PPAR Agonists in Current Clinical Trials against NASH

Subjects: Medicine, Research & Experimental

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The number of patients with nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH) is increasing globally and is raising serious concerns regarding the increasing medical and economic burden incurred for their treatment. The progression of NASH to more severe conditions such as cirrhosis and hepatocellular carcinoma requires liver transplantation to avoid death. Therefore, therapeutic intervention is required in the NASH stage, although no therapeutic drugs are currently available for this. Several anti-NASH candidate drugs have been developed that enable treatment via the modulation of distinct signaling cascades and include a series of drugs targeting peroxisome proliferator-activated receptor (PPAR) subtypes (PPARα/δ/γ) that are considered to be attractive because they can regulate both systemic lipid metabolism and inflammation.

lanifibranor saroglitazar bezafibrate pemafibrate PPAR dual/pan agonist X-ray crystallography

1. Lanifibranor (Peroxisome Proliferator-Activated Receptor Pan Agonist)—Under Consideration for Treating Nonalcoholic Fatty Liver Disease/Non-Alcoholic Steatohepatitis

Lanifibranor (IVA337), developed by Inventiva Pharma (Daix, France), is a non-TZD/non-fibrate peroxisome proliferator-activated receptor (PPAR) agonist that can activate all PPARα/δ/γ subtypes with “well-balanced” potencies/efficacies [1][2]. In researchers' analyses, lanifibranor bound to very similar positions in PPARα/δ/γ-LBD (**Figure 1**A(a)) and activated PPARα/δ/γ-LBD with similar potencies and efficacies in both functional assays (**Figure 1**A(b–e)) [3][4][5][6]. In preclinical mouse experiments led by Inventiva, lanifibranor effectively prevented liver steatosis, inflammation, ballooning, and fibrosis [1]. In a phase 2b trial involving 247 patients with highly active NASH (NCT03008070), the percentage of patients who had a decrease of at least 2 points in the Activity part of the Steatosis, Activity, and Fibrosis score (the scoring system that incorporates scores for ballooning and inflammation) without worsening of fibrosis was significantly higher with a 1200 mg/day lanifibranor dose than with placebo [7][8]. In an ongoing phase 3 trial for NASH in the US and other countries (NCT04849728), 1000 patients will be randomly assigned to receive 800 or 1200 mg/day lanifibranor or matching placebo to investigate the resolution of NASH and the improvement of fibrosis as the primary endpoints.

2. Chiglitazar (Peroxisome Proliferator-Activated Receptor Pan Agonist)—Under Consideration in China

Chiglitazar, a non-TZD PPAR pan agonist, was developed by Chipscreen Biosciences (Guangdong, China). This reagent is not commercially available, and researchers were unable to obtain its pharmacological and cocrystal structure information. Chiglitazar was approved in China in October 2021 for treating type 2 diabetes mellitus (T2DM) and nonalcoholic steatohepatitis (NASH) [9]. In a phase 2 clinical trial for NASH in China (NCT05193916), 100 patients were randomly assigned to receive chiglitazar at 48 or 64 mg daily or a placebo with the liver fat content after an 18-week treatment as the primary endpoint and its results have not yet been posted.

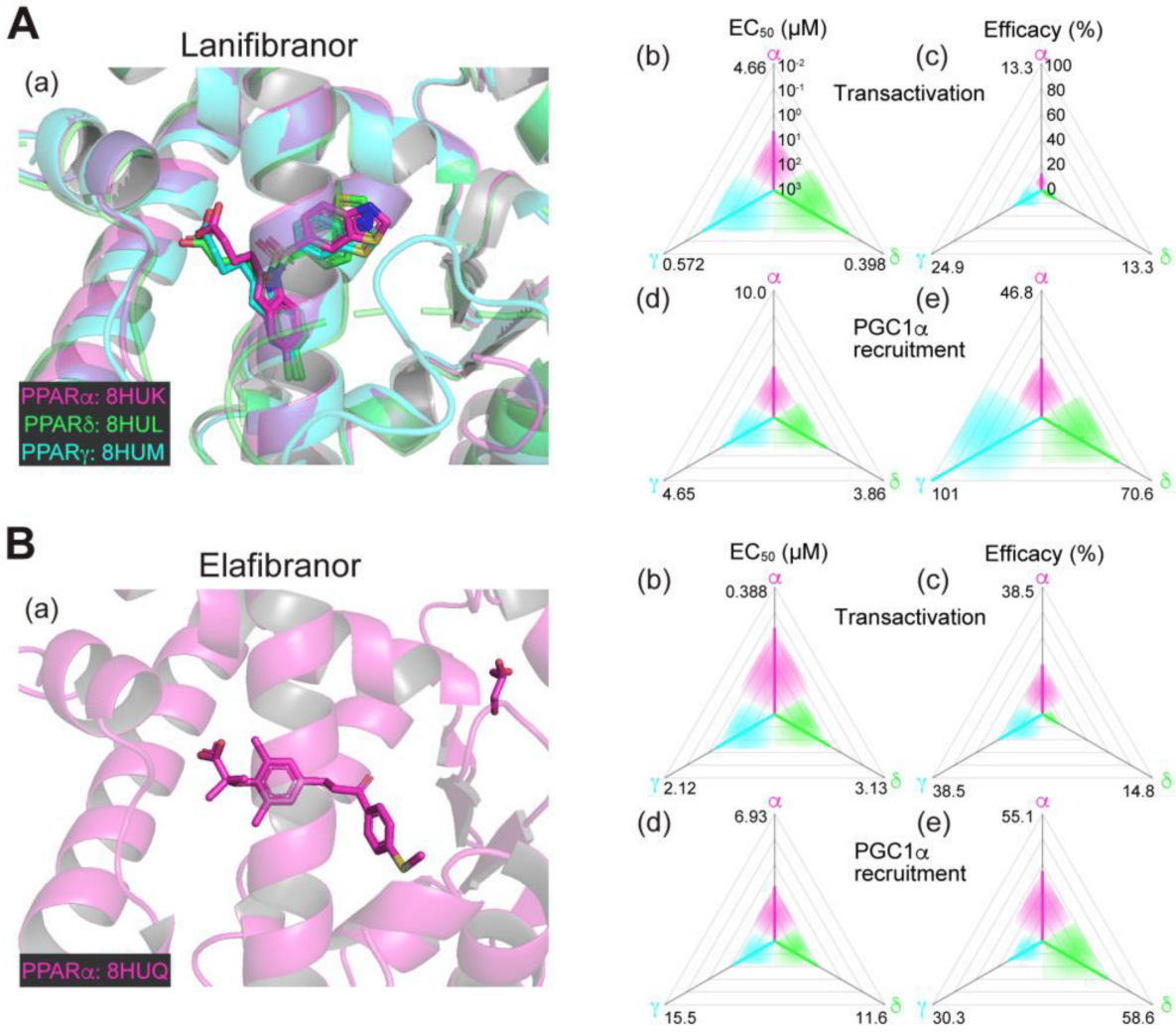


Figure 1. Binding modes in the PPAR cocrystal structures and the potencies/efficacies in transactivation and PGC1α recruitment activity of lanifibranor (**A**), elafibranor (**B**), saroglitazar (**C**), and seladelpar (**D**) against PPARα/δ/γ. (**a**) Merged magnified views of ligands bound to the PPARα (magenta)/δ (green)/γ (light blue)-ligand binding domains revealed by X-ray diffraction analyses of cocrystals; Protein Data Bank (PDB) IDs are shown. PPARδ/γ–elafibranor and PPARδ–saroglitazar cocrystals were not obtained. (**b**–**e**) Potencies as EC_{50} values (μM) (**b**,**d**), and efficacies as % of the maximal responses triggered by the PPARα/δ/γ-selective full agonists (GW7647, GW501516, and GW1929, respectively) (**c**,**e**) in GAL4-based transactivation assay in Cos-7 cells (**b**,**c**) and time-resolved

fluorescence energy transfer (TR-FRET)-based PGC1α coactivator recruitment assay (**d**,**e**). In each ternary plot, the degrees of potency and efficacy are shown by the axes from the triangle center to the three vertices (PPARα in magenta, PPARδ in green, and PPARγ in light blue) on logarithmic (**b**,**d**) and linear scales (**c**,**e**), respectively. All structural and functional data were published by researchers' group [3][4][5][6][10].

3. Elafibranor (PPARα/δ Dual Agonist)—Discontinued

Elafibranor (GFT505), developed by GENFIT (Loos, France), was the first PPAR dual (/pan) agonist to treat NASH that was evaluated in clinical trials. In the analyses, the cocrystals with elafibranor were only obtained with PPARα-LBD (**Figure 1**B(a)), although this can activate all PPARα/δ/γ-LBDs with similar potencies (**Figure 1**B(b–e)) [5]. The reason why PPARδ/γ-LBD cocrystals could not be obtained despite the use of several crystallization methods [6][10] is unknown, but the heat stability analyses using circular dichroism (CD) revealed that elafibranor is an exceptional PPAR ligand in that its binding to PPARα/δ/γ-LBD did not stabilize its active (α-helical) conformation [5]. Supported by several positive results in animal experiments [11][12], elafibranor entered into clinical trials. In the phase 2 clinical trial (NCT01694849), the efficacy and the safety of elafibranor at 80 and 120 mg/day for 52 weeks were evaluated in 275 patients with NASH. Although significant differences were absent in the primary endpoint that was defined as the proportion of patients with resolution of NASH and without fibrosis progression, the new NASH scoring system (proposed at the end of the study) did reveal a significant therapeutic effect [13]. The subsequent phase 3 clinical trial (NCT02704403) enrolled 2157 participants, mainly from the US and Europe. The interim analysis in May 2020 showed that the safety and the tolerability were consistent with previous studies but elafibranor did not have a significant effect on the primary endpoint of resolution of NASH without worsening fibrosis [14]. Consequently, the clinical trial of elafibranor for NASH was discontinued in March 2022.

4. Saroglitazar (PPARα/γ Dual Agonist)—Under Consideration

Saroglitazar is the first glitazar developed by Zydus Therapeutics (Gujarat, India) to be granted for marketing authorization in India for treating diabetic dyslipidemia with its potent PPARα and moderate PPARγ activities [15]. Saroglitazar was then approved in India as an anti-NASH therapeutic in March 2020 but has not been approved in other countries. In researchers' analyses, saroglitazar bound to and activated PPARα/γ-LBD but not PPARδ-LBD because of a steric hindrance (**Figure 1**C(a–e)) [4][6]; therefore, it is considered as a rare approved PPARα/γ dual agonist. No open research regarding the use of saroglitazar in animal experiments has been reported, although several clinical observational studies and case reports have been described from India [16][17][18]. In the phase 2 clinical trial (NCT03061721) involving 106 NAFLD/NASH patients in the US, saroglitazar (1, 2, and 4 mg/day) and placebo were applied for 16 weeks. Saroglitazar (4 mg/day) significantly improved blood ALT levels (the primary endpoint), and the hepatic fat content, insulin resistance, and atherogenic dyslipidemia (the secondary endpoints) [19]. The phase 2b clinical trial (NCT05011305) is currently recruiting US participants with the primary endpoint of resolution of NASH without worsening fibrosis after 76 weeks of treatment with 2 and 4 mg/day doses. Although major adverse events have not been reported in any clinical trial performed in India, careful attention should be

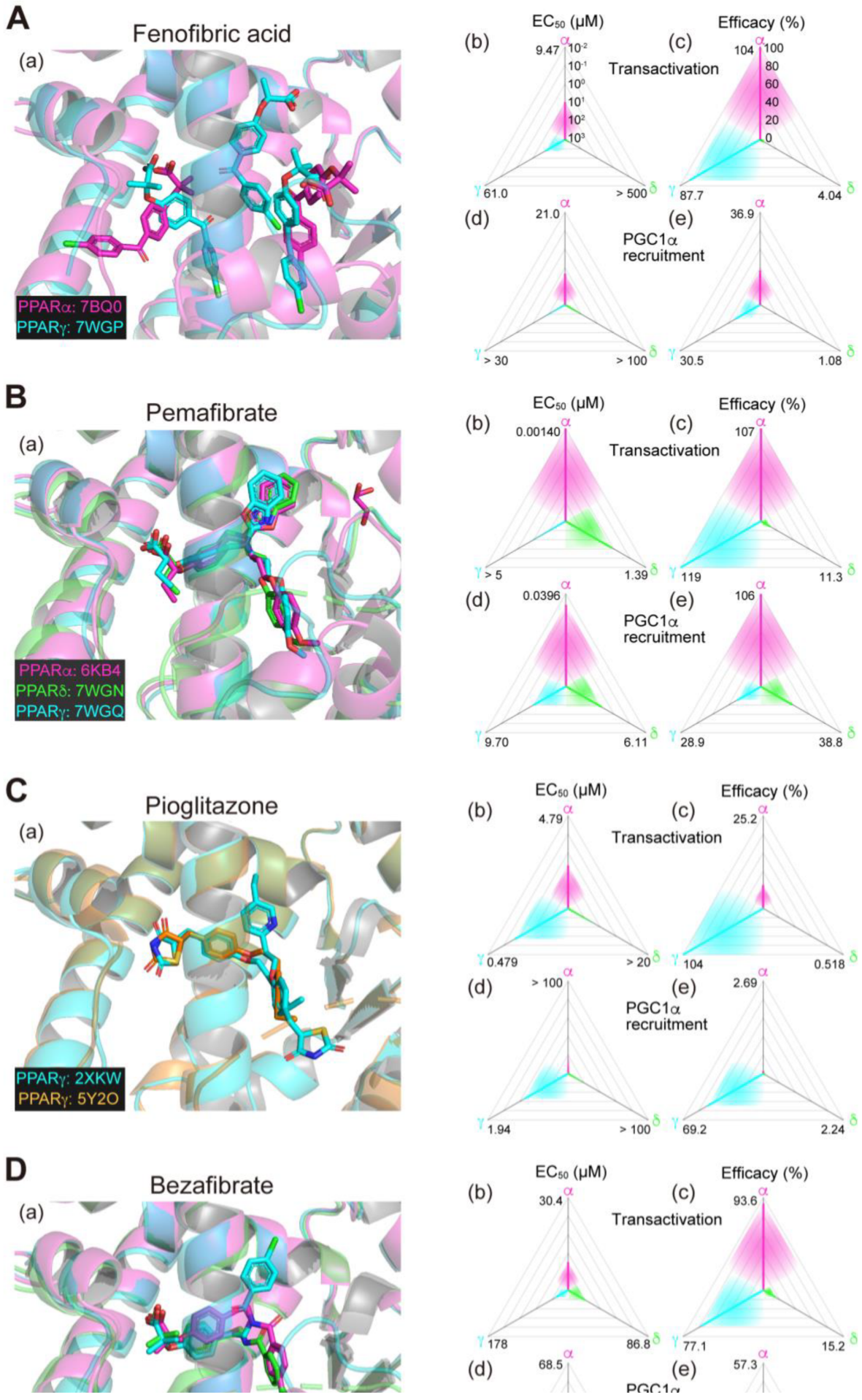
paid to whether saroglitazar improves NASH or not and to what extent the adverse events are compared with those observed with other (abandoned) PPARα/γ dual agonists.

5. Seladelpar (PPARδ-Selective Agonist)—Interrupted

Seladelpar (MBX-8025), developed by CymaBay Therapeutics (Newark, CA, USA), is a rare PPARδ-selective drug. Researchers found that seladelpar bound to all PPARα/δ/γ-LBDs (**Figure 1**D(a)) and activated all PPARα/δ/γ subtypes, but the EC_{50} values in both biological assays were 2–3-fold lower in PPARδ than in PPARα/γ (**Figure 1**D(b–e)) [5]. A phase 2 clinical trial (NCT03551522) had been initiated with 181 patients with NASH in June 2018, but it was interrupted in November 2019 because of atypical histological findings, including histology characterized as an interface hepatitis presentation, with or without biliary injury, in patients who demonstrated improvement or stabilization of their biochemical measures of inflammation and liver injury and no liver-related adverse events after a 52-week treatment [20]. However, a subsequent in-depth investigation by an independent expert review panel (involving world-renowned liver pathologists and histologists) concluded that there was no clinical, biochemical, or histological evidence of seladelpar-related liver injury in the study and unanimously supported re-initiating the clinical development of seladelpar, and thus, the FDA lifted clinical holds on seladelpar in July 2020 [21]. The clinical trial for NASH has not resumed since then.

6. Fenofibrate (PPARα(/γ Dual) Agonist)—Discontinued

Fenofibrate is a widely used fibrate developed by Groupe Fournier SA of France as a hyperlipidemic (triglyceride-lowering) agent that has a relatively low selectivity for PPARα. In the analyses, two and three molecules of fenofibric acid (an active metabolite of fenofibrate) bound to PPARα-LBD and PPARγ-LBD, respectively (**Figure 2**A(a)), and activated both PPARα/γ-LBD but not PPARδ-LBD with some preference for PPARα-LBD (**Figure 2**A(b–e)) [3][6]. Six clinical trials using fibrate for NAFLD/NASH have been conducted but none of them demonstrated significant therapeutic effects. In a double-blind, randomized, placebo-controlled study (NCT02354976), fenofibrate decreased serum triglyceride levels but increased the total liver and liver fat volumes, indicating the complex nature of its pharmacological effects [22]. No new trials have been initiated since then.


A
Fenofibric acid
(a)
PPARα: 7BQ0
PPARγ: 7WGP
(b)
EC50 (μM)
9.47
10-2
10-1
100
101
102
103
61.0
> 500
(c)
Efficacy (%)
Transactivation
104
100
80
60
40
20
0
87.7
4.04
(d)
21.0
> 30
> 100
(e)
36.9
PGC1α recruitment
30.5
1.08
B
Pemafibrate
(a)
PPARα: 6KB4
PPARδ: 7WGN
PPARγ: 7WGQ
(b)
EC50 (μM)
0.00140
> 5
1.39
(c)
Efficacy (%)
Transactivation
107
119
11.3
(d)
0.0396
9.70
6.11
(e)
106
PGC1α recruitment
28.9
38.8
C
Pioglitazone
(a)
PPARγ: 2XKW
PPARγ: 5Y2O
(b)
EC50 (μM)
4.79
0.479
> 20
(c)
Efficacy (%)
Transactivation
25.2
104
0.518
(d)
> 100
1.94
> 100
(e)
2.69
PGC1α recruitment
69.2
2.24
D
Bezafibrate
(a)
(b)
EC50 (μM)
30.4
178
86.8
(c)
Efficacy (%)
Transactivation
93.6
77.1
15.2
(d)
68.5
(e)
57.3
PGC1α

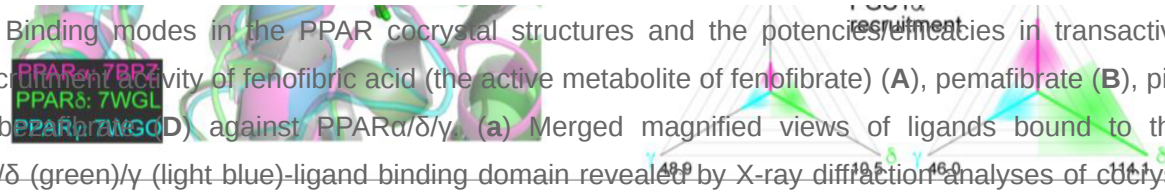


Figure 2. Binding modes in the PPAR cocrystal structures and the potencies/efficacies in transactivation and PGC1α recruitment activity of fenofibric acid (the active metabolite of fenofibrate) (**A**), pemafibrate (**B**), pioglitazone (**C**), and bezafibrate (**D**) against PPARα/δ/γ. (**a**) Merged magnified views of ligands bound to the PPARα (magenta)/δ (green)/γ (light blue)-ligand binding domain revealed by X-ray diffraction analyses of cocrystals; PDB IDs are shown. PPARδ–fenofibric acid and PPARα/δ–pioglitazone cocrystals were not obtained. (**b**–**e**) Potencies as EC_{50} values (μM) (**b**,**d**) and efficacies as % of the maximal responses triggered by the PPARα/δ/γ–selective full agonists (GW7647, GW501516, and GW1929, respectively) (**c**,**e**) in GAL4-based transactivation assay in Cos-7 cells (**b**,**c**) and TR-FRET-based PGC1α coactivator recruitment assays (**d**,**e**). In each ternary plot, the degrees of potency and efficacy are shown by the axes from the triangle center to the three vertices (PPARα in magenta, PPARδ in green, and PPARγ in light blue) on logarithmic (**b**,**d**) and linear scales (**c**,**e**), respectively. All structural (except for **Figure 2**C(a)) and functional data were published by researchers' group [3][4][5][6][10].

7. Pemafibrate (PPARα-Selective Agonist)—Under Consideration in Japan

Pemafibrate (K-877), recently developed by Kowa Company (Nagoya, Japan), is classified as a selective PPARα modulator (SPPARMα) for its high PPARα selectivity and efficacy [22]. Pemafibrate potently decreases blood triglyceride levels and increases HDL-cholesterol levels at doses as low as 0.2 mg/day [23]. Pemafibrate is mainly metabolized by the liver with little excreted into the urine, whereas other fibrates such as fenofibrate and bezafibrate are mainly metabolized by the kidney and can therefore be used in diabetic patients with mild renal impairment [24]. In the analyses, pemafibrate bound to similar positions with its Y-shaped structure that fits into the PPARα/δ/γ-LBP (**Figure 2**B(a)). Pemafibrate only activated PPARα at lower doses but did activate PPARγ and, at much lesser extents, PPARδ at higher doses (**Figure 2**B(b–e)) [3][6]. Therapeutic doses of pemafibrate are very low (0.2 mg/day recommended and 0.4 mg/day at maximum) and it only activates PPARα at those therapeutic doses. In different mouse NASH models, pemafibrate significantly improved NASH conditions such as hepatic inflammation/fibrosis, ballooning degeneration, and biochemical scores [24][25]. A phase 2 clinical trial (NCT03350165) involving 118 patients with NASH in Japan was completed in April 2021 [26]. Pemafibrate did not change the primary efficacy endpoint of the magnetic resonance imaging proton density fat fraction (MRI-PDFF) in the liver, but did significantly reduce liver stiffness as evaluated using magnetic resonance elastography without affecting safety endpoints (incidence of adverse events and adverse drug reactions after the drug administration). Overall, pemafibrate is considered a promising treatment candidate for NAFLD/NASH as well as a potential candidate for combination therapy with statins to treat atherogenic dyslipidemia [27][28][29].

8. Pioglitazone (PPARγ-Selective Agonist)—Under Consideration

Pioglitazone is a TZD-class T2DM drug developed by Takeda Pharmaceuticals (Osaka, Japan) that decreases blood glucose levels by improving insulin resistance in the skeletal muscle and the liver [30]. Two cocrystal structures of PPARγ-LBD–pioglitazone have been reported so far: PDB IDs 2XKW (not yet published) and 5Y2O

[31]. Two incompatible (*R*)-pioglitazone binding modes are present in the former structure but only a single (*S*)-pioglitazone binding mode (that matches one of the two modes in the former) is present in the latter cocrystals (**Figure 2**C(a)). In the functional analyses, pioglitazone activated PPARγ and then PPARα at much lesser efficacies (**Figure 2**C(b–e)) [5] and researchers have so far failed to obtain a PPARα–pioglitazone cocrystal probably because of the low affinity against PPARα. Thus, pioglitazone is actually considered a PPARγ-selective agonist. Although four clinical trials have been conducted using pioglitazone to treat patients with NAFLD who also have T2DM, and its efficacy in insulin-resistant NASH has been recognized in Japanese guidelines, its use in treating patients with NAFLD who did not have T2DM has been limited [32]. In the practice guidance from the American Association for the Study of Liver Diseases, pioglitazone is recommended for patients with or without T2DM with biopsy-proven NASH to improve liver histology, although it should not be used without biopsy-proven NASH because of its safety issues [33]. A phase 3 clinical trial (NCT00063622) involving 247 nondiabetic patients with NASH indicated that pioglitazone (30 mg/day) for 96 weeks was effective even though weight gain was an adverse effect [34]. A phase 2 clinical trial (NCT01068444) on 90 patients with NASH demonstrated the efficacy of a 24-week course of pioglitazone (30 mg/day) in reducing lipidosis and improving the inflammation and histology of NASH without worsening fibrosis [35]. In an ongoing phase 2b trial using pioglitazone (NCT04501406), the primary endpoint is set as an improvement of ≥2 points in the NAFLD activity score without an increase in fibrosis stage. However, it has not yet become the first-line drug for nondiabetic patients with NASH and its main purpose is to improve diabetic symptoms in patients with NASH. When pioglitazone and other TZDs are administered for an extended period, attention should be paid for severe adverse effects, such as weight gain, heart failure, and the risk of bone fractures, caused by prolonged PPARγ activation. In animal experiments, PXL065 (deuterium-stabilized (*R*)-pioglitazone) exerted its therapeutic effect on NASH without causing weight gain or fluid retention, probably through nongenomic actions [36], irrespective of whether the second binding mode is involved or not. Since all TZDs currently in use are stereoisomeric mixtures, the development of new drugs by isomer stabilization is also expected.

9. Rosiglitazone (PPARγ-Selective Agonist)—Discontinued

Rosiglitazone was developed by GlaxoSmithKline and approved in the US and Europe (in 1999 and 2000, respectively) and had been widely used to treat patients with T2DM. However, a meta-analysis in 2007 reported serious concerns about its risk of cardiac injury and its use has been discontinued in many countries since then [37] [38]. In a previous phase 2 clinical trial (NCT00492700) on 63 patients with NASH, rosiglitazone (8 mg/day) taken for one year reduced blood ALT levels and improved fatty degeneration, but had no significant effects on liver fibrosis or NASH activity scores [39]. Subsequently, no benefits were found (beyond the risks) in improving insulin resistance and NASH conditions, even after an additional two-year extension of the treatment period [40].

10. Lobeglitazone (PPARγ Agonist)—Under Consideration in Korea

Lobeglitazone is a TZD that was developed by Chong Kun Dang Pharmaceutical Corp. (Seoul, South Korea) and approved for the management of T2DM in Korea in 2013 [41]. A phase 4 clinical trial (NCT02285205) revealed that treatment with lobeglitazone reduced intrahepatic fat content as assessed by transient liver elastography, and improved glycemic, liver, and lipid profiles in patients with T2DM and NAFLD [42]. Further clinical trials are awaited for a favorable safety profile.

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