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Pan-PPAR Agonists Based on the Resveratrol Scaffold: Biological Evaluation and Docking Studies

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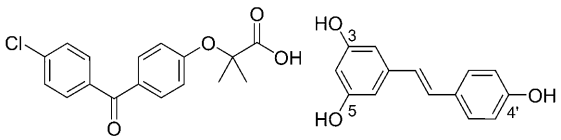
The peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptor superfamily and consist of three receptor isoforms, PPARα, PPARγ, and PPARδ, which play important roles in carbohydrate and lipid metabolism. PPARα agonists such as fenofibrate, or the active metabolite fenofibric acid (**1**), are effective at lowering serum triglycerides and raising high-density lipoprotein (HDL) cholesterol.[1] PPARγ has been identified as a key regulator for insulin sensitivity, glucose homeostasis, and fat storage.[2] PPARδ activation appears to increase fatty acid β-oxidation, insulin sensitivity, and HDL cholesterol. PPARδ agonists have been shown to increase plasma HDL cholesterol levels while decreasing LDL cholesterol and triglycerides in obese and dyslipidemic rhesus monkeys.[3]

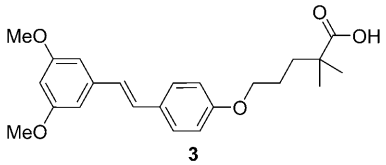
Considering the aforementioned beneficial pharmacological effects of the PPARs, the concept of simultaneously activating all PPAR subtypes with a single compound, that is, a pan-PPAR agonist is extremely attractive, especially for the treatment of metabolic syndrome, which consists of an accumulation of metabolic and cardiovascular risk factors that cause a predisposition to heart attack, stroke, heart failure, sudden cardiac death, and certain cancers.[4] Simultaneous activation of all PPAR subtypes might also decrease the occurrence of adverse side effects.[4]

Stilbene-based components, or stilbenoids, have been suggested to have many health benefits including antioxidant, anti-inflammatory, antileukemic, antibacterial, antifungal, antiplatelet aggregation, vasodilator, and antitumor activities.[5] Resveratrol (*trans*-resveratrol; **2**), the most widely studied stilbene, is a phytoalexin produced naturally by several plants when under attack by pathogens such as bacteria or fungi. Resveratrol is found in the skin of red grapes and is a constituent of red wine; indeed a lower risk of cardiovascular disease has been observed among wine-drinking populations.[6] In mouse and rat experiments, anticancer, anti-inflammatory, blood-sugar-lowering, and other beneficial cardiovascular effects of resveratrol have been reported.[7] Resveratrol protects the heart and blood vessels by directly scavenging oxidants that can cause lipid oxidation and by preventing oxidative-stress-induced apoptosis of endothelial cells.[8] It may also help to prevent heart damage after cardiac arrest. Reduced platelet aggregation by resveratrol can decrease the risk of atherosclerosis.[9] Resveratrol has also been demonstrated to decrease blood lipid levels in animals.[10] Some naturally occurring or synthetic resveratrol analogues have been shown to significantly activate PPARα or to lower plasma lipid levels when fed to hamsters.[11]



fenofibric acid (**1**)

resveratrol (**2**)



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These beneficial effects of resveratrol have attracted much attention, and this compound may provide a scaffold for the development of novel therapeutic drugs, which would probably produce synergistic pharmacological effects. In previous studies, simple functional groups were introduced at the 4′-position, and methoxy groups were introduced at the 3- and 5-positions of resveratrol.[12] From ongoing studies in our research group, a series of phenoxyalkylcarboxylic acid derivatives based on the resveratrol scaffold appear to have good hypolipidemic activity in vivo, and compound **3** was found to be the most potent. It was predicted that the hypolipidemic activity of **3** may be due to the activation of the PPARα, and the results of these studies will be reported elsewhere. In continuation of our drug discovery program on agents for the treatment of metabolic diseases, and in order to gain more insight on the structure–activity relationships, we discovered the pan-PPAR agonists **6** and **9** by combining the resveratrol scaffold with the fibrate head group and methylating the remaining phenolic hydroxy groups. Interestingly, compound **6**, bearing two fibrate head groups, was found incidentally as the by-product of the reaction. Herein we describe the synthesis and in vitro evaluation of these compounds for PPAR transactivation. We also evaluated their in vivo biological activity and carried out docking studies.

The synthesis of the target compounds are shown in Schemes 1 and 2. Compared with **3**, the target compound **6** has two fibrate head groups and one methoxy group. The fibrate head group was introduced at the 3- and 4′-positions of resveratrol by alkylation of the phenolic hydroxy groups with isobutyl-5-chloro-2,2-dimethylvalerate; the remaining phenolic hydroxy group was methylated by methyl iodide. Alkaline hydrolysis of ester **5** gave the target compound **6**. The target

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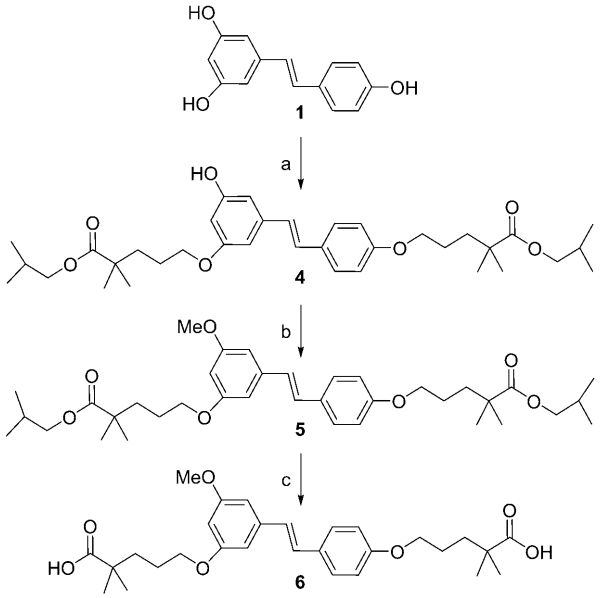
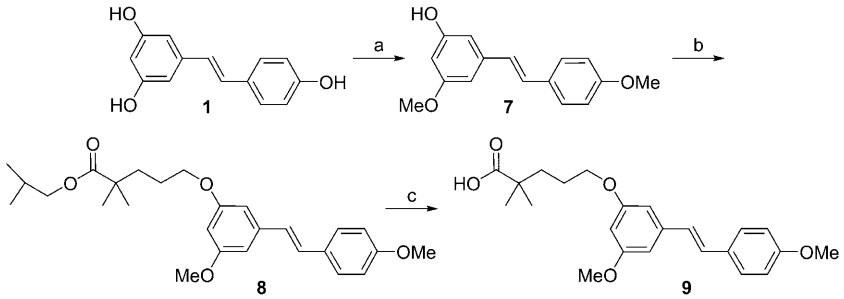


Scheme 1. Reagents and conditions: a) isobutyl-5-chloro-2,2-dimethylvalerate, anhydrous K_2CO_3, DMF, 70 °C, 32 h, 62%; b) CH_3I, anhydrous K_2CO_3, acetone, reflux, 12 h, 73%; c) LiOH, MeOH/H_2O, reflux, 48 h, then HCl, 54%.

compound **9** was afforded by hydrolysis of ester **8**, which was first provided by methylation of the 3- and 4′-positions of resveratrol through a Williamson–Ether method and then alkylation of the phenolic hydroxy group at the 5-position with isobutyl-5-chloro-2,2-dimethylvalerate (Scheme 2). In previous



Scheme 2. Reagents and conditions: a) CH_3I, anhydrous K_2CO_3, acetone, reflux, 12 h, 32%; b) isobutyl-5-chloro-2,2-dimethylvalerate, anhydrous K_2CO_3, DMF, 70 °C, 24 h, 64%; c) LiOH, MeOH/H_2O, reflux, 32 h, then HCl, 72%.

studies, 3,4′,5-trimethoxyresveratrol was obtained through the Williamson–Ether method with methyl iodide.[5a,11,13] In our study, 3,4′-dimethoxyresveratrol (**7**) was obtained by controlling the reaction conditions (molar ratios of reactants and reaction time). All target compounds were confirmed by ^1H and ^{13}C NMR spectroscopy as well as mass spectrometry.

The target compounds were evaluated for their activities as PPAR agonists in U2OS cells. As shown in Table 1, fold activation values of PPARα by compounds **3** and **9** at 3 and 30 μM were first obtained with vehicle control defined as 1-fold activation and fenofibric acid used as positive control. Compounds **3** and **9** showed PPARα agonist activity: at 3 μM, **9** (2.03-fold activation) exhibited higher PPARα activation than fenofibric

Table 1. In vitro PPARα activation by tested compounds.

Compd	Fold PPARα activation[a]	
	3 μM	30 μM
3	1.53 ± 0.11	1.52 ± 0.11
9	2.03 ± 0.28	2.36 ± 0.31
fenofibric acid	1.67 ± 0.11	2.42 ± 0.24

[a] Fold activation at the indicated concentration relative to vehicle control; values are expressed as the mean ± SE ($n = 3$).

acid (1.67-fold) and **3** (1.53-fold). However, at 30 μM, compound **9** demonstrated similar PPARα agonist activity (2.36-fold activation) to that of fenofibric acid (2.42-fold) and again higher potency than **3** (1.52-fold activation).

Comparative dose–response studies of **6** and **9** were further performed with fenofibric acid (a PPARα agonist) toward PPARα, rosiglitazone (a PPARγ agonist) toward PPARγ, and 2-bromohexadecanoic acid (a PPARδ agonist) toward PPARδ. As shown in Table 2, compounds **6** and **9** were identified as pan-PPAR agonists, as they activate all three PPAR subtypes at similar doses and have balanced EC_{50} data for the three PPAR subtypes, albeit with slight selectivity for PPARα. They act as weak agonists of PPARγ and PPARδ relative to rosiglitazone and 2-bromohexadecanoic acid, respectively. Compounds **6** and **9** have similar PPAR agonist activity and selectivity. Although **6**, **9**, and fenofibric acid activate PPARα in a similar manner, PPARγ and PPARδ activation by **6** and **9** is ~5–10-fold more potent than that of fenofibric acid, whereas fenofibric acid is a dual activator of PPARα and PPARγ, with ~10-fold selectivity for PPARα.[14] In general, compounds **6** and **9** are more effective than fenofibric acid in their ability to activate PPARs.

The ability of the compounds to affect lipid/cholesterol homeostasis was initially examined in vivo by using the Triton WR-1339 induced hyperlipidemic mouse model, and the results are listed in Table 3. Compound **6** showed greater activity than **3**, through replacement of the phenolic hydroxy group at the 3-position by a fibrate head group. Out of the three compounds **3**, **6**, and **9**, compound **9** was identified as the most potent followed by **6**; compounds **6** and **9** were more than twice as potent as fenofibric acid at a dose of 300 mg kg^{-1} body weight p.o. At a dose of 100 mg kg^{-1} administered by i.p. injection, compound **6** and fenofibric acid showed similar hypolipidemic activity, and compound **9** was the most potent, lowering triglyceride levels by 80.1% ($p < 0.01$) and total cholesterol by 66.7% ($p < 0.01$). The parent compound, resveratrol, did not show significant hypolipidemic activity at the same dose.

Compounds **3**, **6**, and **9** were further tested for their hypolipidemic activity in vivo in an alloxan-induced diabetic mouse

Table 2. In vitro transactivation activity profile of tested compounds.

Compd	EC_{50} [μM][a] (activation [%][b])		
	PPARα	PPARγ	PPARδ
6	6.87 (137.6)	19.37 (38.9)	26.13 (74.6)
9	8.46 (124.9)	11.94 (43.7)	11.15 (78.2)
fenofibric acid	8.51 (100)	104.72 (35.0)	125.91 (55.4)
rosiglitazone	ND[c]	0.03 (100)	ND
2-bromohexadecanoic acid	ND	ND	4.36 (100)

[a] EC_{50}: concentration that effects 50% maximal activity for a given compound; data represent the mean from at least three independent experiments, each conducted in triplicate. [b] Percent maximal responses relative to control were calculated with fenofibric acid at 10 μM as 100% for PPARα, rosiglitazone at 10 μM as 100% for PPARγ, and 2-bromohexadecanoic acid at 10 μM as 100% for PPARδ. [c] ND: not determined.

Table 3. In vivo efficacy of compounds in acute hyperlipidemic mice.[a]

Compd	300 mg kg^{-1} p.o. (Triton)		100 mg kg^{-1} i.p. (Triton)		150 mg kg^{-1} p.o. (alloxan)	
	TG	TC	TG	TC	TG	GLU
3	47.1*	40.3*	52.2*	50.3*	59.7**	11.1
6	79.7**	61.8**	60.9**	47.0**	63.8**	3.0
9	86.1**	66.0**	80.1**	66.7**	67.2**	8.6
resveratrol	12.8	9.4	18.1	11.2	NT[b]	NT
fenofibric acid	38.7*	30.6*	59.1*	46.2*	54.6**	13.2

[a] Values are expressed as percent decrease; TC: total cholesterol, TG: triglycerides, GLU: glucose; $^{**}p<0.01$, $^{*}p<0.05$ relative to model group. [b] NT: not tested.

model at a dose of 150 mg kg^{-1} p.o. (Table 3). In this particular mouse model, triglycerides and blood glucose levels are significantly higher than normal. The test compounds showed good lowering of triglycerides, and are more potent than fenofibric acid. Compound **9** was the most potent, lowering triglyceride levels by 67.2% ($p<0.01$), followed by **6** (63.8%). Because this animal model is mainly type 1 diabetic, none of the compounds exhibited potent blood glucose lowering activity.

We next observed the effects of these compounds on body weight, liver weight, liver coefficient (liver weight/body weight ratio), spleen weight, spleen coefficient (spleen weight/body weight ratio), and serum biochemical parameters in hyperlipidemic Balb/c mice fed a fat emulsion at a dose of 80 mg kg^{-1} body weight daily for 19 days. The results are listed in Table 4. The most potent compound **9** lowered triglyceride levels by 64.5% ($p<0.01$), and **6** lowered the triglycerides by 34.0% ($p<0.05$). The reference compound fenofibric acid lowered the triglycerides by 50% ($p<0.01$). The liver weight and liver coefficient were significantly increased in the model group ($p<0.05$) compared with the control group. Treatment with fenofibric acid and compounds **6** and **9** further exacerbated hepatomegaly, because the liver weight and the liver coefficient of mice in these groups were increased relative to the model group ($p<0.01$). The present study supports the concept that long-term treatment with PPARα agonists induces hepatomegaly in rodents. When administrated to rodents, fibrates produce a liver-specific response, resulting in peroxisomal proliferation, hepatomegaly, and ultimately hepatocellular carcinoma.[15] This effect has been demonstrated to be mediated by PPARα.[15] The magnitude of this response appears to vary considerably among species. In non-human primates and humans, PPARα agonists neither induce peroxisome proliferation nor the development of liver cancer.[16] Indeed, fibrates have been prescribed extensively for more than 30 years, and an increased risk of liver cancer has never been reported in humans.[17] It is therefore likely that com-

Table 4. Effects of compounds on hyperlipidemic Balb/c mice fed a fat emulsion.[a]

Parameters			Compound		
	control	model	**6**	**9**	fenofibric acid
Body weight [g]:	22.98 ± 3.12	23.87 ± 2.14	24.52 ± 1.44	20.88 ± 3.10	22.81 ± 1.45
Liver weight [g]:	0.95 ± 0.11	1.22 ± 0.21$^{\#}$	2.21 ± 0.17**	2.37 ± 0.35**	2.00 ± 0.13**
Liver coefficient [%]:	4.15 ± 0.61	5.10 ± 0.41$^{\#}$	9.02 ± 0.65**	11.37 ± 0.58**	8.78 ± 0.54**
Spleen weight [mg]:	73.54 ± 16.54	78.33 ± 17.22	76.67 ± 19.66	66.67 ± 18.62	73.33 ± 16.33
Spleen coefficient [%]:	0.32 ± 0.05	0.32 ± 0.04	0.31 ± 0.07	0.31 ± 0.04	0.32 ± 0.06
TG [mM]:	0.64 ± 0.12	2.14 ± 0.72$^{\#\#}$	1.41 ± 0.26*	0.76 ± 0.20**	1.07 ± 0.27**
			−34.0	−64.5	−50.0
TP [g L^{-1}]:	62.89 ± 2.12	63.55 ± 2.96	62.95 ± 1.90	62.45 ± 1.44	63.67 ± 2.50
BUN [mM]:	6.99 ± 0.98	7.36 ± 0.80	6.93 ± 0.39	7.56 ± 0.61	6.39 ± 0.66
CREA [μM]:	43.62 ± 5.21	42.75 ± 3.59	44.47 ± 5.03	42.85 ± 3.53	48.07 ± 6.28
ALT [U L^{-1}]:	22.33 ± 2.25	38.00 ± 6.96$^{\#\#}$	36.00 ± 7.43$^{\#\#}$	34.83 ± 4.44$^{\#\#}$	35.17 ± 5.53$^{\#\#}$
AST [U L^{-1}]:	57.50 ± 6.62	78.83 ± 7.52$^{\#\#}$	71.33 ± 8.64$^{\#}$	74.50 ± 4.85$^{\#\#}$	75.17 ± 6.82$^{\#\#}$

[a] TG: triglycerides, TP: total protein, BUN: blood urea nitrogen, CREA: creatinine, ALT: alanine transaminase, AST: glutamic-oxaloacetic transaminase; $^{\#}p<0.05$, $^{\#\#}p<0.01$ relative to normal group; $^{**}p<0.01$ relative to model group.

pounds **6** and **9** would not induce hepatotoxicity in humans, although this requires further investigation. Compared with the control group, mice in the model group had significantly increased serum alanine transaminase (ALT; $p<0.01$) and glutamic-oxaloacetic transaminase (AST; $p<0.01$). Fenofibric acid and compounds **6** and **9** failed to decrease serum ALT ($p>0.05$) and AST ($p>0.05$) levels relative to the model group at the same dose. No changes in spleen weight, spleen coefficient, total protein (TP), blood urea nitrogen (BUN), or creatinine (CREA) were observed.

Table 6. Docking of compounds in PPARα, PPARγ, and PPARδ.

Compd	Affinity [kcal mol^{-1}]			H-bond residues		
	PPARα	PPARγ	PPARδ	PPARα	PPARγ	PPARδ
6	−8.5	−8.4	−9.0	Thr283, Tyr314, Tyr464, Gly335	Ser289, His323, Tyr327, His449, Tyr473	Thr289, Thr292, Ala342, Asn343, His449, Tyr473
9	−8.2	−8.6	−9.1	Tyr279, Tyr314, Tyr464	Ser342, His449, Tyr473	Thr289
fenofibric acid	−7.7	−8.2	−8.4	Ser280, Tyr314, Tyr464	Ser289, His323, Tyr327, His449, Tyr473	His449, Tyr473

The antidiabetic effect of compounds was further evaluated in KKAy mice, which exhibit obesity, insulin resistance, and symptoms of type 2 diabetes. Compound **6** decreased blood glucose levels by 41.5% after daily administration at 150 mg kg^{-1} for 21 days, and compound **9** similarly effected a 34.6% decrease, demonstrating the glucose-lowering efficacy of both compounds in vivo; fenofibric acid lowered glucose levels by 18.9%, as shown in Table 5. Compounds **6**, **9**, and fenofibric acid all significantly decreased triglycerides (TG; >30%). Moreover, the three compounds caused weight loss to varying degrees; compound **6** effected 3.18 g weight loss per mouse on average ($p<0.05$).

Table 5. In vivo efficacy of compounds in KKAy mice.[a]

Compd	Dose [mg kg^{-1}]	GLU [mM]	TG [mM]	Body weight gain [g]
model	–	17.50 ± 4.69	5.08 ± 1.47	0.4
6	150	10.24 ± 3.60*	3.13 ± 0.98*	−3.18*
		−41.5	−38.4	
9	150	11.44 ± 3.19*	2.89 ± 0.59**	−1.92
		−34.6	−43.1	
	75	13.90 ± 0.93	4.63 ± 0.94	−0.43
		−20.6	−8.9	
fenofibric acid	150	14.20 ± 3.37	2.92 ± 0.12**	−0.57
		−18.9	−42.5	

[a] **$p<0.01$, *$p<0.05$, compared with model group.

Molecular modeling (docking) studies were carried out to gain more insight on the binding mode of the compounds with PPARs. Proposed binding poses of compounds **6**, **9**, and fenofibric acid are superimposed on the co-crystal structures of the PPARα–GW409544 complex, the PPARγ–rosiglitazone complex, and the PPARδ–GW2433 complex, as illustrated in Figure 1. The affinities and hydrogen bonding residues are listed in Table 6.

The Y-shaped ligand binding pocket of PPAR can be divided into three arms. Arm I consists mainly of polar residues and includes the activation function helix 2 (AF-2 helix), which activates transcription if the acid head group of the PPAR agonist forms a hydrogen bond network with the corresponding residues of the helix. The hydrophobic moiety of PPAR agonists either interacts with the hydrophobic arm II (tail-up pocket) or with the partly hydrophilic arm III (entrance region of the ligand binding pocket, tail-down pocket). Some PPAR agonists with a branched hydrophobic moiety are able to interact with both hydrophobic arms.[18]

GW409544 is a full PPARα and PPARγ agonist.[19] GW409544 was mainly docked into arms I and II of the binding pocket of PPARα, while **6** was docked into arms I and III. The conformation of **9** was almost identical to that of GW409544, as shown in Figure 1a. Unlike compounds **6** and **9**, docking of fenofibric acid shows the two phenyl rings as mainly docked into the "benzophenone" pocket. This revealed that **6** and **9** may bind to the receptor in a mode different from that of fenofibric acid. In complexes of PPARα with compound **6** or fenofibric acid, hydrogen bonding interactions were observed between the carboxylic acid group and the amino acids Tyr314 and Tyr464, which are considered key interactions for activation of the receptor. Notably, the methoxy group at the 5-position of compound **9** makes hydrogen bond interactions with Tyr314 and Tyr464 and the carboxylic acid group docked into arm II. The affinities for PPARα obtained computationally are in agreement with the activation activity in vitro.

Figure 1b shows the docking poses of compounds **6**, **9**, and fenofibric acid in comparison with the co-crystallized binding conformation of rosiglitazone. The acid head groups of **9** and fenofibric acid, as well as the acid head group at the 3-position of **6**, make several specific hydrogen bonding interactions with the key amino acid residues Ser289, His449, and Tyr473. Rosiglitazone, a PPARγ agonist, binds in a U-shaped conformation (arms I and II) while occupying only 40% of the ligand binding

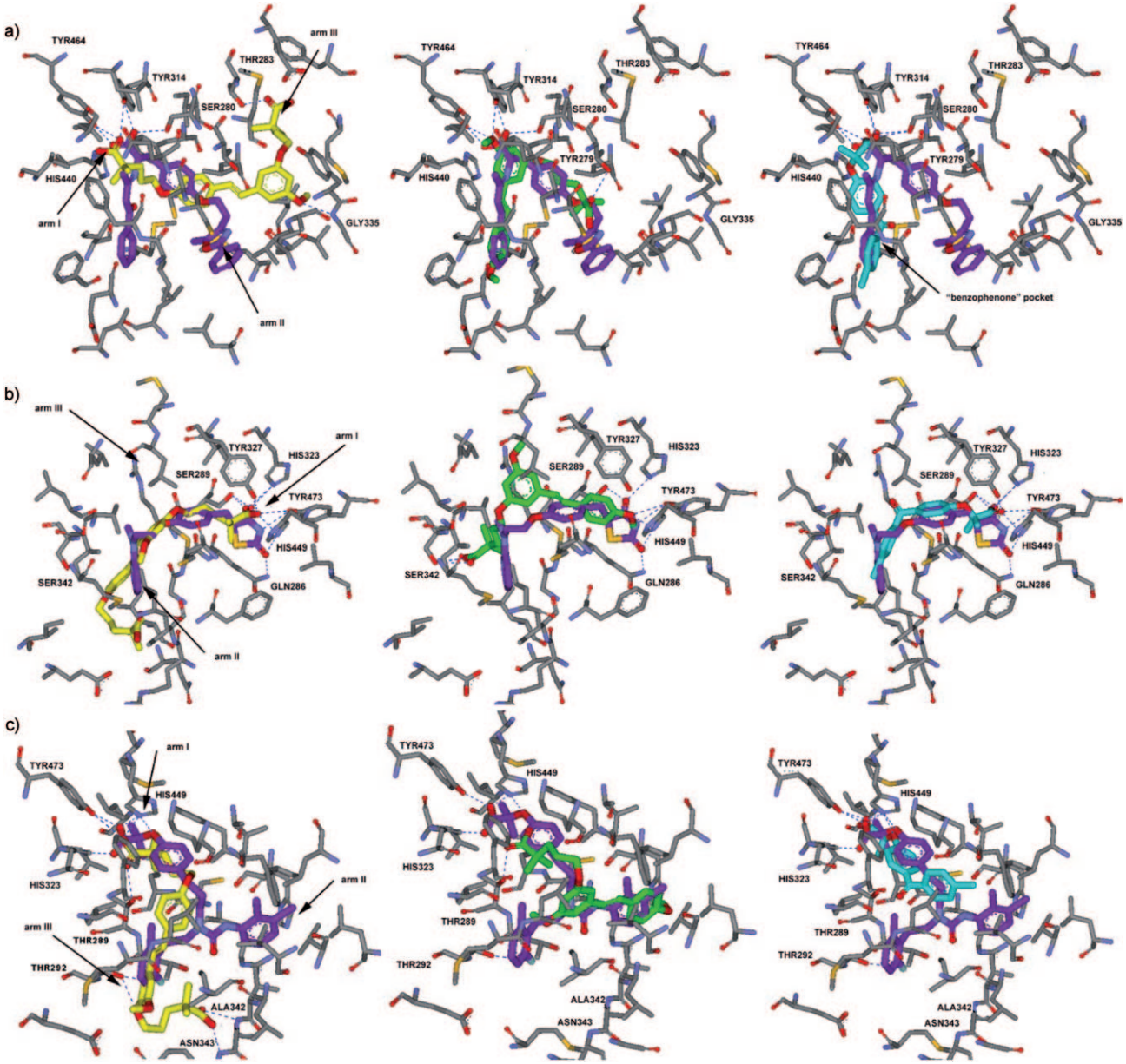


Figure 1. a) From left to right: compounds **6** (yellow), **9** (green), and fenofibric acid (cyan) docked into the co-crystal structure of PPARα in complex with GW409544 (purple) (PDB ID: 1K7L); b) From left to right: compounds **6** (yellow), **9** (green), and fenofibric acid (cyan) docked into the co-crystal structure of PPARγ in complex with rosiglitazone (purple) (PDB ID: 2PRG); c) From left to right: compounds **6** (yellow), **9** (green), and fenofibric acid (cyan) docked into the co-crystal structure of PPARδ in complex with GW2433 (purple) (PDB ID: 1GWX). Selected residues within 4 Å of the bound ligand are shown in all panels. The important residues involved are labeled. H-bond interactions are shown as dashed lines.

site.[14] Compound **6** and fenofibric acid occupy arms I and II of the binding pocket, like rosiglitazone. Relative to fenofibric acid, compound **6** occupies more of arm II of the binding pocket of PPARγ due to the long acid head group at the 4′-position, and compound **9** occupies three arms of the Y-shaped pocket. Furthermore, both **6** and **9** are stabilized by hydrophobic interactions with the binding pocket. These favorable interaction profiles for **6** and **9** in the PPARγ ligand binding domain (LBD) may explain their greater activity in the PPARγ transactivation assay than fenofibric acid in vitro.

In complexes of PPARδ with compound **6** or fenofibric acid, hydrogen bonding interactions were observed between the carboxylic acid group and the key amino acid residues His449 and Tyr473 (Figure 1 c). Compound **9** forms a hydrogen bond with Thr289, and no other key polar interactions were observed between **9** and PPARδ. GW2433 is a high-affinity ligand for human PPARδ, which fills all three arms of the Y-shaped pocket of PPARδ.[14] Compounds **6** and **9** docked into two arms of the Y-shaped pocket, whereas fenofibric acid occupied only arm I. Moreover, due to the long acid head group at the 3-position of **6**, this compound occupies more of arm III of the binding pocket than does GW2433. Furthermore, **6** and **9** are stabilized by hydrophobic interactions with the binding pocket. These may be the reasons why **6** and **9** exhibit more

potent activation of PPARδ than fenofibric acid in vitro. The affinities for PPARδ obtained computationally are generally in agreement with the activation activity in vitro.

In conclusion, the pan-PPAR agonists **6** and **9**, which are based on the resveratrol scaffold, show significant lowering of triglycerides and are more potent than fenofibric acid in two acute in vivo hypolipidemic activity tests. Compound **9** lowered triglycerides by 64.5% ($p < 0.01$) in hyperlipidemic Balb/c mice fed a fat emulsion at a daily dose of 80 mg kg^{-1} body weight for 19 days. Compound **6** decreased blood glucose levels by 41.5% in KKAy mice after daily administration at a dose of 150 mg kg^{-1} for 21 days. This activity was closely followed by compound **9** (34.6%), demonstrating the good glucose-lowering efficacy of both compounds in vivo. Docking studies revealed that **6** and **9** dock into the active sites of PPARα, PPARγ, and PPARδ. The conformations of **6**, **9**, and fenofibric acid, and their interactions with amino acid residues in the PPAR LBD may determine their differences in activity. Further work is needed to evaluate the biological profile of this class of ligands. Moreover, further research is required in order to determine whether the compounds can produce synergistic pharmacological effects by combining the pharmacophore moieties with the natural scaffold. The studies reported herein provide a good starting point for the development of novel pan-PPAR agonists for the treatment of metabolic diseases.

Experimental Section

The details of compound synthesis, characterization data, biological evaluation, and computational studies are available in the Supporting Information.

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Keywords: metabolic diseases · molecular modeling · pan-PPAR agonists · receptors · resveratrol

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