Development of Heterocyclic PPAR Ligands for Potential Therapeutic Applications

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Abstract: The family of nuclear peroxisome proliferator-activated receptors (PPARα, PPARβ/δ, and PPARγ) is a set of ligand-activated transcription factors that regulate different functions in the body. Whereas activation of PPARα is known to reduce the levels of circulating triglycerides and regulate energy homeostasis, the activation of PPARγ brings about insulin sensitization and increases the metabolism of glucose. On the other hand, PPARβ when activated increases the metabolism of fatty acids. Further, these PPARs have been claimed to be utilized in various metabolic, neurological, and inflammatory diseases, neurodegenerative disorders, fertility or reproduction, pain, and obesity. A series of different heterocyclic scaffolds have been synthesized and evaluated for their ability to act as PPAR agonists. This review is a compilation of efforts on the part of medicinal chemists around the world to find novel compounds that may act as PPAR ligands along with patents in regards to PPAR ligands. The structure–activity relationship, as well as docking studies, have been documented to better understand the mechanistic investigations of various compounds, which will eventually aid in the design and development of new PPAR ligands. From the results of the structural activity relationship through the pharmacological and in silico evaluation the potency of heterocycles as PPAR ligands can be described in terms of their hydrogen bonding, hydrophobic interactions, and other interactions with PPAR.

Keywords: peroxisome proliferator-activated receptors; ligands; a thiazolidinedione; structure–activity relationship interactions

1. Introduction

Nuclear receptors are a type of protein that recognize steroid and thyroid hormones in the body [1]. Nuclear receptors tend to influence the growth, homeostasis, and metabolism of organisms by binding to DNA and regulating the expression of specific genes. As a result of their ability to modulate transcription, these are known as transcription factors [2,3]. The nuclear receptor superfamily’s peroxisome proliferator-activated receptor (PPAR) is a ligand-dependent transcription factor [4]. To build a heterodimer, all PPARs interact with the retinoid X receptor [5–7]. In 1990, PPARs were first observed in rodents [8]. PPARs are receptors associated with a superfamily of nuclear receptors that also contain steroids, retinoid receptors [9], thyroid hormone receptors, and Vit. D receptors [10]. They are multiple and persuasive regulators of various cellular functions and metabolic functions such as glucose and lipid homeostasis, cholesterol, and energy balance [11,12]. Peroxisome proliferator-activated receptors are a subgroup of the ligand-dependent transcription factor that contains peroxisome proliferator response elements as transcription factors to regulate transcriptional activity [13–15].

2. Structure of PPAR

The three-dimensional structure of PPARs includes the N-terminus and C-terminus where DNA binding domain and ligand-binding domain are attached, respectively, [16]. They
are translocated to the nucleus and heterodimerized with retinoid X receptors (RXR) [17]. In targeted genes, the PPREs (peroxisome proliferator hormone response elements) are particular DNA areas that interact with PPARs [18,19]. They are connate in the fatty acid-binding protein like PPAR-responsive gene promoters that activate transcription of multiple genes involved in various physiological processes shown in Figure 1 [20,21]. The protein structure of various PPARs is fetched from the protein data bank using three PDB ids such as 2P54 (PPARα), 2A5G (PPA, Rβ,), and 3VI8 (PPARγ), shown in Figure 2 [22–26].

![Figure 1. Mechanism of biological responses through PPAR.](image1)

![Figure 2. 3D structure of PPARα/β/γ.](image2)

### 3. Types and Expressions of PPARs

The transcriptional factors of peroxisome proliferator-activated receptors (PPARs) contain three different isoforms, namely nuclear receptor subfamily PPARα or NR1C1, PPARβ/δ or NR1C2, and PPARγ or NR1C3 [27–29]. These isoforms are expressed in multiple tissue and organs with identical character and ligand specificity [30]. The PPAR-α is expressed mainly in the liver but is also present in muscle, bone, and heart. The PPAR-δ is expressed in most parts of the body and regulates energy expenditure [31,32]. The PPAR-γ is expressed in vascular smooth muscle cells, and endothelial cells [33,34]. The expression of various types of PPARs is shown in Figure 3 [35–37].
### 4. Functions of PPARs

In the human body, the three forms of PPARs are responsible for the activation of most of the enzymes that are required for fatty acid oxidation, glucose metabolism, and lipid metabolism [38]. These PPARs perform specific or distinct functions such as cellular energy balancing, and maintenance of energy homeostasis on their own or by helping each other [39]. Energy metabolism at a molecular level through PPARs is still not explained but when ligands are attached to these receptors, they transcript the genes involved in regulatory energy functions [40]. The PPARα is involved in the activation of gene-encoding enzymes such as carnitine palmitoyl transferase 1 (CPT1), fatty acid transport protein, acyl-CoA dehydrogenase or oxidase, or synthase required in the fatty acid oxidation pathway [41]. It also reduces plasma triglyceride levels and increases high-density lipoprotein, which gives benefits such as ketogenesis [42]. The PPARβ controls fatty acid metabolism, increases insulin sensitivity, obesity resistance, suppression of macrophage-derived inflammation, and also the formation of oxidative muscle fibers. The PPARγ promotes fatty acid uptake, and adipokine production raises insulin sensitivity, also in adipogenesis [43–46]. Other functions associated with PPARs are described in Figure 4 [47–49].

In several areas of medicinal chemistry, heterocyclic molecules are indispensable [50,51]. These compounds constitute nitrogen, sulfur, and oxygen atoms with various positional combinations in the cyclic ring [52]. Medicinal chemists and researchers always explore heterocycles due to their vital contribution to drug discovery and design by boosting the novel lead moieties with potential biological action in medicinal chemistry [53]. Based on statistics, more than 85% of biologically potential chemical moieties contain heterocyclic motifs [54]. Some of the most common heterocycles are pyrimidine, imidazole, oxazole, tetrazole, triazine, triazole, thiazole, indole, pyridine, thiophene, pyrazole, coumarin, oxindole, furen, etc. [55–58]. These heterocyclic nuclei possess a broad spectrum of medicinal potential such as an anti-microbial [59], antimalarial [60], anti-anxiety [61], anti-cancer [62], anti-depressant [63], anti-tubercular [64], anti-virus [65], anti-protozoal [66], and anti-convulsant, etc. Several heterocyclic analogs have been reported to affect PPAR in different diseases [67–72]. Apart from commercially available marketed drugs, Table 1 depicts the patented drugs acting on PPARs.
In this review, we have tried to compile the literature of the recent past (2016–2022) discussing heterocyclic derivatives, wherein we have discussed various scaffolds showing their potential as PPAR ligands concerning different activities. The SAR of these derivatives will be discussed to pave the way for the development of new, safe, and economical ligands shortly. Various heterocyclic moieties that act on the PPAR receptors have been summarized and displayed in Table 2.
### Table 2. Summary of various heterocycles with the different substitutions for Peroxisome proliferator-activated receptor.

| Heterocycles          | Most Potent Substitution                  | Activity                                                                 | Reference |
|-----------------------|-------------------------------------------|--------------------------------------------------------------------------|-----------|
| Thiazolidinediones    | Allyl derivative (1a)                      | EC$_{50}$ of $-4.95$ µM in the human PPAR-$\gamma$ transactivation assay  | [83]      |
|                       | Amino derivative (3b)                      | 1.7 times more than reference compounds in glucose uptake assay          | [84]      |
|                       | Chloro derivative (8a)                     | 63.15%, PPAR-$\gamma$ transactivation                                    | [85]      |
|                       | Dichloro derivative (9a)                   | (−11.6930) Docking score                                                | [86]      |
|                       | Nitro and carboxylic acid derivative (10d) | (−17.44) Docking score                                                  | [87]      |
|                       | Flouro derivative (12e)                    | Reduced 0.09-fold the expression gene of PPAR$\gamma$ in cultured adipocytes compared to the control group | [88]      |
|                       | Ocadiazole                                  | No substitution (13d)                                                    | [89]      |
|                       | ADAM (14)                                  | 2.5-fold greater efficacy in activating PPAR$\alpha$                     | [90]      |
|                       | Bromo derivative (15a)                     | Potency and selectivity towards PPAR$\alpha$/$\delta$ receptors with PPAR$\alpha$/$\delta$/$\gamma$ EC$_{50}$ values  | [91]      |
|                       | Flouro derivative (16d)                    | PPAR$\alpha$ −0.06 ± 0.0005, PPAR$\delta$ −0.07 ± 0.0006               | [92]      |
|                       | Bemzoimidazole                              | Chloro derivative                                                        | [93]      |
|                       | Fluoro and chloro derivative (20c)         | $-68 \pm 29$                                                            | [94]      |
|                       | Chloro and iodo derivative (21c)           | $-10.6 \pm 0.4$                                                          | [95]      |
|                       | Methoxy derivative (24a)                   | -                                                                        | [96]      |
|                       | Phenyl derivative (27b)                    | PPAR$\alpha$ Imax% 22 ± 16                                              | [102]     |
|                       | p-halogenated phenyl substituted            | Increased PPAR$\gamma$ activity by almost 4- to 5-fold                   | [103]     |
|                       | Thiazole                                   | -                                                                        | [104]     |
|                       | Fluoro and nitro derivative (29b)          | -                                                                        | [105]     |
|                       | Chloro and phenyl derivative (31a)         | PPAR$\alpha$/$\delta$/$\gamma$ profile at potency and efficacy level(31a, Emax = 50%) | [106]     |
|                       | Cyclicexyl derivative (32a)                | 24.43% Reduction in blood glucose level                                  | [107]     |
|                       | phenyl derivative (33h)                    | hPPAR$\alpha$ (LBD)-GAL4 EC$_{50}$ (µM) -7.51                           | [108]     |
|                       | Furan                                      | hPPAR$\gamma$ (LBD)-GAL4 EC$_{50}$ (µM) -2.97                           | [108]     |
|                       | Trifluoro carbon phenyl derivative (34a)   | 16.2-fold and 8.4-fold more PPAR-$\alpha$/$\delta$ agonistic activity than PPAR$\gamma$ | [109]     |
|                       | Trifluoro carbon phenyl derivative (35a)   | High potency toward PPAR-$\alpha$/$\delta$ (0.26 ± 0.08 µM              | [110]     |
|                       | Benzopyran                                 | Nitro derivative (36b)                                                   | [111]     |
|                       | Butane derivative (37c)                    | hPPAR$\alpha$ and $\gamma$ with % values of 91% and 88% using a transactivation assay | [112]     |
|                       | Di-hydroxyl derivative (38b)               | Ki value 1.41 µM                                                         | [113]     |
|                       | Cyanophenyl (43a)                          | IC$_{50}$ 6.5 µM time-resolved FRET technique                            | [118]     |
Table 2. Cont.

| Heterocycles | Most Potent Substitution | Activity | Reference |
|--------------|--------------------------|----------|-----------|
| 44           | EC₅₀ (nM) = −170 ± 10    |          | [119]     |
| 45a          | HepG2 and A549 cell growth with IC₅₀ values of −0.54 and −0.47 μM, respectively, CCK-8 assay |          | [120]     |
| 46           | -                        |          | [121]     |
| Methoxy and cyclohexyl derivative | IC₅₀ values = 0.350 fluorescence polarization assay | | [122] |
| 50a          | glucose uptake activity in vivo evaluation, with −37.05 ± 0.44 | | [124] |
| o-Tolyl (51a) | -                        |          | [124]     |
| 52           | -                        |          | [125]     |
| 53a          | -                        |          | [126]     |
| Ethycyclopropane derivative (54a) | - | | [127] |

5. Recent Developments in the Medicinal Chemistry of PPARs

5.1. Thiazolidinediones

Sulfur and nitrogen-containing five-membered ring heterocycle is a thiazole, its non-aromatic simple being thiazolidine. At the point when thiazolidine is enriched further with two carbonyl groups at positions two and four, the ring framework is named 2,4-thiazolidinedione (TZD). TZD’s anti-diabetic properties were found in the early 1980s. Therefore, they were introduced during the 1990s as insulin-sensitizing glucose-lowering drugs for the treatment of type 2 diabetes mellitus (T2DM). They work fundamentally by initiating PPAR-γ, which thus controls glucose, lipids, and protein digestion. Troglitazone was the first medicine containing TZD pharmacophore but it had to be removed in the United States because of idiosyncratic hepatotoxicity that resulted in fatalities. Based on reports from other nations, it was also discontinued in the United Kingdom. In the years 1999 and 2000, rosiglitazone and pioglitazone were introduced in the US and Europe, in combination with other hypoglycaemic agents such as, e.g., thiazolidinedione plus metformin [128]. Several existing drugs that have a TZD motif in their structure have been displayed in Figure 5. Many chemists have reported the information on structurally modified TZD molecules exhibiting potential towards PPARs receptors that has been been described here.

![Image of TZD scaffold containing PPAR ligands](image)

Figure 5. TZD scaffold containing PPAR ligands present in the market.

Darwish et al. designed and synthesized some thiazolidinedione derivatives with the aim of finding agonistic activity at the PPARγ receptor. According to the study, nineteen
derivatives of thiazolidinedione were synthesized in which nine compounds exhibited promising activity. All the derivatives were tested for PPARγ receptor agonistic activity by using a luciferase-based genetic reporter assay. The result showed that bromophenyl and biphenyl-containing compounds exhibited moderate activity whereas five compounds showed five-fold more activity. There was a rigidity of the biphenyl nucleus, which was why bromophenyl derivatives were more active than biphenyl derivatives. As shown in Figure 6, trifluoro methyl (1a) containing derivatives diminishes activity due to their bulk and rigidity. The allyl derivative (1b) exhibited higher agonistic activity compared to rosiglitazone with 55-fold activation and an impressive EC\textsubscript{50} of 4.95 \(\mu\)M in the human PPAR-\(\gamma\) transactivation assay [83].

![Figure 6. Structural activity relationship of thiazolidinediones hybrids (1) as potent PPAR ligands.](image)

The same group of authors continued their research on PPAR-\(\gamma\) receptors and designed benzhydrol and an indol-based series of derivatives in the search for new candidates of thiazolidinediones chemotypes as dual PPAR-\(\gamma\)/FFAR1 agonists. The optimization of compounds based on the exhibiting affinities towards PPAR-\(\gamma\) and the FFAR1 receptor at the low micromolar range selected compounds 2a, 2c, and 2d. The in vivo pharmacological study resulted in the compound 2c (EC\textsubscript{50} = 17.75 \(\mu\)M) exhibiting better anti-hyperglycemic activities than 2a (21.34 \(\mu\)M), 2c (Inactive), and the reference compound (Rosiglitazone) in fat-fed animal models. Molecular docking studies were carried out to check the binding with the receptor. The SAR study of synthesized series and their important substitution is shown in Figure 7 [129].

Chhajed et al. designed and synthesized a benzylidene amino-benzylidene-thiazolidine-2,4-dione scaffold containing derivatives to find novel PPAR-\(\gamma\) agonists. The research framework began with virtual screening by using molecular docking studies on the ligand-binding domain of PPAR-\(\gamma\) that filtered out ten compounds based on their affinity. Therefore, these compounds were processed for synthesis. The molecular docking was carried out on the 3-D structure of PPAR-\(\gamma\) (PDB ID: 2XKW) using a molecular design suite (MDS). From the molecular docking studies, the researchers observed significant binding of the derivatives with the receptor having a good docking score wherein the substitution at a para position on phenyl ring possessed better affinity comparison with the ortho- and meta-substituted compounds. Further, the substitution of amino and nitro at the para
position showed a great affinity with score of −9.22 and −8.47, respectively. The binding of TZD molecules was demonstrated via H-bonding, where aniline, carbonyl oxygen, and benzylidene moiety bound with Arg288, Ile326, and lle281 or lle341, respectively. The authors also noted H-bonding and pi-interaction with Ala292 and Met329. Gly284, Leu330, Cys285, and Met348. Synthesized molecules were tested for glucose uptake assay for the 3T3-L6 cell line using rosiglitazone as a standard reference. The results revealed that compounds 3a, 3b, 3c, and 3d increased glucose uptake 1.6, 1.8, 1.6, and 1.7 times more than reference compounds, respectively. The study showed that compounds bearing electron-donating groups such as NH2 and CH3 and electron-withdrawing groups such as the halogens (Br, F, and Cl) were responsible for PPAR-γ agonist activity. Lipophilicity also played a significant role in the activity, which was corroborated by the introduction of methyl and ethyl groups to the phenyl ring. The results of in vitro pharmacological activity matched with the docking study (Figure 8) [84].

![Figure 7. Structural activity relationship of Thiazolidinediones hybrids (2) as potent PPAR ligands.](image)

![Figure 8. Structural activity relationship of Thiazolidinediones hybrids (3) as potent PPAR ligands.](image)
Szychowski and co-workers reported some 4-thiazolidinedione derivatives as new candidates for the treatment of cancer. In this study Les-2194 (4), Les-3377 (5), Les-3640 (6) (4-thiazolidinedione derivatives) along with rosiglitazone, and pioglitazone were tested for their involvement in PPARs receptors in the mechanism of pro-apoptotic action and their cytotoxicity using the squamous carcinoma (SCC-15) cell line. The PPARα, PPARβ, and PPARγ mRNA expression were examined using 4-thiazolidinedione compounds and PPAR-specific siRNA. Cell survival, cell metabolism, and caspase-3 activity were also assessed after PPARα, PPARβ, and PPARγ siRNA gene suppression. The mRNA expression of PPARs decreased in SCC-15 cells treated with Les-2194, Les-3377, and Les-3640. The cytotoxic effect of the examined drugs (50 µM) was prevented by PPARγ knockdown. In SCC-15 cells, it was found that the new anticancer 4-thiazolidinedione compounds act mostly via the PPARγ pathway (Figure 9). The authors found that all the compounds emerged as PPARγ modulators. Silencing the PPARγ gene raises the PPARα and PPARγ mRNA in SCC-15 cells, which is interesting. The anticancer activity of the newly discovered chemicals was better than that of rosiglitazone and pioglitazone [130].

Abdellatif et al. designed and synthesized pyrazole containing two series of thiazolidine and thiazolidinone derivatives attached with methylene or methylenehydrazone linkers to target the PPARγ receptor. The luciferase-based genetic reporter assay carried out for all synthesized analogs to screen the activity of PPARγ receptors that showed methanesulfonamide (7a) and methoxy (7b)-substituted thiazolidinedione derivative along with chloro (8a) and bromo (8b)-substituted thiazolidinone derivatives increased the PPARγ receptor activation and displayed 52.11%, 59.63%, 63.15%, and 55.24% PPAR-γ transactivation, respectively. The docking study revealed that the Y shape was successfully adopted by the tested compounds 7a, 7b, 8a, and 8b, and two of them, 7a and 8b, docked with PPAR-γ (PDB ID: 4O8F) in the same region as rosiglitazone, while the other two interacted with the receptor in the left motif as pioglitazone (Figure 10) [85].
Figure 10. Structural activity relationship of thiazolidinedione (7 and 8) hybrids as potent PPAR ligands.

Srivastava et al. reported 2,4-thiazolidinedione derivatives (Figure 11) and screened for anti-diabetic, free radical scavenging activities, and anti-inflammatory activity. The in-silico studies were also carried out using molecular docking to analyze some important structural features in the binding manner of reference anti-diabetic drugs with the active protein binding sites of PPARγ (PDB ID: 2PRG). Compound 9a (dichloro derivative) exhibited significant antidiabetic potential along with anti-inflammatory and antioxidant potential. Numerous possible interactions were analyzed and compared with the reference compound (pioglitazone). Compounds 9a, 9b, and 9c had docking scores of −11.6930, −10.1553, and −11.1008, respectively, which were quite close to pioglitazone (−12.8116). The amino acid residues Ser A289 and His A323 demonstrated two hydrogen bond interactions with compound 9a. Compound 9b had one keto group that hydrogen-bonded with water in combination with Ser 342 and another keto group that hydrogen-bonded with another molecule of water in interaction with Arg. As seen in Figure 9, compound 9c establishes a hydrogen bond with Ser A342. By forming a hydrogen bond with Glu A343 and another interaction with HOH 604 linked with Ser 342, pioglitazone demonstrated a binding pattern [86].

Figure 11. Regions of thiazolidinedione (9) hybrids are required for binding to PPAR.

Bansal et al. also reported TZD derivatives (Figure 12) associated with the pyrazole motif, docked against PPAR-γ and α-amylase, and further screened for antidiabetic, antioxidant, and anti-inflammatory activities. Compound 10d was found to have a strong blood glucose reducing effect and was a promising inhibitor of α-amylase. Compound 10a showed it had potential as an anti-inflammatory drug that reduced MDA, IL-1, and TNF-α (inflammatory markers), as well as having some antioxidant activity. Compounds 10b (−16.13), 10c (−16.79), and 10d (−17.44) had higher docking scores in the PPARγ interaction than the pioglitazone (−12.605). Hydrogen bond interactions were observed in compound 10b which included the interaction of one keto group with an HOH molecule.
along with Arg288, another keto group with Ser342, and an acidic hydroxyl group with an
HOH molecule in association with Ser342. The hydroxyl group of compound 10c showed
H-bonding interactions with HOH when combined with Glu272; additionally, other H-
bonding interactions involving Glu272, and Gln271 were found. In association with Gly284;
compound 10d revealed only one water molecule binding. The acidic head of pioglitazone
displayed interaction with the HOH molecule associated with Arg288. The structure of
potent derivatives is shown in Figure 12 [131].

Figure 12. Series of thiazolidinedione hybrids (10) as potent PPAR ligands.

Dai and co-workers carried out the virtual screening and biological evaluation by
analyzing the change in gene profile in the humanized mice treated for the discovery of
a novel potent selective PPARα agonist. Virtual screening was performed on the crystal
structure of the PPARα and two different PDB IDs, 3ETI and 3SP6, were selected (Figure 13).
Molecular docking was also performed by using Glide 5.5 in Schrödinger2009. Based on
the study, compound 11 was found as a potent PPARα agonist where it regulated the
target genes responsible for functions such as fatty acid metabolism, activities related
to lipid-lowering, and inflammation. The structure of potent compound 11 is shown in
Figure 11. [87].

Figure 13. Workflow for the virtual screening of thiazolidinedione hybrids (11) as potent PPAR ligands.

Recently, Shakour et al. reported a new series of imidazolyl-methyl-1,2,4-thiazolidinediones
12 (a–m) along with in silico studies. Anti-hyperglycemic activity was carried out on 3T3
cells compared with a diabetic control group. Molecular docking was performed on the PPARγ receptor using PDB code 5Y2O with a considerable RMSD value (0.02). All synthesized compounds were docked with the help of MOE software. Based on the results of in silico studies, these synthesized compounds exhibited a good score ranging from $-10.55$ to $-12.69$ kcal/mol compared with pioglitazone ($-11.17$ kcal/mol). Compounds with methyl benzene substitution at $R_2$ position and fluoro at $R_1$ and ethyl substitution at $R_2$ showed cation-$\pi$ bond interaction and hydrogen bond with Arg288 and His449, respectively. Moreover, it was demonstrated that fluoro-substituted analog reduced 0.09-fold the expression gene of PPARγ in cultured adipocytes compared to the control group. The study described the SAR of imidazolyl-methyl-1,2,4-thiazolidinedione derivative as those compounds containing non-substituted S-benzyl ring were comparatively more active than imidazole containing S-methyl groups in decreasing blood glucose levels. Substitutions at the hydrophobic region affect the range of the PPARγ agonistic activity such as methyl group substitution at sulfur having more potency than non-substituted and fluorine substitution at sulfur. Moreover, the benzyl group replaced with the alkyl group at the hydrophobic region reduced the activity as follows: $\text{CH}_3\text{CH}_2 > \text{CH}_3\text{CH}_2\text{CH}_2 > \text{CH}_3$. As shown in (Figure 14). Although the literature has reported that PPARγ agonists are associated with an increase in body weight, interestingly in this study 12e did not induce variation in body weight as compared to pioglitazone [88].

![Structural activity relationship of thiazolidinedione hybrids (12) as potent PPAR ligands.](image)

### 5.2. Oxazole and Oxadiazole

Oxazole is a five-membered heterocyclic ring compound that contains oxygen and nitrogen at the first and third positions, respectively, and also one carbon situated between oxygen and nitrogen.

Oxadiazoles are five atoms containing heterocycles with two nitrogens and one oxygen. These atoms can have a different distribution in the ring to generate 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,5-oxadiazole, or 1,2,3-oxadiazole compounds. The background of oxazole-containing compounds suggests that they exhibit promising potential as PPAR ligands and also generate multiple side effects. In July 2013, aleglitazar was stopped in phase III due to heart failure, bone fractures, and gastrointestinal bleeding; muraglitazar was suspended in phase III due to risks regarding cardiovascular events; ragaglitazar was withdrawn during phase III because of tumors found in the urinary bladders of mice (Figure 15). The chemical and biological potential of oxazole analogs as PPAR ligands have been studied widely over the years.
For the treatment of various metabolic disorders, targeting PPARs is a well-established strategy, along with inhibiting Acetyl-CoA carboxylase (ACCs) gaining attention via the prevention of de novo lipogenesis. Therefore, Okazaki et al. synthesized a series of acetamides as ACC2 inhibitors along with the dual agonistic activity of PPARα/δ based on the structural or molecular similarity between these targets. These synthesized analogs were evaluated for their ACC-inhibitory activity and PPAR-agonistic activity which revealed analogs 13f exhibited significant activity. The structural activity relationship study displayed that analogs 13a, 13b, and 13d were active at a submicromolar concentration where 13b and 13d exhibited potency toward ACC2 and PPARα/δ. The phenoxy group (13c) containing PPAR-selective analogs (13f and 13a) also showed potency towards ACC inhibition. Acetamide and oxadiazole attached with the help of a methylene bridge were required for the PPARα- and ACC-inhibitory activity and the replacement of methylene with monomethyl methylene reduced the activity (Figure 16). The enantiomer of most potent analogs 13c and 13d were synthesized and the researcher found that the (S)-isomers of 13c and 13d displayed more ACC2-inhibitory activity than the (R)-isomer [89].

Figure 16. Structural activity relationship of oxadiazole hybrids (13) as potent PPAR ligands.
Arnesen and coworkers identified two oxohexadecenoic acids isolated as isomeric forms from the marine microalga *Chaetoceros kariannus*. The IUPAC names of these acids are oxohexadecenoic acid (7E)-9-oxohexadec-7-enoic (OFAI), and (10E)-9-oxohexadec-10-enoic acid (OFAII), and they exhibit the dual agonistic effect of PPARα/γ. Based on the potency of these acids towards PPARα/γ, the authors designed an analog of 3,5-disubstituted isoxazole fatty acid to find a selective agonist of PPARα. The molecular modeling of synthesized analog 6-(5-heptyl-1,2-oxazol-3-yl)hexanoic acid (ADAM) displayed binding with Tyr501, His447, and Ser317 amino acids required for PPARα activation. Moreover, they had trouble attaching with the polar part of amino acid residues in PPARγ that is responsible for the AF2 stabilization and co-activator recruitment (Figure 17). The pharmacological evaluation revealed that ADAM increases the expression of CPT1A in the primary mouse hepatocytes and Huh 7 cell line [90].

![Figure 17. Structural activity relationship of oxazole hybrids (14) as potent PPAR ligands.](image)

Jiang and their team reported a new series of isoxazole analogs as a selective agonist of PPARα/δ receptors (Figure 18). These synthesized analogs were screened using nuclear hormone assay (NHR assay) where GW7647, L-165,041, and troglitazone were used as a standard for PPAR α, δ, and γ, respectively, revealing that extension of the carbon chain diminishes activity. For example, chalcone replaced with isoxazole ring led to a loss of in vitro activity. Analogs 15a and 15b possessed 8–28 fold more PPARα agonistic activity along with good EC50 values of 8 nM and 27 nM, respectively. However, cyclization of the isoxazole and phenyl groups (polycyclic isoxazole) showed negligible potential in improvisation of activities. Among all of the synthesized compounds, analog 15a exhibited potency and selectivity towards PPARα/δ receptors with PPARα/δ/γ EC50, EC50 γ/α ratio, and EC50 γ/δ ratio value was 8/5/2939 nM, 367, 588, respectively, (Figure 19) [91].

![Figure 18. The rationale behind choosing oxazole hybrids as potent PPAR ligands.](image)
To discover new drug candidates for the treatment of type 2 diabetes that possess characteristics of both thiazolidinedione and fibrates, Kaur et al. designed new 1,2,4-oxadiazole-based trans-acrylic acid analogs as PPAR\(\alpha/\gamma\) dual agonists. These analogs had aryl or methylene linkers in between the lipophilic tail and pharmacophore head to serve as PPAR\(\alpha/\gamma\) dual agonists in silico studies of these analogs using autodock vina along with toxicity, and ADME properties were performed. The in-silico studies revealed that the effect of aryl substituents at positions five and six on the pharmacological profile of the partial PPAR\(\alpha/\gamma\) agonists with toxicity (Figure 20). The in vivo pharmacological screening of the diabetic rat model revealed that these analogs had significant efficacy with \(\alpha\) and \(\gamma\) receptors (Figure 20). The in vitro pharmacological screening of the diabetic rat model revealed that non-substituted and fluoro-substituted analogs exhibited a significant reduction in glucose levels in blood plasma and cholesterol levels compared to pioglitazone [92].

5.3. Benzoimidazole

At the fourth and fifth locations of the imidazole ring, the benzoimidazole molecule is formed by combining the benzene and imidazole ring systems. They have both acidic and basic characteristics. The NH group is both acidic and basic in this case. Obermoser et al. synthesized 5- or 6-substituted benzo[d]imidazoles as PPAR\(\gamma\) agonists. Therefore, the effect of aryl substituents at positions five and six on the pharmacological profile of the partial PPAR\(\gamma\) agonist 4'-((2-propyl-1H-benzo[d]imidazol-1-yl)methyl)-[1,1'-biphenyl]-2-carboxylic acid was examined. The substitution of para-\(\text{OCH}_3\)-phenyl enhanced potency...
and efficacy regardless of location. Due to the strong hydrophobic interactions with Phe363 in the ligand-binding region, both drugs are complete agonists. Partial agonist OH or Cl substitution at the phenyl ring resulted in higher efficacy than telmisartan or lead. Moreover, hydrogen or halogen bonds with Phe360 at helix 7 were postulated through molecular modeling (Figure 21). These interactions were thought to fix helix 7, and induced a partial agonist conformation of the protein receptor. The results of the luciferase transactivation correlate quite well with the theoretical concerns of those from a time-resolved fluorescence resonance energy test as well as those from a hPPARγ-LBD assay recruitment and corepressor recruitment (TR-FRET) experiment in which the coactivator (TRAP220, PGC-1a) and corepressor recruitment patterns of (NCoR1) release were studied [93].

**Figure 21.** Structural activity relationship of Benzimidazole hybrids (17 and 18) as potent PPAR ligands.

Shinozuka and co-workers synthesized novel PPARγ ligands to avoid adverse effects related to PPARγ ligands via inhibiting with helix 12 ligand-binding site. The interaction with helix 12 is responsible for the effects of the TZD group of drugs so a selective PPARγ agonist (DS-6930) was identified as a lead compound. Subsequently, in vivo efficacy, in vivo ADME properties, and in vitro activity were performed. GAL4-PPAR-LBD reporter gene assays were used to test PPARγ transcriptional activities on COS-7 cells compared with rosiglitazone. The benzene ring in 19a was responsible for the optimum yield of compound 19b which showed a maximum in vitro activity. The locations of halogen atoms determined therapeutic action wherein the analog 19b (3-Cl-4-F) had reduced activity. In ZDF rats, compound 19b had substantial PG lowering effects that were the same as rosiglitazone along with fewer PPARγ-related side effects, such as hemodilution. The binding mechanism of compound 19b with PPARγ was investigated and shown to have no contact of 19b on Tyr473 at helix 12. The lipophilic interactions of the 4-chloro-3-fluorophenoxy group also found that compound 19b produced minor hepatotoxicity during toxicological testing (Figure 22) [94].
Yamamoto et al. synthesized dibenzooxepine derivatives and pharmacological evaluations were performed. These compounds were tested using the following operation that includes Chimeric GAL4-PPARγ transactivation reporter assay (for PPARγ agonistic activity using transiently transfected HEK293EBNA cells), MKN45 cell aggregation assay, metabolic stability assay human liver microsomes, pharmacokinetic studies, xenograft study, RT-qPCR, and Hematocrit test. The summarized result of the biological evaluation showed that 20a possessed a high level of MKN-45 gastric cancer cell aggregation activity, which was a sign of PPAR-induced cancer differentiation; moreover, 20a was metabolically unstable during activation so Yamamoto et al. identified a metabolically weak area of the work and effectively discovered a 3-fluoro dibenzoxapine derivative (20b) with better metabolic stability. When compared to 20b, imidazo[1,2-a]pyridine derivative (20c) showed powerful MKN-45 gastric cancer cell aggregation activity as well as superior PK profiles. In mice, compound 20c inhibited the growth of the AsPC-1/AG1 pancreatic tumor (Figure 23). Furthermore, even with oral treatment of 200 mg/kg in healthy mice, the drop in hematocrit was tolerated [95].

Figure 22. Structural activity relationship of Benzimidazole hybrids (19) as potent PPAR ligands.

Figure 23. Structural activity relationship of Benzimidazole hybrids (20) as potent PPAR ligands.

An et al. discovered 1′-homologated adenosine derivatives 21a–21t as modulators of dual PPARγ/δ with a lack of binding towards adenosine receptors that was possible due to the 1′-homologation strategy. The biological evaluation of these synthesized compounds
was also performed to measure PPAR-binding profiles using the time-resolved fluorescence energy transfer (TR-FRET)-based nuclear receptor-binding assay effect on adiponectin biosynthesis using the adipogenesis model of hBM-MSCs and pharmacological profile of the dual PPARγ/δ modulator using a TR-FRET assay. The results of the assay showed that none of the compounds showed binding towards PPARs but analogs 21a, 21c, 21d, and 21n–21p (2-Cl derivative) showed promising binding towards the PPARγ/δ receptor. Especially, compound 21i–21l with 1-propynyl at the C2 substituent position lost the binding affinity to PPARδ, whereas the binding towards PPARγ was maintained except 4j, indicating that the PPARδ ligand-binding pocket (LBP) could not accommodate relatively bulkier substitutions on the C2 position. In hBM-MSCs, analogs 21a, 21c, 21d, 21i, 21k, 21l, 21n, 21o, and 21p significantly increased adiponectin production compared to the ID vehicle control during adipogenesis, but analogs 21e–21h and 21q–21t were inactive at PPARs. Analogos 21d and 21p emerged as the most powerful compounds in the 4′-thio- and 4′-oxonucleosides, respectively, whose adiponectin secretion-promoting PPAR/dual modulators may have therapeutic promise against cancer and metabolic illnesses, according to the biological screening (Figure 24) [96].

**Figure 24.** Structural activity relationship of Benzimidazole hybrids (21) as potent PPAR ligands.

Li and the group reported analogs of benzimidazole scaffold as a dual agonist of PPARα/δ for the treatment of non-alcoholic fatty liver disease. A cell-based assay was used for the evaluation of in vitro activities of analogs on PPARs. The results from the structural activity relationship of benzimidazole derivatives showed that compounds 22a and 22b exhibited a lower selectivity towards PPARs whereas they substituted additional CF3 and Cl in the benzimidazole motif. In particular, substituting chloride where there was methyl at the right benzene yielded compound 22c, which had stronger PPARα/δ activity and showed selectivity against PPARγ compared to the parent compound. Additionally, fluorine replacement greatly reduced agonistic activity on PPARα/δ/γ, demonstrating that hydrophobic interaction in this location is important for agonistic activity. Following that, the researcher looked at the significance of the carboxylic acid motif. Removing a methyl group from the acid moiety decreased PPARα/δ/γ activity, but increased selectivity against PPARγ. The docking study was also performed for the most promising candidate on PPARα/δ (PDB code: 3CI8 and 1GWX) using MOE. Compound 22c displayed significant fitting toward PPARα/δ binding pockets. The H-bonding interaction of compound 22c with His440, Tyr314, and Ser280 was due to the presence of carboxylic acid. Furthermore, the benzimidazole scaffold was placed into a PPARα hydrophobic pocket. The binding manner of compound 22c toward PPARδ was different from PPARα. The reason behind this was the rotation angle between benzimidazole and benzene present in compound 22c. The carboxylic acid of Compound 4 displayed three hydrogen bonds with His449, His449, Tyr473, and His323. Furthermore, the oxygen atom of compounds 22c and His449 showed hydrogen bonding interaction (Figure 25) [97].
Tyr473, and His323. Furthermore, the oxygen atom of compounds 22c and His449 showed hydrogen bonding interaction (Figure 25) [97].

![Figure 25](image)

**Figure 25.** Structural activity relationship of Benzimidazole hybrids (22) as potent PPAR ligands.

Since the use of PPAR γ full agonists in the treatment of type-2 diabetes mellitus has been linked to several negative side effects, the development of new alternative candidates as PPAR γ ligands has gotten a lot of attention in recent years. The old drug library was repurposed using a host-based medication repurposing technique using SB-VHTS. Herein Ma et al. identified fenticonazole (Figure 26), which was a CFDA-approved imidazole-containing antifungal drug, as a potent PPAR γ modulator. The pharmacological investigation of fenticonazole (23) showed such desired drug properties primarily by potently activating the expressions of adiponectin and GLUT4, inhibiting the expressions of TNF-α, IL-6, and IL-1, blocking PPAR Ser273 phosphorylation that leads to adipogenesis without mediation by CDK5 and inducing the expressions of key adipogenic genes CD36, LPL, AP2, FASN, C/EBP, and PPAR γ. Molecular docking validation was also performed at the active site of PPAR γ (PDB code: 6MS7) using the CDOCKER mode in Discovery Studio 3.1, resulting in a promising binding mode between the fenticonazole and ligand-binding site of PPAR γ, which included a hydrogen-bonding network between the oxygen, sulfur, and nitrogen atoms of fenticonazole and the PPAR γ residues Tyr327, Cys285, and Ser342 [98].

![Figure 26](image)

**Figure 26.** Structure of fenticonazole (23).

Recently, Bhalla et al. carried out a synthesis of a new series of C4-benzimidazolylxylophenyl-substituted trans-β-lactam analogs by changing various aliphatic and aromatic functionalities on imine and ketene viz. –Cl, –SC6H5, –SeC6H5, –OCH3, –CH2Cl(p), –CH2OCH3(p) and –CH2SeH5. The synthesized analogs were screened for molecular docking with PPAR using FLEXx software to determine their antidiabetic potential. When compared to the C3 functionality of the β-lactam unit, the docking analysis demonstrated that N1 functionality has a significant impact on the binding affinity of the molecules. Furthermore, β-lactam 24a with a paramethoxyphenyl group at N1 shows promise for future anti-diabetic drug development (Figure 27) [99].
5.4. Thiazole

Thiazole is a five-membered heterocyclic molecule with one sulfur and one pyridine-type nitrogen atom at position three of the cyclic ring structure. The thiazole core, found in the center unit of molecules, exhibits PPAR activity as well as other biological functions (Figure 28).

Piperine is a dietary alkaloid responsible for the pungency of black pepper (Family: Piperaceae) so Kharbanda et al. carried out the isolation of Piperine from Piper nigrum L. after hydrolysis and treated it under basic conditions to produce piperic acid, which served as a precursor in the synthesis of piperine analogs that contains benzothiazole moiety. The antidiabetic potential of all piperine-containing benzothiazole derivatives was screened using the OGT test, followed by an assessment of active derivatives using the STZ-induced diabetic model. Interestingly, synthesized piperine analogs exhibited promising anti-diabetic action as compared to rosiglitazone (standard). Furthermore, the agonistic effect of these active analogs towards PPARγ was tested, demonstrating their mode of action. Most of the synthesized piperine derivatives were active antidiabetic agents with compounds 25a and 25b showing maximum effect (Figure 29). These compounds showed their activity by increasing PPARγ gene expression. Additionally, compounds 25a and 25b did not promote excess body weight, which is normally observed in patients suffering from diabetes [100].

Figure 27. Structural activity relationship of Benzimidazole hybrids (24) as potent PPAR ligands.

Figure 28. Thiazole scaffold containing PPAR ligands present in the market.

Figure 29. Structural activity relationship of thiazole hybrids (25) as potent PPAR ligands.
Li et al. designed some hybrid compounds of AM-4668, CP-1 (FFA1 agonist), and GW501516 (selective PPARδ agonist) as dual agonists of FFA1 and PPARδ in the treatment of several metabolic disorders. The potential of hybrid analogs was screened on the FFA1 and PPARδ receptors using Chinese hamster ovary cells and Gal4 receptor cell-based assay, respectively. Analog 26 was identified as an orally bioavailable agonist of FFA1 and PPARδ with EC50 values of 68 nM and 102 nM, respectively, which also showed selectivity toward PPARs. Along with selectivity and potency, analog 26 displayed a good pharmacokinetic profile with good plasma exposure and decreased glucose level. The docking studies revealed that analog 26 showed H-bonding interaction with His449, Tyr473, and His323 with the help of carboxylic acid as a scaffold. Moreover, the hydrophobic pocket (Ile249, Leu255, and Ala258) of PPARδ was well attached to the trifluoromethyl group of left benzene (Figure 30) [101].

Ammazzalorso et al. designed a series of benzothiazole derivatives to antagonise the activation of PPARs. The activity of the synthesized analogs was investigated on the human PPARs through transactivation assay using Wy-14,643, L-165,041, and rosiglitazone as references for PPARα-δ-γ, respectively. The study revealed that analogs 27a–g exhibited inactivity for activation of PPARα-δ-γ. Thus, researchers investigated the antagonist potential of analogs via a competitive binding assay that resulted in analogs 27a–g selectively antagonized PPARα with a 22–57% range of inhibition. Analog 27b containing bulkier group at amide displayed better antagonistic activity toward PPARα and all synthesized analogs were comparatively inactive towards PPARδ-γ (Figure 31). The anti-proliferative action of synthesized analogs was explored using various tumor cells such as AsPC-1 and Capan-2 for pancreatic, HT-29 and SW480 for colorectal, along with PTJ64i and PTJ86i for paraganglioma cancer cell lines. With regard to referencing PPARα agonist (GW6471), analog 27b reduced the PTJ64i and PTJ86i cell viability (inhibition rate >90%) and also exhibited viability in pancreatic and colorectal cancer cells (up to 68–75%). Therefore, analog 27b was the most promising candidate as a PPARα antagonist [102].

Enhancing insulin sensitivity via targeting PPARγ and β-catenin is one of the attractive pathways for the treatment of T2DM; therefore, Mourad et al. synthesized analogs of α-phthalimido-o-toluoyl2-aminothiazole hybrids and carried out the anti-diabetic activity.

**Figure 30.** Structural activity relationship of thiazole hybrids (26) as potent PPAR ligands.

| R          | Phenyl group at R had been found to be the most promising candidate as a PPARα antagonist |
|------------|---------------------------------------------------------------------------------------|
| a = C6H5  | Bulkier group at amide displayed better antagonistic activity towards PPARαs and all synthesized analogues were fully inactive towards PPARδ/γ |
| b = Ph    |                                                                      |
| c = pNHCOCH3Ph |                                                                  |
| d = Bn   |                                                                      |
| e = CH(CH3)2Ph |                                                                  |
| f = (CH3)2Ph |                                                                      |
| g = (CH3)3Ph |                                                                      |

**Figure 31.** Structural activity relationship of thiazole hybrids (27) as potent PPAR ligands.
Three of the synthesized analogs modulated PPARγ gene expression that displayed partial agonistic activity towards PPARγ. Upon treatment of compounds with 3T3-L1, the cells displayed induction PPARγ2 mRNA level. Moreover, compounds 28c, 28g, and 28a showed better PPARγ2 mRNA levels compared to the reference drug. Therefore, 28c, 28g, and 28a also displayed 4–5 fold more PPARγ activity than rosiglitazone. The structural activity relationship studies revealed that substitution at the aryl thiazole ring showed variance in the biological potential of synthesized molecules. Accordingly, methoxyl (28c) and hydroxyl (28g) analogs exhibited partial PPARγ potency due to the electron density of the group (Figure 32). Intriguingly, the partial PPARγ activity along with anti-diabetic action exhibited by p-halogenated phenyl-substituted thiazole 28f was higher than the corresponding chloro analog (28d). The docking study revealed that synthesized analogs had distinctive attachments at the LBD of PPARγ and generated H-bonding interaction with Ser342 amino acid residue [103].

| R1 | R2 | R3 | R4 | R5 |
|----|----|----|----|----|
| a  | H  | H  | H  | H  |
| b  | H  | CH3| H  | H  |
| c  | H  | OCH3|H | H  |
| d  | H  | Cl | H  | H  |
| e  | H  | NO2| H  | H  |
| f  | H  | Br | H  | H  |
| g  | H  | H  | OH | H  |
| h  | H  | OCH3|OCH3| H  |

![Figure 32. Structural activity relationship of Thiazole hybrids (28) as potent PPAR ligands.](image)

Recently, Patchipala et al. reported some new analogs of the thiazole-pyridine scaffold by condensation of 4,4,7,7-tetra-methyl-4,5,6,7-tetrahydrobenzo[d]thiazol-2-amine with 6-chloronicotinate and evaluated for their anti-diabetic activity by in vivo housing Swiss albino mice. The in silico screening of these analogs was performed with human PPARγ protein complexed with RXR alpha Nuclear Receptor (PDB ID: 3DZY). All synthesized compounds showed a reduction in glucose level when compared with glibenclamide where fluoro and nitro (29b) containing analog had the highest activity. Additionally, the in silico binding studies revealed that fluorobenzaldehyde with methoxy (29b) and nitro (29c) displayed impressive interaction with human PPARγ complexed with RXR alpha Nuclear Receptor in comparison to Rosiglitazone (Figure 33) [104].

![Figure 33. Structural activity relationship of thiazole hybrids (29) as potent PPAR ligands.](image)
5.5. Indole

The aromatic heterocyclic organic compound indole is a six-membered benzene ring fused to a five-membered pyrrole ring, giving it a bicyclic structure. In 2017, Fu et al. reported a new series of pyrazole-containing indolizine (30a–e) and screened for anti-inflammatory activities for the treatment of Crohn’s disease. The pharmacological evaluation performed using LPS-stimulated peritoneal macrophages revealed that analog 30d displayed a reduction in secretion of TNF-α which was the outcome of the activation of the macrophages. Interestingly, the western blotting, Luciferase assay, and immunofluorescence showed positive results regarding the potency of analog 30d and also helped in the mechanism of anti-mucosal inflammatory potential. The mechanism underlying that, analog 30d, activates the PPARγ receptor that leads to suppression of NK-κB activation (60 μm), and the result was similar to the 5-ASA (5-Aminosalicylic acid) (Figure 34) [105].

![Figure 34. Structural activity relationship of indol hybrids (30) as potent PPAR ligands.](image)

The following year, Boubia et al. reported a series of indol sulphonamide analogs to find suitable candidates for the activation of PPARα/δ/γ. Moreover, compounds were tested for human PPARs in vitro study utilizing cell-based Gal-4 transactivation assays. The structures of the proposed analogs contain three pharmacophoric features such as indole, chain linker, and aryl sulphonamide. The SAR study revealed that chain linker with a three-carbon atom chain exhibited an optimum PPARα/δ/γ profile at potency and efficacy level. (31a, Emax = 50%). Therefore, substitutions at the fifth position of indole were screened and mainly hydrophobic groups such as 5-Chloro, 5-trifluoromethyl, and 5-methyl showed good activity towards PAN PPARs, whereas 6-position and 4-position were shown to be adverse and fully unbalanced for PPAR activity. Interestingly, using electron-donating and electron-withdrawing groups, the para and meta locations of the phenyl of aryl sulphonamide resulted in active compounds that inclined toward PPARγ activity (Figure 35). Finally, lanifibranor showed strong anti-fibrotic action in mice using the liver fibrosis model, as well as outstanding anti-hyperglycemic and hypolipidemic potential [106].
El-Zahabi and co-workers reported some analogs of phthalimide-sulfonylurea hybrids that act as PPARγ ligands. The biological evaluation of hybrid analogs was carried out through in vivo anti-hyperglycaemic activity in streptozotocin-induced hyperglycaemic rats using glibenclamide (sulfonylurea drug) and an oral glucose tolerance test (OGTT) that showed compounds 32c, 32d, 32g, 32h, 32j, and 32k to exhibit a potential 24.43 to 21.43% reduction in blood glucose level in comparison to Glibenclamide (29.3%). However, the activity was less than the reference drug. On the other hand, the result of the OGTT revealed promising PPARγ agonistic activity via increasing glucose utilization and insulin sensitization. In silico studies were also carried out using four different methods including molecular docking, pharmacophore screening, QSAR, and ADMET. The docking studies were performed on a PPARδ crystallographic structure (PDB ID: 1FM6) using MOE software. Impressive free energies against PPARγ were found in compounds 32c, 32d, 32j, and 32m. When compared to the generated pharmacophore model, compounds 32c, 32j, 32k, 32l, and 32n displayed the best match values (Figure 36). The QSAR studies highlighted that these compounds possessed significant binding affinities towards PPARγ and insulin secretion [107].
5.6. Furan

Furan is a heterocyclic organic molecule made up of a five-membered aromatic ring containing four carbon atoms and one oxygen atom. Various furan derivatives as PPAR ligands have been thoroughly investigated in terms of chemistry and biological activity over the years.

Li et al. reported a series of hybrid compounds of PPARs and FFA1 agonists to elucidate the dual agonistic activity for the treatment of type 2 diabetes. The PPAR agonistic activity of these hybrid compounds was tested by Gal4 receptor cell-based assay using GW7647, Rosiglitazone, and GW0742 as the positive control. Hybrid compound 33a increased the PPARγ agonistic activity and led to a 20-fold decrease in PPARδ agonistic activity. The length of the linker also affected the potency, wherein shortening the linker decreased the potency of PPARγ and PPARδ. Compounds 33b and 33c, which are 2-position substitution derivatives, exhibited impressive PPARγ and PPARδ agonistic activity compared with the parent compound 33a. Various substitutions were carried out at 3-position for FFA1 and PPARs. The agonistic activity of 3-Cl (33d) > 3-Me (33e) > 3-tBu (33f) > 3-Ph (33a) for PPAR suggested that the steric effect at the 3-position may affect the strength of the receptor (Figure 37). Due to the small ligand-binding pocket at this location, PPAR has a low affinity for ligands. Especially, the 4-position phenyl-substituted derivative 33h showed greater agonistic activity on the PPARα in comparison to other analogs. Induced-fit docking studies were also performed on the FFA1, PPARγ, and PPARδ by using PDB codes: 4PHU, 2Q8S, and 1GWX, respectively. The resulting compound 33i showed multiple types of interaction with amino acid residues. Hydrogen-bonding interactions were displayed by the acidic moiety and carboxylic acid of compound 33i compared with the parent compound 33a, which are 2-position substitution derivatives. These synthesized candidates were tested for the agonistic activity of human PPARα, δ, and γ by in vitro GAL4-PPAR transactivation assay on transfected COS7 cells whereas GW7647, GW501516, and rosiglitazone were used as reference. The results of the in vitro assay found that compound 34a displayed 16.2-fold and 8.4-fold more PPARα/δ agonistic activity than PPARγ and also exhibited better agonistic activity (Figure 38). Molecular docking was also performed in Schrödinger 2009 using PDB ID: 4CH4 (PPARα) and 3SP9 (PPARδ). Compound 34a and GFT505 were docked, wherein compound 34a displayed hydrogen bonding with Tyr314, His 440, Ser 280, and Tyr464 residues of PPARα and His 287, Thr252, Thr253, His 413, and Tyr437 residues of PPARδ [109].
Liu et al. synthesized a series of novel dual PPAR-α/δ agonists to target PPARs. The in vitro evaluation revealed that the compound substituted with trifluoro carbon possessed high potency toward PPAR-α/δ (0.26 ± 0.08 μM 0.50 ± 0.10 μM) and higher selectivity against PPARγ (−4.22 ± 0.18 μM) than that of GFT505 (Figure 39). The molecular docking studies also showed considerable binding affinity towards LBD of PPARα/δ compared to GFT505 that displayed H-bond interactions between the ligand and important amino acids such as Tyr314, His 440, Ser 280, and Tyr464. Moreover, H-bond interactions were displayed between the ligand and His 287, His 413, Thr252, Thr437, and Tyr253 of PPAR δ [110].

Figure 38. Structural activity relationship of Furan hybrids (34) as potent PPAR ligands.

Figure 39. Structural activity relationship of Furan hybrids (35) as potent PPAR ligands.

5.7. Benzopyran

Benzopyran are polycyclic molecules in which a benzene ring and pyran ring are fused with various levels of saturation. The name benzopyran is widely used to refer to polycycles fused with a pyran ring (chromenes) but also applies to heterocycles bearing a dihydropyran (chromans). A lot of benzopyrans have been explored for their potential for PPARs.

Niu et al. reported a series of coumarin–chalcone fibrates that exert an agonistic effect on PPARα/γ along with antioxidant potential. The pharmacological evaluation of the synthesized molecule was carried out through transactivation assay using firefly luciferase reporter gene technology in HERK293 cells. Fenofibrate (PPARα) and rosiglitazone (PPARγ) were used as positive control. Among these synthesized analogs 36a, 36b (most potent), and 36c exhibited significant agonistic potential towards PPARα with EC_{50} 12.69 μM, −6.99 μM (4.3-fold more potent than Fenofibrate), and −11.03 μM, respectively. In addition, analogs, 36a, 36b, and 36c also displayed PPARγ agonistic activities with EC_{50} -5.19 μM, −0.91 μM, and −11.03 μM, respectively. The SAR study showed that alteration at C6′
position with a nitro group (electron-withdrawing in nature) raises the agonistic efficacy towards PPARα/γ (Figure 40). Moreover, benzopyran moiety with a double bond was required for the PPARα/γ potential [111].

**Figure 40.** Structural activity relationship of coumarin–chalcone hybrids (36) as potent PPAR ligands.

Bermejo and their team reported prenylated benzopyrans polycerasoidol (37a) and polycerasoidin (37b) and their semisynthetic analogs as potential PPARα/γ agonists. These nine analogs were screened for PPARα/β/γ activities using a transactivation assay that revealed polycerasoidol and its analog (37c) exhibited agonistic activity towards PPARγ and the % value was 95% and 86%, respectively. Interestingly, analog 37d displayed maximum activity towards hPPARα and γ with % values of 191% and 88%, respectively (Figure 41). The importance of these groups for optimum ligand binding to the PPARx (PDB code: 4BcR) and PPARγ (PDB code: 4eMA) domains was discovered by molecular modeling. His323, Tyr327, His449, and Tyr473 form significant H-bond interactions with Polycerasoidol. At the C-9′ position of 1, the carboxylic acid group was found to be the preferred PPARγ receptor binding site and served as an anchoring point in docking research and MD simulations. Furthermore, polycerasoidol (37a) inhibited mononuclear leukocyte adherence to the defective endothelium in a concentration-dependent manner through RXR/PPARγ interactions, resulting in a powerful anti-inflammatory impact [112].

5,7-dihydroxy-8-(1-(4-hydroxy-3-methoxyphenyl)allyl)-2-phenyl-4H-chromen-4-one (38) was found to be a lead compound for adiponectin secretion-inducing activity isolated from the natural honeybee propolis. Ahn et al. designed and synthesized 38 and its analogs along with the screening of activity towards PPARs. According to the target identification investigation, analogs 38a and 38b interacted directly with PPARα/β/γ. Overexpression of HO-1 mediated by compound 38a is most likely linked to PPAR pan-modulatory potential, accepting the fact that PPAR agonists can kill cancerous cells. The binding processes of chromenone analogs showed similarity with PPARα/γ partial agonists; according to a docking study between 38b and the PPAR-LBD, they connect with the hydrophobic LBD of PPARs. Analog 38b did not affect WY14643 or pioglitazone’s ability to induce adiponectin secretion. Compound 38b may have a different effect on adiponectin secretion than a specific PPAR partial agonist (Figure 42). Furthermore, 38b demonstrated distinct cellular phenotypic consequences in the transcriptional control of lipid metabolic enzymes, separating it from selective PPAR mono-agonists [113].
2-Prenylated benzopyrans (PB) address a category of natural and synthetic agents displaying a broad scope of potential. Polycerasoidol is a characteristic PB found in *Polyalthia cerasoides* (Annonaceae) from their stem bark that shows both PPARα and PPARγ agonistic potential. Recently, in 2022, Vila et al. designed three series of prenylated benzopyrans containing multiple motifs such as polycerasoidol and trans-δ-tocotrienolic acid along with isoprenoid units in the hydrocarbon side chain at the 2-position of the chroman-6-ol motif and carried out their hPPAR transactivation activity. The pharmacological evaluation revealed that the seven-carbon side-chain analogs (α1–α4) showed selectivity for hPPARα, while the nine-carbon side-chain analogs (β1–β4) did the same for hPPARγ. The side chain extension to 11 or 13 carbons (γ1–γ4) brought about weak activation of PPARα/γ. Hence, 2-prenylated benzopyrans of the seven- and nine-carbon side chain (polycerasoidol analogs) are great lead compounds for creating valuable contenders to forestall cardiovascular illnesses related to metabolic disorders (Figure 43) [114].

Figure 41. Structural activity relationship of benzopyran hybrids (37) as potent PPAR ligands.

Figure 42. Structural activity relationship of chromenone hybrids (38) as potent PPAR ligands.
Bavachinin (7-O-Methylbavachinin) is a novel natural pan-PPAR agonist from the fruit of the traditional Chinese glucose-lowering herb malaytea scurfpea. It shows stronger activities with PPAR-γ than with PPAR-α and PPAR-β/δ (EC50 = −0.74 µmol/L, −4.00 µmol/L, and −8.07 µmol/L in 293T cells, respectively). Many derivatives have been synthesized from these natural compounds. Du et al. carried out the synthesis of a similar type of modification in bavachinin derivatives for PPARγ agonist candidates. In total, 30 molecules, including flavanone and flavone analogs, were tested by reporter gene assays for PPARγ agonistic potency. From the pharmacological results, the SAR study revealed that when an isopentenyl group and methoxy group attached at the C-6 and C-7 positions, respectively, they showed better PPARγ agonist activity in the A-ring. At the C-6 position, the findings also imply that an aliphatic chain is necessary for PPAR agonistic potential. Altering the hydroxyl group at C-4’ to an aromatic ester group improves PPARγ agonistic potential, but changing the hydroxyl group to an aliphatic ester or ether lowers it in the B-ring. The phenyl ring structure is required for PPARγ agonistic potential, and substituting thiazole, imidazole, or pyridine rings reduces it significantly. Alteration of a single bond at C-2 and C-3 position to double bond improved the PPARγ agonist activity in the ring-C (Figure 44) [115].

Yi et al. designed and synthesized derivatives of bavachinin with variation at ring A, ring B, and ring C and tested for pan-PPAR agonistic activity using reporter gene assays. The order in which the N element appears is important for the pan-PPAR agonist activity; N-substituted analogs at the C3 and Cl, 3 positions (of the C-ring) lowered pan-PPAR agonistic potential, and Cl position N-substitute derivative 41 increased the activity. The findings imply that adding N-atom to the Cl did not affect BVC’s pan-PPAR agonistic action (Figure 45). When compared to bavachinin, Analog 41 is a powerful pan-PPAR agonist.
with significantly higher PPAR $\alpha/\beta$ agonistic potential and similar PPAR-$\gamma$ agonistic potential. [116].

![Chemical structure of 2-formyl-komarovicine (42)](image)

**Figure 45.** Structural activity relationship of bavachinin hybrids (41) as potent PPAR ligands.

### 5.9. Miscellaneous

Adiponectin is a key adipocytokine produced by adipocytes in mammals. Low adiponectin expression has been linked to a variety of human metabolic disorders and malignancies, Ahn et al. synthesized 2-formyl-komarovicine (Figure 46) and evaluated adiponectin secretion by performing the phenotypic assay on human bone marrow–mesenchymal stem cells (hBM-MSCs). The synthetic 2-formyl-komarovicine induced the production of adiponectin and displayed binding towards PPAR$\gamma$ in a concentration-dependent manner. The molecular docking studies revealed that 2-formyl-komarovicine connected with the PPAR$\gamma$ ligand-binding domain’s hydrophobic pocket, but had an inability to interact and stabilize helix H12 [117].

![Chemical structure of 2-formyl-komarovicine (42)](image)

**Figure 46.** Chemical structure of 2-formyl-komarovicine (42).

Dixit et al. designed Y-shaped barbituric acid (BA) derivatives via molecular docking and then synthesized fourteen of them using the OH-protection-deprotection technique for PPAR$\gamma$ activation. The time-resolved FRET technique was used for the analysis of the competitive binding of synthesized molecules towards PPAR$\gamma$. The binding affinity of symmetrically substituted derivatives was higher than that of unsymmetrically substituted derivatives. The binding affinities of nitrobenzyl (43b) and cyanophenyl (43a)-substituted derivatives were found to have better activity with $-10.1$ $\mu$M and $-6.5$ $\mu$M, respectively, while monoacetate (43c) and diacetate (43d) derivatives were devoid of activity (Figure 47).
The in silico studies revealed that synthesized analogs showed H-binding interaction with the H-3 helix (amino acid residues = Ser289, His449, His323) and the H-12 helix (Tyr473). When synthesized analogs were substituted with the hydrophobic group, they displayed a score similar to the rosiglitazone. The most important keynote was BA derivatives along with substitution with weakly polar side chains achieve the requisite good level of PPARγ binding affinities [118].

2,4-dichloro-N-(3,5-dichloro-4-(quinoline-3-yloxy)phenyl)benzenesulfonamide (INT131) had great potential toward PPARγ receptors, with a Ki of 10 nM; therefore, Frkic et al. designed and synthesized analogs of the INT131 utilizing chemical alteration of the A ring. This SAR investigation determined the impact of A ring substituents, their positions on the A ring, and various rings at position A on transcriptional activity, as well as how these substituents affect the compound 44 scaffold’s interaction with the PPARγ receptor. Seven ligands with improved PPARγ potency were discovered in the SAR of compound 44 analogs. They differed from 44 in that they had bulky replacements at position 2 of benzene A, which facilitate better lock-and-key fitting in the PPARγ LBD. The SAR data further highlighted the relevance of a sulfonamide linker in position A, as well as a substituted, 6-membered benzyl ring (Figure 48) [119].

Tetrazanbigen is a sterol isoquinoline analog that exhibits potential toward human cancer cell lines through induction of lipoapoptosis, but this compound has some disadvantages such as poor water solubility and low efficiency. Therefore, Gan et al. synthesized a series of Tetrazanbigen analogs intending to improve water solubility and anti-cancer activities via acting on PPARγ. The CCK-8 assay revealed that analog 45a showed promis-
ing inhibition of HepG2 and A549 cell growth with IC$_{50}$ values of -0.54 and -0.47 µM, respectively. Furthermore, the in vitro antiproliferative activity was performed by using an in vivo xenograft model in which analog 45a exhibited a reduction of tumor growth at a dose of 10 mg/kg. Moreover, the water solubility of the analog 45a was found to be 31.4 mg/mL, which was 1000-fold higher than that of Tetrazanbigen (4 µg/mL) (Figure 49) [120].

**Figure 49.** Structural activity relationship of isoquinoline hybrids (45) as potent PPAR ligands.

Using a mammalian one-hybrid experiment, Zhao et al. extracted and found the naturally occurring picrasidine N from *Picrasma quassioides* (family: Simaroubaceae) as an agonist of PPARβ/δ and described from a library of plant extracts. The biological evaluation proved that compound 46 exhibited activity towards PPARβ/δ. Furthermore, analog 46 increased PPARβ/δ transcriptional activity in a PPRE-driven luciferase reporter gene test. Furthermore, analog 46 preferentially increased ANGPTL4 mRNA expression. This is in contrast to those known as PPARβ/δ agonists (Figure 50), which have been shown to stimulate the expression of not only ANGPTL4 but also additional PPARβ/δ target genes such as PDK4, ADRP, and CPT-1 [121].

**Figure 50.** Structural activity relationship of picrasidine N hybrids (46) as potent PPAR ligands.
Ibrahim et al. designed quinazoline-4(3H)-one sulfonylurea hybrids that exert dual agonistic activity of PPARγ and SUR. The biological evaluation of synthesized derivatives was screened for in vivo anti-hyperglycemic activity in streptozotocin-induced hyperglycemic rats where glibenclamide and rosiglitazone were used as a reference drug. In vitro PPARγ-ligand binding and insulin assay were also examined. Based on the biological evaluation, compound 47d reduced the 46.42% blood glucose level and become the most potent candidate. Beside compound 47a, 47c, 47f, 48f, and 49e possessed the highest affinities with IC50 values -0.371, -0.350, -0.369, -0.408, and -0.353 μM, respectively. The most potent insulin-secreting activities were exhibited by compounds 47a, 47c, 47f, 48d and 49a with EC50 values of -0.97, -1.01, and -1.15 μM, respectively. Docking and pharmacophore studies revealed that compounds 47d, 47f, 48f, and 48g had significant dock scores and PPARγ binding affinity. Compounds 47a, 47c, 47f, 48d, and 48i had the best binding values to the pharmacophore model [122].

![Figure 51](image1.png)

**Figure 51.** Structural activity relationship of quinazoline hybrids (47) as potent PPAR ligands.

The activities of compounds with para-methoxy substitution were better than that of para-methyl substituted analogs, indicating that grafting a methoxy group, at the 4-positions is beneficial for the activity.

| R     | R1   |
|-------|------|
| a     | CH3  |
| b     | CH3  |
| c     | CH3  |
| d     | CH3  |
| e     | CH3  |
| f     | CH3  |

![Figure 52](image2.png)

**Figure 52.** Structural activity relationship of quinazoline hybrids (48) as potent PPAR ligands.

The % reduction in blood glucose levels incorporating cyclohexyl moiety were found to be higher than that of corresponding members incorporating n-butyl group.

| R     | R1_1 | X     |
|-------|------|-------|
| a     | CH3  | Cyclohexyl |
| b     | CH3  | Phenyl  |
| c     | CH3  | Butyl   |
| d     | CH3  | Cyclohexyl |
| e     | CH3  | Phenyl  |
| f     | CH3  | Butyl   |
| g     | CH3  | Cyclohexyl |
| h     | CH3  | Phenyl  |
| i     | CH3  | Butyl   |

The same group of researchers reported quinolaxine derivatives exhibiting dual agonistic activity of PPARγ and SUR. Based on the biological evaluation, compound 49a reduced the 50.58% blood glucose level and became the most potent candidate. Besides, compound 49e was reduced by 43.84%. The results of the PPARγ binding affinity test using...
Fluorescence Polarization Assay revealed that compounds 49a, 49b, 49d, and 49e showed higher affinities with IC$_{50}$ values of -0.482, -0.491, -0.350, and -0.369 µM, respectively. The most potent insulin-secreting activities were exhibited by 49a and 49b with EC$_{50}$ values of -0.92 and -0.98 µM, respectively. Docking tests were carried out along with pharmacophore investigations to support the biological activity of the synthesized compounds against SURs (Figure 53). The results of molecular modeling studies revealed that the majority of the produced compounds had a significant affinity for PPAR and SUR [132].

**Figure 53.** Structural activity relationship of quinoxaline hybrids (49) as potent PPAR ligands.

LY518674 is a potent agonist of PPARγ that has already progressed to clinical trial phases, so based on the pharmacophore of LY518674, Yu et al. reported a novel DY series of PPARα modulators for NAFLD treatment. The pharmacological evaluation of synthesized analogs revealed that analogs exhibited promising activity at the PPARα. Furthermore, the analogs were inactive towards PPARα and PPARδ at up to 10–30 µM and displayed selectivity towards PPARα (potency EC$_{50}$ = -0.85 – -12 nM). The docking study also supported the results of the pharmacological evaluation and displayed major interaction of 50a with PPARα (PDB id 1k7l), such as 4-methoxybenzil tail at R1 attached with lipophilic region B, and showed hydrophobic interaction with the amino acid residues (I272/V332/I339/L344). At R$_2$, the site c region showed π-stacking interaction of 4-methyl benzyl moiety with F273 and F351 at a distance of 6.3 Å between ring centers (Figure 54) [123].

Mandal et al. designed analogs of rhodanine with phenyl replacement at the fifth place of the ring to find new ligands for the PPAR-γ receptor for conceivable antihyperglycemic potential and carried out their molecular modeling against PPAR-γ (PDB ID: 2PRG). All analogs were tested for in vitro glucose uptake assay. The analogs containing p-methoxy benzyl (51a and 51b) ring showed impressive glucose uptake action. Therefore, both of the analogs were screened for in vivo antihyperglycemic study which resulted in a more impressive antihyperglycemic potential than pioglitazone. The SAR studies revealed that compounds with an o-Tolyl (51a$_{1-5}$) at the third position demonstrated moderate to high glucose uptake activity in vivo evaluation, with 37.05 ± 0.44 being the most active value compared to pioglitazone (39.18 ± 0.63). The isopropyl (51b$_{1-5}$) at the third position in the
‘B’ family of compounds demonstrated moderate activity. The presence of an unsubstituted phenyl group at the third position of the rhodanine ring in the ‘C’ series showed low active molecules, probably due to the lack of strong intermolecular interaction revealed by docking analysis. The p-methoxy benzyl group in the fifth position of the rhodanine ring showed higher potency due to its favorable interaction with protein amino acids, as evidenced by molecular docking, implying that an electron-donating group at the para position of the benzyl substitution may increase activity, whereas an electron negative group at the ortho position of the benzyl substitution may result in moderate activity (Figure 55). Thus, the rhodanine ring is required for glucose absorption activity; nevertheless, electron-donating substitutions at the third and fifth positions of the rhodanine nucleus may yield a contender [124].

Figure 54. Structural activity relationship of triazole hybrids (50) as potent PPAR ligands.

Figure 55. Structural activity relationship of rhodanine hybrids (51) as potent PPAR ligands.

TNBG-5602 (52) is a recently designed compound containing an isoquinoline motif. Thus, Hu et al. showed the anticancer impact of 52 using in vitro and in vivo models and examined its conceivable anticancer potential. The antiproliferation impact of 52 in vitro was assessed in human liver disease cell line QGY-7701. The antiproliferation action of
52 in vivo was surveyed in a xenograft model. The outcome of the CCK-8 test revealed that 52 can successfully restrain the expansion of liver disease cells in vitro. In a xenograft liver disease model, 52 could astoundingly hinder the development of growths. During in vitro and in vivo examinations, the scientist noticed that 52 initiated the lipid collection in malignant growth cells and tissues. Moreover, the review demonstrated that the anticancer impact of 52 might be applied through enacting PPARγ and downregulating multiplying cell atomic antigens (PCNA). They found that 52 can expand the outflow of PPARγ at the mRNA and protein levels in vitro and in vivo. Further investigation discovered that a PPARγ agonist (RSG) can upgrade the lipid aggregation of 52, while a PPARγ inhibitor (T0070907) can switch the lipid-amassing of 52. Also, RSG can significantly improve the antiproliferation of 52, while T0070907 can to some extent turn around the antiproliferation impact of 52 in QGY-7701 cells. Moreover, RSG can improve the downregulation of PCNA of 52, while T0070907 can invert the downregulation of PCNA of 52 (Figure 56). This information recommended that 52 instigated lipid accumulation and antiproliferation in liver disease cells by expanding the declaration of PPARγ to diminish the expression of PCNA [125].

Xie et al. designed 1,3-benzodioxole-based fibrate scaffold analogs and screened them using hyperlipidemia mice. The pharmacological evaluation revealed that analogs with longer alkyl chain length showed more impressive activity against hyperlipidemia than fenofibrate (FF). They also exhibited a promising reduction of plasma lipids, such as total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterin (LDL-C). The affinity activity of the protein PPAR (PDB ID: 1K7L) was studied using the docking approach. The PPARα binding activity of aroxyalkyl carboxylic acids was shown to be worse than that of carboxylic esters in these molecular docking investigations. Sesamol esters have a higher PPARα affinity than ethanol esters among esters. Sesamol has a synergistic role, and its PPARα affinity activity was greatly increased following esterification with carboxylic acid, despite its low PPARα affinity activity. They also discovered that the affinity of these analogs for PPARα was related to the length of the alkyl chain (n) between the aroxy and carbonyl groups. Affinity increases with the length of the alkyl chain (Figure 57). Compound 53α had the best affinity activity, with a score of -6.3502 kJ/molK, higher than the FF (-5.7012 kJ/molK), and appears to have an impressive affinity for the PPARα. In the Triton WR 1339 hyperlipidemic mice model, the results of docking were similar to the results of pharmacological evaluation [126].
Pharmacological evaluation of ZLY06 revealed a significant reduction in glucose levels in HF/STZ and ob/ob mice. It also promoted glucolipid metabolism without gaining weight, fatty acid oxidation, and inhibition of hepatic lipid accumulation [127].

Li et al. identified a partial agonist of dual PPARα/δ by using a conformational restriction strategy. The discovery of a PPARα/δ partial agonist (ZLY06 (54a)) was the resulting structure of cyclization of GFT505. The SAR studies displayed that the chalcone part of the GFT505 replaced with aurone scaffold reduced the PPARα potency but induced potency towards PPARγ. Ethyoxyl compound exhibited potency towards PPARδ/γ but reduced the PPARα activity. Herein, the alkoxy series were selected for further substitution that revealed straight-chain alkanes had more active than branched alkanes. Therefore, ZLY06 displayed best activities towards PPARδ/γ and selectivity towards PPARα. Interestingly, phenoxy acetic acid-containing analogs had low agonistic activity towards PPARs but displayed the contribution of methyl and phenoxy acetic acid moiety (Figure 58). The pharmacological evaluation of ZLY06 revealed a significant reduction in glucose levels in HF/STZ and ob/ob mice. It also promoted glucolipid metabolism without gaining weight, fatty acid oxidation, and inhibition of hepatic lipid accumulation [127].

Figure 57. Structural activity relationship of 1,3-benzodioxole hybrids as potent PPAR ligands.

Figure 58. Structural activity relationship of GFT505 hybrids as potent PPAR ligands.

6. Conclusions

The involvement of PPARs with multiple pathophysiological conditions has been categorically documented in the last two decades. Scientists have attempted to target
these receptors with a variety of heterocyclic compounds in a bid to come up with novel medicaments for disease conditions. This article has successfully compiled the published reports on the use of various heterocycles over the last few years (2016–2022) where significant advancements have been made towards the development of PPAR ligands as potential medication focuses with a promising therapeutic profile. An attempt has been made to briefly portray PPARs receptors, their physiological role, and market drug use, along with clinical information. Further, the fusion of different heterocyclic cores to bring about improvement in terms of their efficacy and interactions has also been highlighted. In addition to this, current advancements in the field of the medicinal chemistry of PPAR ligands, with the latest reference to structural alteration on heterocyclic cores, as well as the mechanism of action, SAR, and in silico analysis, have also been discussed. Overall, this article should provide an excellent commentary for prospective researchers in the field.

7. Future Perspectives

PPARs are still being investigated in terms of their potential in metabolic diseases, despite the controversy surrounding the clinical activities of PPAR agonists. It is important to note that those SAR investigations demonstrated that PPAR ligands play a role in T2DM, cancer, inflammation, and/or non-alcoholic fatty liver disease in a largely consistent manner. Numerous investigations using mouse models and human surrogate studies have been demonstrated. Each PPAR agonist must be judged on its own merits because of the variety of SAR actions and toxicity. As mentioned in this review, the activation of the PPAR family of genes is complex and unexpected. It may be the balance of stimulation of α, β, γ, or individuals that determines efficacy and toxicity, including late toxicity. There is no “class effect” within the PPAR family; therefore, each agent needs to be viewed as an individual. Each agent in this class must undergo an individual evaluation, including clinical outcome studies, as required by the FDA. The activation or inhibition of PPARs may have a variety of negative impacts since they regulate a wide range of cell processes in different organs. Indeed, with different PPAR agonists, significant therapeutic, as well as toxicological profile variations, have been noted, posing difficult problems for the field’s researchers. The area is primed for a renewed surge in interest and effort to develop novel PPAR-centered therapeutics for numerous diseases with the arrival of the relatively recent discoveries of PPAR receptor allostery and allosteric ligands. These discoveries are anticipated to result in the creation of a new class of PPAR modulators called allosteric ligands, which will have less toxicity and more focused pharmacological effects than canonical ligands.

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List of Abbreviations

- 5-ASA: 5-Aminosalicylic acid
- ACCs: Acetyl-CoA carboxylase
- ADAM: 6-(5-heptyl-1,2-oxazol-3-yl)hexanoic acid
- BVC: Bavachinin
- CPT1: Carnitine palmitoyl transferase 1
- FF: Fenofibrate
- hBM-MSCs: human bone marrow-mesenchymal stem cells
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