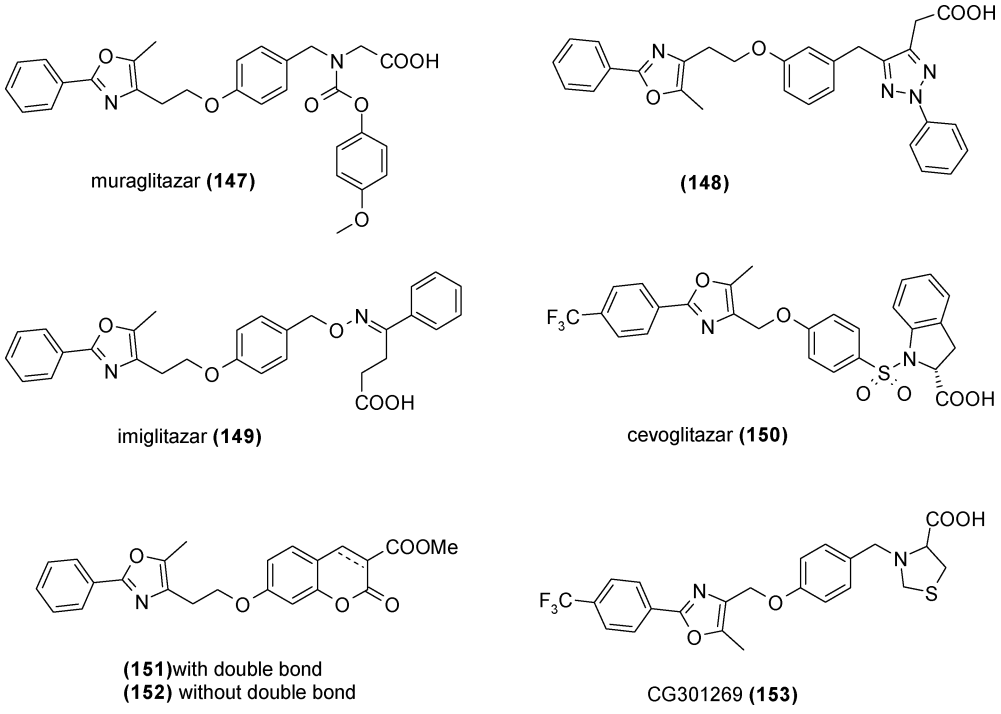

Figure 27. Other synthetic PPARα/γ agonist ligands.

stroke, and transient ischemic attacks.[152] .SARs of the oxybenzylglycine series were developed by examining the effects of a conformational restriction at the carbamate *N*-acid moiety, leading to the triazole acid analogue **148**.[153] This compound exhibited very potent dual PPARα and PPARγ agonist activity in vitro and also showed excellent antidiabetic and antidyslipidemic activity in a diabetic db/db mouse model. Imiglitazar (**149**) was a novel oxyiminoalkanoic acid derivative with potent PPARα/γ activities.[154] In various rodent models of insulin resistance and type 2 diabetes mellitus, **149** showed favorable pharmacokinetic properties, with good absorption and duration, and exhibited marked glucose- and lipid-lowering activities without causing significant body weight gain. Unfortunately, **149** was placed on clinical hold because of findings of abnormalities in liver enzymes in a small number of patients during the course of phase 3 studies. Cevoglitazar (**150**), developed by Novartis, is a very potent pharmacological agent that improves insulin sensitivity, glucose tolerance, and plasma lipid and inflammatory markers in animal models predictive of type 2 diabetes and metabolic syndrome in humans. More remarkably, **150** shows a desirable antiobesity effect in both genetically obese and diabetic ob/ob mice and obese insulin-resistant cynomolgus monkeys. These preclinical results demonstrated that **150** holds promise in the treatment of diabetes and obesity-related disorders because of its unique beneficial effect on energy balance, in addition to improving glycemic and metabolic control.[155] A series of benzopyran derivatives were synthesized, and their insulin-sensitizing activities were evaluated in 3T3-L1 cells. Compounds **151** and **152** exhibit more potent insulin-sensitizing activity than **28**. When comparing these compounds, the single-bond and double-bond derivative did not show much difference in activity. Compound **152** shows PPARα/γ dual agonist activity and exerts potent and efficacious hypoglycemic, hypolipidemic, and insulin-sensitizing effects in ob/ob mice. It not only lowers lipids in peripheral circulation but also reduces triglyceride deposits in skeletal muscle.[156] Various substitutions on the phenyl ring of the 2-(5-methyl-2-aryloxazol-4-yl)ethanol block were designed but led to compounds less potent than **152**. Recently, a novel PPARα/γ dual agonist, **153** (CG301269), has been reported to enhance fatty acid oxidation in vitro and ameliorate insulin resistance and hyperlipidemia in vivo.[157] In db/db mice, **153** reduced inflammatory responses and fatty liver without body weight gain. These data suggest that **153** might be a potential lead compound against obesity and related metabolic disorders.

2.4.2. Dual PPARγ/δ Agonists. In recent years, an interest in PPARγ/δ coagonists has developed. Both PPARδ and PPARγ improve insulin sensitivity and glucose tolerance. Furthermore, activation of PPARδ is beneficial in terms of plasma lipoprotein levels and reduced adiposity. Combined activation is believed to correct metabolic disorders associated with T2DM with greater efficacy than single PPAR activation. The beneficial effects on lipid homeostasis and the ability to stimulate reverse cholesterol transport are expected to significantly impede progression of atherosclerosis, which could contribute to lowering of the mortality rates of type 2 diabetic patients. Furthermore, the propensity of PPARδ activation for improving insulin sensitivity and increasing fatty acid oxidation suggests that a dual PPARγ/δ agonist could attenuate the undesired weight gain occurring with selective PPARγ agonists. However, reports of PPARγ/δ dual agonists are limited. Berger et al. first reported a series of phenylacetic acid derivatives such as **154** (L-165461), **155** (L-783483), and **156** (L-796449), which showed potent activity toward PPARγ and PPARδ, and were able to normalize glucose and triglyceride levels (Figure 28). Liu et al. developed general solid-phase synthesis of lipophilic carboxylic acids that led to identification of a potent PPARγ/δ dual agonist fibrate derivative, **157**.[158] This compound showed good plasma exposure in rats and demonstrated antihyperglycemic and antihyperlipidemic efficacy in diabetic fatty Zucker rats. However, no data regarding other key end points such as effects on body weight or inflammation markers were reported.

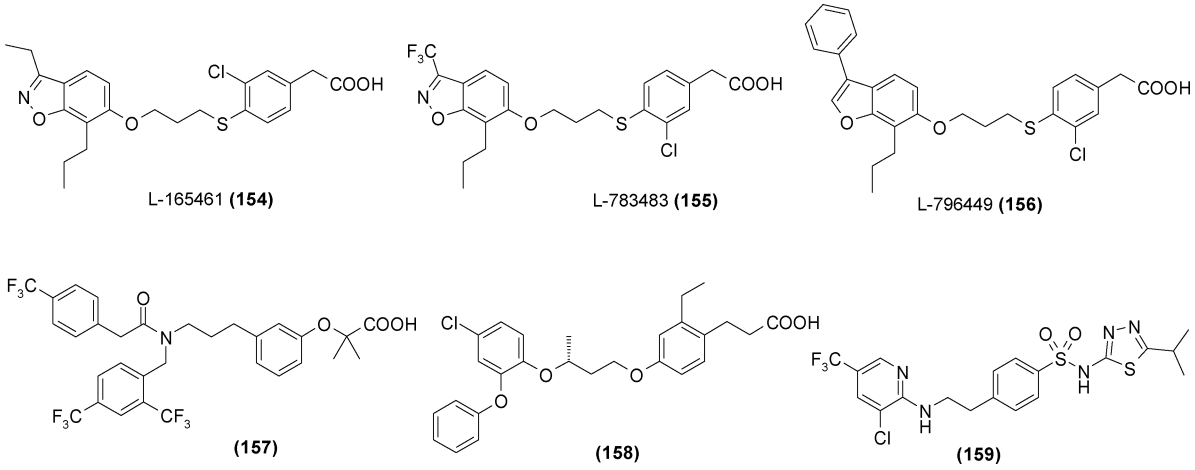

Figure 28. Dual PPARγ/δ agonist ligands.

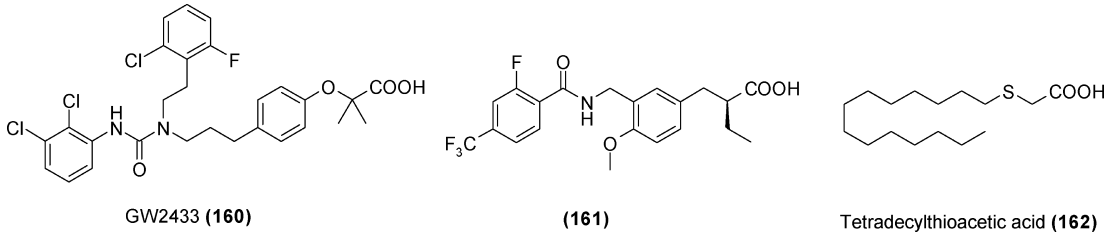

Figure 29. Dual PPARα/δ agonist ligands.

More recently, Lilly Research Laboratories have described (*R*)-**158**, a dual PPARγ/δ agonist, with approximately 17-fold greater functional PPARβ/δ potency in cell-based transactivation assays compared to PPARγ.[159] This dual agonist improved insulin sensitivity and reversed hyperglycemia with minimal weight gain in preclinical models of type 2 diabetes. In ZDF rats, (*R*)-**158** lowered plasma glucose levels in a dose-dependent manner and reduced plasma free fatty acids. Further studies demonstrated that (*R*)-**158** significantly enhanced whole body insulin sensitivity in response to a glucose challenge comparable to **28**. Animals treated with (*R*)-**158** and **28** at equivalent glycemic efficacy doses showed significant weight gains, but those animals receiving (*R*)-**158** showed ~50% less weight gain and a markedly lower increase in fat mass. These preclinical studies provide evidence supporting the hypothesis that a dual PPARγ/δ agonist could attenuate undesired weight gain side effects prevalent with marketed TZD. The appropriate γ/δ ratios that deliver optimal glucose control with minimal adverse side effects remain to be identified. Starting from an initial HTS hit, Sanofi-Aventis described a novel series of sulfonylthiadiazoles as partial PPARγ/δ agonists, represented by **159**.[160] This compound displays favorable in vitro data combined with a promising pharmacokinetic profile. In normolipidemic mice, **159** clearly decreases triglycerides and increases cholesterol levels. The latter effect was probably mediated by PPARδ, as no effect on cholesterol was observed after PPARγ activation. With respect to antidiabetic efficacy, **159** is as active as **97** and **28**, respectively, the PPARδ and PPARγ reference drugs, in prevention of diabetes development in db/db mice, thus further validating the premise that dual and partial agonists of PPARγ and -δ might be valuable in this area. In contrast, the primary hypothesis that mixed partial dual PPARγ/δ agonists might overcome or decrease the side effects of PPARγ agonists, such as weight gain, was not supported by in vivo results.

2.4.3. Dual PPARα/δ Agonists. The observation that both PPARα and PPARδ agonists increased HDL-C levels in human and animal models prompted development of new molecules targeting both PPAR isotypes, with the hope of potentiating individual effects on HDL-C induction. Only a few dual PPARα/δ agonists have been reported and are still at the discovery stage, such as the fibrate analogue **160** (GW2433) (Figure 29).[161] Some optically active α-ethylphenylpropionic acid derivatives have also been reported, represented by **161**, based on structural modifications of the potent PPARα selective agonist **14**. This new PPARα/δ dual agonist shows potent human nanomolar effects on PPARα and PPARδ compared to PPARγ. In this compound, the three-atom unit linker -CH_2-NH-CO- of **14** was modified to a -CO-NH-CH_2- linker that appeared to increase both PPARα and PPARδ transactivation activities. Furthermore, the activity of this compound resides almost exclusively in the (*S*)-enantiomer.[162] Tetradecylthioacetic acid (**162**), a modified fatty acid, is a pan-PPAR agonist of moderate potency with predominant PPARα and PPARδ activation, hence representing a novel promising treatment strategy for dyslipidemia.[163] It was demonstrated that **162** attenuated dyslipidemia in patients with type 2 diabetes mellitus during a 4-week period and that the treatment was well tolerated. Results suggested that these effects may occur through mechanisms involving PPARα/δ dual activation, resulting in increased mitochondrial fatty acid oxidation. A mixed PPARα/δ agonist, GFT505 (structure not disclosed) originated from GENFIT's selective nuclear receptor modulator (SNuRM) platform set up to identify innovative drug candidates that are more effective and safer than current therapies. Results from the clinical trial clearly demonstrated the potential of the drug candidate to reduce overall

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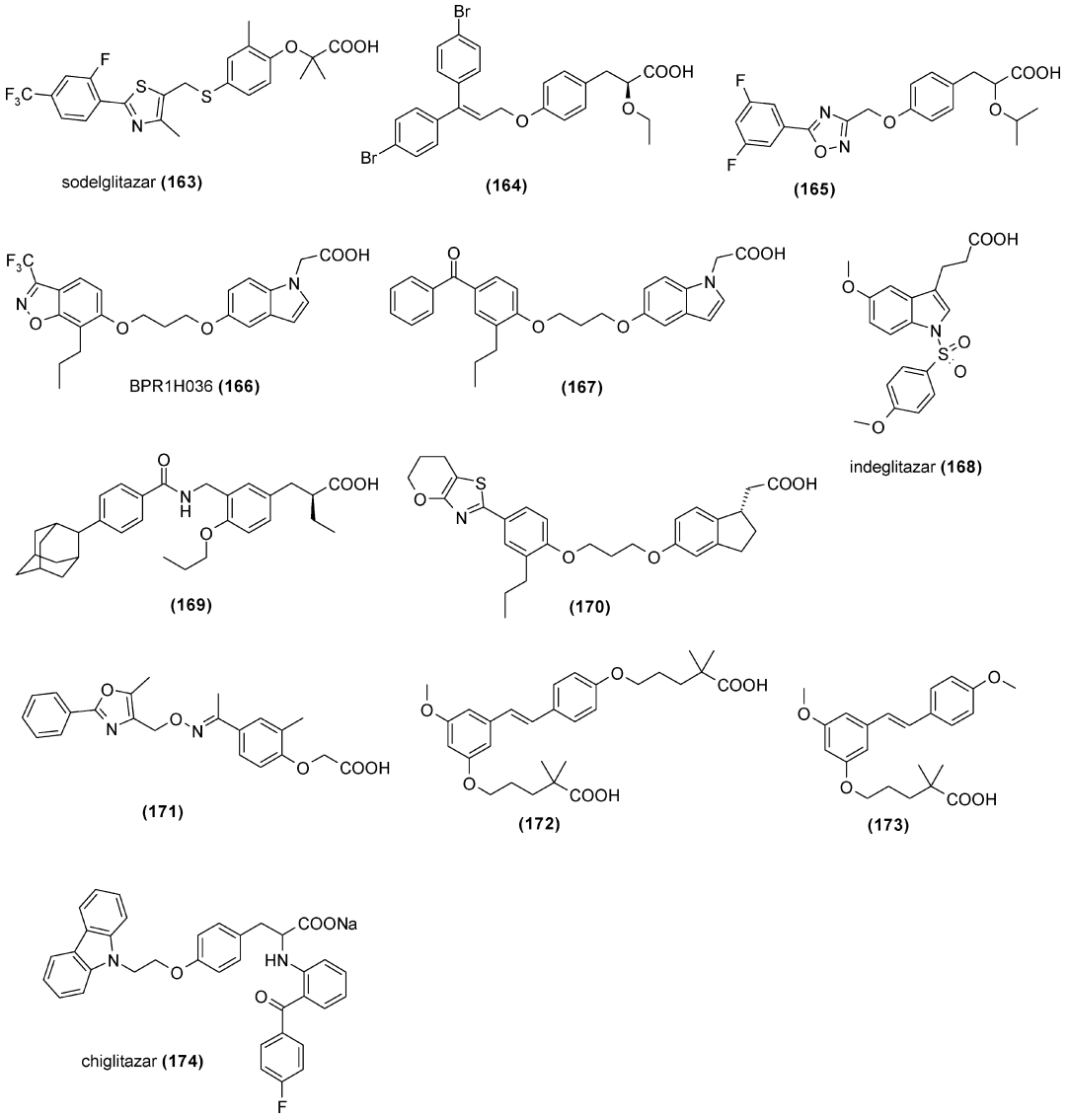

Figure 30. Pan PPAR $\alpha/\gamma/\delta$ agonists.

cardiovascular risk in prediabetic patients suffering from impaired fasting plasma glucose, impaired glucose tolerance, and abdominal obesity. After completing all preclinical development steps and demonstrating its excellent safety profile in phase 1 studies, this compound has shown therapeutic efficacy in two pilot phase 2a clinical trials.

2.5. Pan-Agonists. Along with the dual agonists, PPAR pan-agonists that would combine the agonistic activities of PPARγ, PPARα, and PPARβ/δ in a single ligand are also being explored and may prove to be the ultimate combination of PPAR activities for treatment of type 2 diabetes and its further complications. Indeed, PPAR pan-agonists would regroup the beneficial effects of the three PPARs by normalizing insulin resistance, plasma lipids, and adiposity. They are believed to be more effective than dual PPAR agonists.[164] Some PPAR pan-agonistic compounds with potential antihyperglycemic, lipid-modulating, and insulin-sensitizing activities have been recently reported and have elicited much interest due to their pharmacology. The reported PPAR pan-agonists effectively lowered plasma glucose levels, improved insulin sensitivity, and exerted positive effects on lipid and cholesterol homeostasis by reducing serum triglycerides and elevating HDL cholesterol, with lower weight gain and less fluid retention than for classical glitazones. Bezafibrate was the first pan-PPAR agonist used in therapy. First developed as a PPARα selective agonist, this fibrate analogue was shown, in further pharmacological evaluations, to activate all three subtypes with the same effectiveness.

Sodelglitazar (**163**), an oral PPAR pan-agonist destined for treatment of type II diabetes, was discontinued in phase 2 of clinical trials in October 2009 because of adverse effects (Figure 30). Some phenylpropionic acids have also been reported, represented by compound **164**, a potent pan-PPAR agonist identified from SAR evaluations of the known dual PPARα/γ activator **126**.[165] It displayed equal potency and efficacy on all three receptors. This compound was synthesized by maintaining the acidic part of a dual PPAR activator unchanged and modifying only the carbazole lipophilic part with a diphenylpropene moiety. GlaxoSmithKline has reported a series of α-isopropoxyphenylpropanoic acids containing oxadiazole tails initially developed as PPAR dual agonists; however, some of these compounds have shown weak agonistic activity toward PPARδ as, for example, compound **165**.[166] The in vitro binding and transactivation studies of **166** (BPR1H036), a compound belonging to a new chemical class with indole as a core skeleton, revealed that

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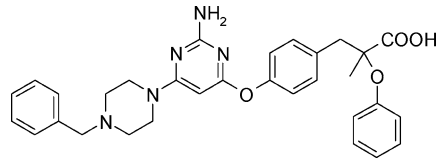
this compound was a potent PPAR pan-agonist.[167] In vitro biochemical studies of glucose uptake, adipocyte differentiation, and insulin-sensitizing activity have shown that **166** is an excellent candidate for further studies as an antidiabetic agent. The compound has demonstrated highly efficacious glucose-lowering activity in in vivo studies in KKAy mice and an excellent pharmacokinetic profile. The same authors further explored new hydrophobic building blocks such as the 6-benzoyl-1-propylnaphthalen-2-yl tail part of the indole-based PPAR agonists.[168] The hydrophobic tail part of **167** showed an intensive hydrophobic interaction with the protein, resulting in potent PPAR pan-agonistic activity. Cocrystallographic characterization of the lead molecule indeglitazar (**168**) in complex with each of the three PPARs revealed the structural basis for its PPAR pan-activity and its partial agonistic response toward PPARγ.[169] Compared with full PPARγ agonists, **168** is less potent in promoting adipocyte differentiation and only partially effective in stimulating adiponectin gene expression. Evaluation of the compound in vivo confirmed a reduced adiponectin response in animal models of obesity and diabetes while revealing strong beneficial effects upon glucose, triglycerides, cholesterol, body weight, and other metabolic parameters. Compound **168**, developed by the Plexxikon Company, has now progressed to phase 2 clinical evaluations for type 2 diabetes mellitus. A representative phenylpropanoic acid derivative bearing 4-adamantylphenyl substituent **169** proved to be a well-balanced PPAR pan-agonist able to regulate expression of genes involved in lipid and glucose homeostasis and may prove to be useful as a candidate drug for treatment of altered PPAR function.[170] The 4-thiazolylphenyl tail portion combined with the indanylacetic acid headgroup led to compound **170**, which had balanced PPAR$\alpha/\gamma/\delta$ pan-agonistic activities in vitro.[171] Compound **170** exhibited excellent ADME properties and superior therapeutic potential compared to known PPARγ-activating agents by favorably modulating lipid levels in hApoA1 mice and hyperlipidemic hamsters while normalizing glucose levels in diabetic rodent models. A novel series of oxazole-containing phenoxyacetic acid derivatives were found to be PPAR pan-agonists by incorporating an oxime ether linker between the lipophilic tail and the acidic head, as exemplified by compound **171**.[172] This compound shows potent and balanced PPAR pan-agonistic activity in vitro and exhibits potent antihyperglycemic and antihyperlipidemic effects in rodents. Further research into optimizing this series to develop compounds with desired ADME and toxicity profiles is in progress. The PPAR pan-agonists **172** and **173**, which are based on the resveratrol scaffold, demonstrate significant lowering of triglycerides and were shown to be more potent than fenofibric acid in two acute in vivo hypolipidemic activity tests.[173] These compounds also demonstrated good glucose-lowering efficacy in KKAy mice after daily administration at a dose of 150 mg kg^{-1} for 21 days. However, further research is necessary to determine whether the compounds can produce synergistic pharmacological effects by combining pharmacophore moieties with the natural scaffold. Chiglitazar (**174**) was first described as a PPARα/γ dual agonist but showed relatively weak PPARδ activity and was developed by Chipscreen Biosciences as a pan-agonist.[174] Compound **174** thus far has a promising efficacy and toxicity profile, with favorable pharmacokinetic behavior in both preclinical and clinical studies. A proof-of-concept phase 2a trial with over 240 patients was completed using a four-arm, double-blind active control (30 mg of **27**) design. Research on **174** showed dose-dependent effects on Hb1Ac, FPG, and 2hPG, with improvement in lipid profiles and clear improvement of side effects compared to the control. Phase 2b is currently underway.

3. NOVEL THERAPEUTICAL PERSPECTIVES FOR PPAR LIGANDS

3.1. Dual Functional Ligands. The development of a single compound displaying multitarget capacities would provide enhancement of efficacy and/or improvement in safety compared to the present one-drug−one-target methods. Indeed, new pharmacological compounds having the ability to simultaneously target more than one receptor, with the exception of the PPAR subtypes, have been described.

3.1.1. Dual Functional Agents as PPARγ Agonists and 11β-HSD1 Inhibitors. PPARγ and 11β-HSD1 are attractive therapeutic targets for type 2 diabetes.[175] However PPARγ agonists increase adipogenesis, which causes the side effect of weight gain, whereas 11β-hydroxysteroid dehydrogenase type 1(11β-HSD1) inhibitors prevent adipogenesis and may be beneficial in treatment of obesity in diabetic patients. A series of α-aryloxy-α-methylhydrocinnamic acids as dual function agents that simultaneously activate PPARγ and inhibit 11β-HSD1 have been reported. They were designed according to a combination of the known structure of the PPARγ agonist and 11β-HSD1 inhibitor and led to compound **175** (Figure 31). This



(175)

Figure 31. Dual PPARγ agonist and 11β-HSD1 inhibitor.

compound exhibits hypoglycemic and hypolipidemic efficacy comparable to that of **28** in different animal models. More importantly, it does not promote adipogenesis and decreases fat mass and body weight. Thus, although the exact molecular basis remains to be determined, compounds with both PPARγ agonistic and 11β-HSD1inhibitory activities might represent a new class of molecules with novel mechanisms for treatment of type 2 diabetes. It was also shown that **2** exhibited hypolipidemic effects in KKAy mice by down-regulating genes of the fatty acid synthesis pathway; antidiabetic properties occurred as a result of decreased hepatic glucose output, improved insulin sensitization, and down-regulation of 11β-HSD1 mRNA.[176]

3.1.2. Dual Functional Agents as PPAR Agonists and Cannabinoids. Cannabinoids act at two cannabinoid receptors (CB_1 and CB_2) and have been used medicinally for years as anti-inflammatory and analgesic agents. However, these compounds show some side effects, including psychotropic effects. Much recent evidence suggests that endocannabinoids are natural activators of PPARα.[177] Study of cannabinoid effects on PPARs began with the investigation of *N*-oleylethanolamide (**176**) (Figure 32), a naturally occurring lipid derivative structurally related to anandamide and that shares the anorexic property of other cannabinoids. In vivo, **176** reduces body weight via a PPARα-dependent mechanism. Indeed, **176** regulates feeding and body weight, stimulates fat utilization, and has neuroprotective effects mediated through activation of PPARα. Similarly, palmitoylethanolamide regulates feeding and lipid metabolism and has anti-inflammatory properties mediated by

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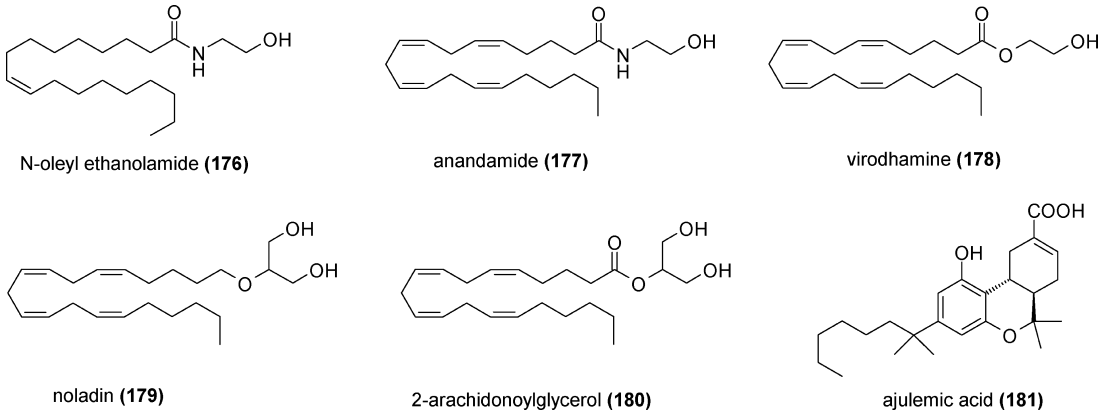

Figure 32. Dual functional agents as PPAR agonists and cannabinoids.

PPARα, like the other cannabinoids anandamide (**177**), virodhamine (**178**), and noladin (**179**). Some endocannabinoids also activate PPARγ. Compound **177** and 2-arachidonoylglycerol (**180**) have anti-inflammatory properties mediated by PPARγ. Similarly, ajulemic acid (**181**), a structural analogue of Δ^9-tetrahydrocannabinol (THC), causes anti-inflammatory effects in vivo through PPARγ and is completely free of psychotropic activity. This discovery represents a promising possibility for cannabinoid use as a therapeutic agent but also points to PPAR as new targets for neuroprotective treatment. This emerging evidence suggests that compounds able to act on both CB_2 and PPARγ receptors may be of therapeutic benefit in debilating pathological conditions affecting the central nervous system, such as strokes, multiple sclerosis, Alzheimer's disease, and other chronic neurodegenerative disorders.

3.1.3. 5-ASA, a New Ligand for PPARγ with Anti-Inflammatory Activity. In the past few years, the three PPAR subtypes have emerged as key regulators of inflammatory and immune responses, opening up a new era in development of therapeutic drugs useful in the treatment of chronic inflammatory diseases such as atherosclerosis, obesity-induced insulin resistance, and neurodegenerative diseases. It has been shown that PPAR act directly to negatively regulate gene expression of proinflammatory genes in a ligand-dependent manner by antagonizing the activities of other transcription factors such as members of the NF-κB and AP-1 families. A major mechanism that underlies the ability of PPARs to interfere with the activities of these transcription factors has been termed transrepression. PPARγ acts by inhibiting signal-dependent transcription factors that mediate inflammatory programs of gene activation. Several mechanisms underlying negative regulation of gene repression by PPARs have been described in recent studies using siRNA, microarray analysis, and macrophage-specific knockout mice. PPARγ is a negative regulator of macrophage activation, and activated macrophages are the major source of TNFα, which is both cytotoxic and proinflammatory. 5-Aminosalicylic acid **182** (5-ASA, mesalazine, mesalamine) (Figure 33) is an anti-inflammatory drug currently used to treat inflammation of the digestive tract, ulcerative colitis, and mild-to-moderate Crohn's disease. It has been shown in numerous experimental models of colitis to decrease inflammation.[178] Compound **182** therapy had been widely used empirically in patients with inflammatory bowel disease, since mechanisms mediating its action had not been determined. Its mechanism of action has been clarified as being PPARγ-dependent. Compound **182** prevents a radiation-induced increase in cytokine and chemokine expression. Understanding the mechanisms behind **182** might lead to development of **182** analogues with stronger affinity for PPARγ and fewer side effects. Indeed, for that purpose, several molecules with similarities to **181** have been developed, including **183** ((*R*)-(−)-GED-0507-34).[179] Compound **183** has demonstrated 100- to 150-fold higher antiinflammatory activity than **182**. This compound is giving promising results in both in vitro and in vivo experimental models of colitis, and its specificity appears to be very good, without any adverse events. It is currently in phase 2 of clinical trials.

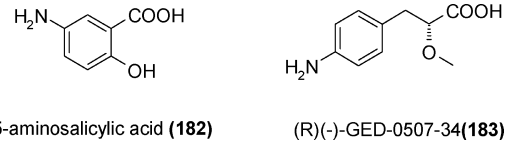

Figure 33. 5-ASA and GED-0507-34.

3.1.4. Dual Functional Agent as a PPAR Agonist and COX Inhibitor. Epidemiological observations indicate that long-term treatment with ibuprofen of patients suffering from rheumatoid arthritis results in reduced risk and delayed onset of Alzheimer's disease (AD). Ibuprofen, a commonly used over-the-counter nonsteroidal anti-inflammatory drug (NSAID) that is a cyclooxygenase (COX) COX-1 and COX-2 inhibitor as well as a weak PPAR agonist, decreases production of nitric oxide (NO), protects neurons against glutamate toxicity and decreases production of proinflammatory cytokines. Ibuprofen crosses the blood−brain barrier and suppresses neuritic plaque pathology and inflammation in the AD brain. Because of neuroprotective activity, relative safety, and its long history of use, ibuprofen is currently being developed for clinical use in AD. These results suggest that a dual PPAR agonist and a COX inhibitor may represent a promising new therapeutic avenue for treatment of neurodegenerative diseases such as AD. The effects of a COX-2 inhibitor in combination with a PPARγ ligand against pancreatic cancer have also been recently examined.[180] NS-398 (structure not disclosed), a selective COX-2 inhibitor, and **28** exert a synergistic effect upon inhibition of proliferation and induction of apoptosis in human pancreatic cancer cell line SW1990. The synergistic effect may enable use of a specific COX-2 inhibitor at lower and safer concentrations and may pave the way for more effective treatment of human pancreatic cancer. These results suggest that COX-2 inhibition and PPARγ activation represent new molecular targets for effective therapy against pancreatic cancer.

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CONCLUSION

Cardiovascular complications have been known to alter the lifestyle and reduce the life expectancy of patients with type 2 diabetes. PPARs are crucial in regulation of energy homeostasis, with each of the three subtypes of PPAR receptors controlling particular aspects. Since the cloning of PPAR as an orphan receptor, various ligands and target genes have been identified. Indeed, PPAR agonists have emerged as a promising group of agents for treating type 2 diabetes and associated cardiovascular risk factors represented by the marketed TZD, **27**, and **28**. Natural and synthetic ligands for the three subtypes have been reported, mainly focusing on PPARγ. The identification of new ligands, added to improved knowledge of their specificity, will enlarge the panel drugs for therapeutic intervention in various energy homeostasis disfunctions. In particular, PPARα and PPARγ seem to be antagonizing partners in maintenance of lipid homeostasis. The PPARδ/β isotype function has been the least documented thus far and would benefit from further development of pharmacological tools. However, its ubiquitous expression, particularly high during development, suggests that PPARδ/β could be implicated in cell proliferation/differentiation or in more basic cellular functions such as cell membrane synthesis. On the basis of the relatively few compounds marketed until now, PPAR ligands have attracted much unfavorable attention because of their potential side effects, most explicitly exemplified by the withdrawal of troglitazone and the strong but controversial suspicion of cardiac hypertrophy. Ongoing pharmaceutical research is continuing to pursue PPAR ligands with enhanced therapeutic efficacy and better safety margins. Thus, compounds with dual PPARγ and PPARα activity have been proposed to combine the benefits of insulin sensitization with lipid lowering in a single drug to reduce hyperglycemia and hyperlipidemia and to simultaneously prevent progression of cardiovascular complications. Unfortunately, clinical development of PPARα/γ dual agonists such as **124** and **146** has been discontinued because of their undesirable pharmacological effects. The side effects of these agents may be due to their unbalanced supratherapeutic activity toward PPARγ and PPARα. Therefore, dual agonists with selective and balanced agonistic activity toward PPARα/γ could constitute an appropriate therapeutic option. In the search for new PPAR agonists, some PPARα/δ and PPARγ/δ dual agonists have also been investigated, followed by pan-agonists having the full spectrum of $\alpha/\delta/\gamma$ activity. The SPPARM concept offered great promise for developing compounds with greater efficacy and reduced adverse effects. To date, the search for novel SPPARMs has focused on PPARγ, but some SPPARαM and SPPARδM have been under investigation. These agents could retain efficacious insulin-sensitizing properties while minimizing adverse side effects. However, despite the diversity of the new ligands for PPARs, only a few compounds are currently under clinical development. Recent studies have reported new PPAR ligands based on the concept of multitargeted drugs, with the development of PPAR-11β-HSD1, PPAR-CB_2, PPAR-COX dual functional agents, in order to enhance efficacy and/or improve safety compared to present one-drug−one-target methods. Furthermore, topical use could also provide interesting results, as shown by ongoing pharmaceutical research, focusing on the development of 5-ASA analogues that have emerged in the use of new PPAR ligands as anti-inflammatory drugs.

Since their marketing, glitazones have been plagued by a long history of suspected iatrogeny. Their ancestor **26** quickly cast a shadow over the entire glitazone family because of its hepatotoxicity. This was not, however, a class effect, and it was settled by withdrawing **26** in 1997 in the U.K. and in 2000 in the U.S., leaving **27** and **28** on the market. More serious adverse effects were soon uncovered, pointing to a negative effect of PPARγ agonists in two areas. The first is intrinsic to the pleiotropic mechanism of action of this nuclear receptor, which leads inter alia to adipocyte proliferation, therefore fostering weight gain in a population of patients most of whom are already struggling with their weight. This adverse effect was the motor for newer, less weight-gain-inducing mixed PPAR compounds. It can be coped with by following a strict diet, but the latter is a worsening factor when adhering to such long-term treatment. The second is even more serious and can be regarded as the kiss of death for PPARγ agonists. Both **27** and **28** induce fluid retention which, taken together with weight gain, is an aggravating factor in heart congestion. Moreover, while this issue remains hotly debated, **28** has been strongly suspected of worsening the heart condition of patients already at risk of heart failure, with data suggesting an increase in heart-related mortality under treatment. For this reason, **28** was initially given black box labeling on possible heart side effects in 2007 and was taken off the market in the EU in late 2010; in the U.S., further serious limitations to its use came out that same year. Thus, **27** currently remains the only thiazolidinedione still on the market, but it too is being challenged. In fact, a postmarketing safety study demonstrated an increase in bladder cancer risk. Although modest, this increase was felt to sufficiently alter the benefit/risk balance to warrant effective discontinuation of a molecule already reduced to second- or third-line use on French and German markets in June 2011; however, it simply led to further contraindications by the EMA. In conclusion, cardiovascular safety is the new bottleneck for PPAR agonists, with regulations requesting more stringent and complete drug trials before approval. It should be kept in mind that even drugs deemed successful against their intended target might well display severe adverse effects after marketing because of their widespread use, itself shedding new light on their still not fully understood mechanisms of action. Only one of the possible uses of the intricate cell-type-differentiated gene regulation patterns of the PPARs was harnessed, with only scarce knowledge of their full range of effects. They have proven to be both efficient and potentially dangerous, and the current dislike of PPAR as a therapeutic tool can be viewed as a risk management paradigm: a danger that is not entirely elucidated represents too great a risk.

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Notes

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Biographies

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was focused on the development of new PPARs ligands in the treatment of type 2 diabetes.

Amaury Farce received his Ph.D. in Molecular Modeling in 2005 at the University of Lille 2, France, and was appointed Assistant Professor in 2007. His research interests are focused on using computational tools to model ligand−target interactions on subjects ranging from metabolic syndrome to RCPGs ligands and the induced conformationl changes of the receptor through cancer therapy.

Nicolas Lebègue obtained his Master's degree in Organic and Macromolecular Chemistry at the University of Lille 1, France, followed by a Ph.D. in Medicinal Chemistry on the design, synthesis, and pharmacological evaluation of new antimitotic compounds at the Faculty of Pharmacy of Lille. He then joined Pr. Daniel Lesieur Laboratory at the same faculty and holds the position of Principal Research Investigator in the development of new PPAR ligands for the treatment of type 2 diabetes and metabolic syndrome in collaboration with Servier Laboratories, Paris, France.

Nicolas Renault earned his Master's degree in 2005 with extensive training in computational drug design in the research center of L'Oreal in Paris, France. He began his career at the University of Paris 5, France, on pathologic consequences of protein mutations from structural bioinformatics studies. He graduated in 2010 from the University of Lille 2, France, with a Ph.D. degree under the supervision of the Pr. Philippe Chavatte. He has coordinated a high-throughput virtual screening platform with successful applications of structure-based design of melatoninergic, serotoninergic, and cannabinergic ligands. He also contributed to many in silico studies of the design of novel anti-inflammatory agents.

Christophe Furman earned his Ph.D. in Pharmaceutical and Biological Sciences (2001) at the University of Lille 2, France, under the supervision of Pr. Patrick Duriez in the research unit headed by Pr. Jean-Charles Fruchart at Pasteur Institute of Lille. His research interests during his thesis period have included the study of the protection of endothelial cells exposed to oxidative stress by polyphenols and PPAR activators. During a postdoctoral training in this lab, he studied the regulation of the antioxydant system (i.e., thioredoxin system) by PPAR activators. Since 2005, he has worked for the Albert Lespagnol Pharmaceutical Chemistry Institute in Lille where he is responsible for binding platforms and where he develops themes for therapeutic innovation in pathologies related to the environment.

Régis Millet received his Ph.D. in Medicinal Chemistry at the University of Lille 2, France, under the supervision of Pr. Jean-Pierre Hénichart, where he developed and synthesized new dual NK1/NK2 neurokinin receptor antagonists. After two postdoctoral appointments in collaboration with UCB Pharma, Braine l'Alleud, Belgium, at Albert Lespagnol Pharmaceutical Chemistry Institute and with CNRS, France, at Institute of Biology of Lille, he has been appointed Assistant Professor of Medicinal Chemistry at University of Lille 2, where he is currently a group leader of his drug discovery research team. His research has included contributions to the medicinal chemistry of NK_1/NK_2 neurokinin antagonists, inhibitors of farnesyltranferase, inhibitors of thioredoxine reductase, agonists CB_2, and PPARs modulators.

Saïd Yous received his Ph.D. in 1991 in Medicinal Chemistry from the University of Lille 2, France, under the supervision of Pr. Daniel Lesieur. His work on the design and synthesis of new melatoninergic ligands has led to the preparation of agomelatine (Valdoxan, Melitor, Thymanax) now marketed as antidepressant. He then joined Pr. Jean-Pierre Hénichart's laboratory at Albert Lespagnol Pharmaceutical Chemistry Institute as Principal Research Investigator in the development of new angiotensin II antagonists in collaboration with UCB Pharma, Braine l'Alleud, Belgium. He was then promoted to Assistant Professor in 1997 at Faculty of Pharmacy of Lille. His current research interests include the design and synthesis of ligands for melatoninergic, serotoninergic, and dopaminergic systems.

Silvia Speca is currently a Ph.D. student in Internal Medicine and Applied Immunology at the University of L'Aquila, Italy.

Pascal Berthelot was studied chemistry at the Faculty of Pharmacy at the University of Lille 2, France, where he obtained his pharmacist certificate in 1976. The same year he then joined Pr. Michel Debaert's group at the same institution. He received two Ph.D. degrees in 1980 and 1986. He is currently Professor of Medicinal Chemistry at the Faculty of Pharmacy of Lille. He has wide-ranging research interests in heterocyclic chemistry in the domains of anticancer and antidepressant drugs and PPARs ligands.

Pierre Desreumaux has M.D. and Ph.D. degrees and is a Professor of Gastroenterology at the University of Lille, France. Pierre Desreumaux heads the Academic Research Center on Inflammatory Digestive Diseases, devoted to translational research through the study of immunological/bacteriological mechanisms and the development of new therapeutic targets in the regulation of digestive inflammation. This research group located within the Medicine Faculty of Lille is an attractive research center on inflammation that quickly turns fundamental ideas into medical innovations. Besides these academic activities, Pierre Desreumaux is a member of the Scientific Committee of INSERM since 2008 and the founder of DigestScience, a European foundation for research on intestinal diseases.

Philippe Chavatte received his Doctorate of Pharmacy in 1983 and his Ph.D. in Microbiology in 1988 from University of Lille 2, France. He received his Ph.D. in Life and Health Sciences in 1997 from University of Lille 1, France. Philippe Chavatte joined the Faculty of Pharmacy at University of Lille 2 as Assistant Professor and currently is Professor of Medicinal Chemistry at the same institution. He is also Director of the Albert Lespagnol Pharmaceutical Chemistry Institute in Lille. His research interests lie in the application of molecular modeling to discover and develop new drugs against inflammatory bowel diseases (IBD) and, more particularly, for a new identified and validated therapeutic target in IBD: PPARγ.

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■ ABBREVIATIONS USED

AD, Alzheimer's disease; AF-1, ligand-independent activation function 1; AF-2, ligand-dependent activation function 2; AP-1, activator protein 1; apoA1, apolipoprotein A1; apoCIII, apolipoprotein CIII; ARB, angiotensin receptor blocker; COX, cyclooxygenase; DBD, DNA binding domain; HDL, high density lipoprotein; LBD, ligand binding domain; MS, metabolic syndrome; NF-κB, nuclear factor κB; NSAID, nonsteroidal anti-inflammatory drug; PPAR, peroxisome proliferator-activated receptor; PPRE, peroxisome proliferator response element; RXR, retinoic acide receptor; SPPARM, selective PPAR modulator; T2DM, type 2 diabetes mellitus; TZD, thiazolidine-2,4-dione; VLDL, very low density lipoprotein

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