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Prenylated Chrysin Derivatives as Partial PPARγ Agonists with Adiponectin Secretion-Inducing Activity

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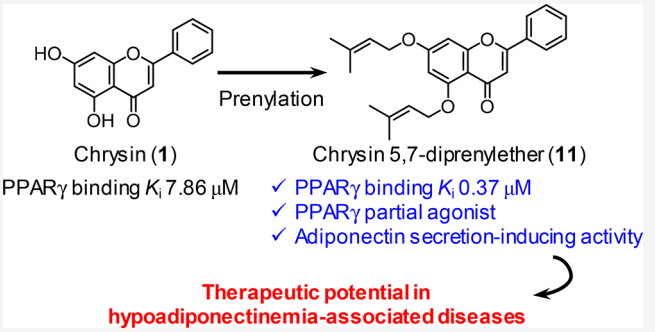
ABSTRACT: Decreased circulating adiponectin levels are associated with an increased risk of human metabolic diseases. The chemical-mediated upregulation of adiponectin biosynthesis has been proposed as a novel therapeutic approach to managing hypoadiponectinemia-associated diseases. In preliminary screening, the natural flavonoid chrysin (**1**) exhibited adiponectin secretion-inducing activity during adipogenesis in human bone marrow mesenchymal stem cells (hBM-MSCs). Here, we provide the 7-prenylated chrysin derivatives, chrysin 5-benzyl-7-prenylether compound **10** and chrysin 5,7-diprenylether compound **11**, with the improved pharmacological profile compared with chrysin (**1**). Nuclear receptor binding and ligand-induced coactivator recruitment assays revealed that compounds **10** and **11** functioned as peroxisome proliferator-activated receptor (PPAR)γ partial agonists. These findings were supported by molecular docking simulation, followed by experimental validation. Notably, compound **11** showed PPARγ binding affinity as potent as that of the PPARγ agonists pioglitazone and telmisartan. This study presents a novel PPARγ partial agonist pharmacophore and suggests that prenylated chrysin derivatives have therapeutic potential in various human diseases associated with hypoadiponectinemia.



KEYWORDS: *Prenylated chrysin derivative, Adiponectin, Peroxisome proliferator-activated receptor, Human bone marrow mesenchymal stem cells, PPARγ partial agonist*

Adiponectin is an adipocyte-derived cytokine with diverse biological activities, including the improvement of insulin sensitivity, the inhibition of inflammation, and the regulation of metabolic processes.[1] Regarding the increase in ectopic fats in the liver and vascular tissues, many studies have shown that hypoadiponectinemia is associated with human metabolic diseases, such as type II diabetes, fatty liver disease, and atherosclerosis.[2−4] Moreover, the relative decrease in circulating adiponectin is linked to an increased risk of obesity-related malignancies, such as hematologic, endometrial, colon, renal, and liver cancers.[4,5] Thus, the administration of recombinant adiponectin has been suggested as a possible strategy for treating conditions associated with hypoadiponectinemia.[6,7] However, recombinant adiponectin requires extensive post-translational modification and oligomerization, which limits its therapeutic applications.[8,9] Therefore, compounds that can promote adiponectin secretion from adipocytes have been proposed as novel therapeutic agents for treating various metabolic diseases and cancers.[10−12]

Cellular adiponectin biosynthesis in adipocytes is mainly regulated by the peroxisome proliferator-activated receptor (PPAR).[13,14] Three PPAR subtypes, PPARα, PPARγ, and PPARδ, have been extensively studied as drug targets in treating human metabolic diseases.[11,12,15,16] Among the three PPAR subtypes, PPARγ plays a pivotal role in regulating adipocyte function.[13,17] The transcriptional activation of PPARγ improves insulin sensitivity and modulates inflammatory processes.[14] Recent evidence has shown that PPAR-induced adiponectin secretion alleviates obesity-associated nonalcoholic fatty liver disease (NAFLD).[14,18] Many thiazolidinedione (TZD) class PPARγ agonists, highly potent adiponectin secretion-inducing compounds, have been approved as antidiabetic drugs. However, most TZD class PPARγ agonists have been withdrawn from use as antidiabetic therapeutics, or their clinical usage has been limited because of serious safety issues, such as cardiovascular adverse outcomes and liver toxicity.[19] To improve the adverse effects of potent TZD drugs, PPARγ partial agonists that selectively

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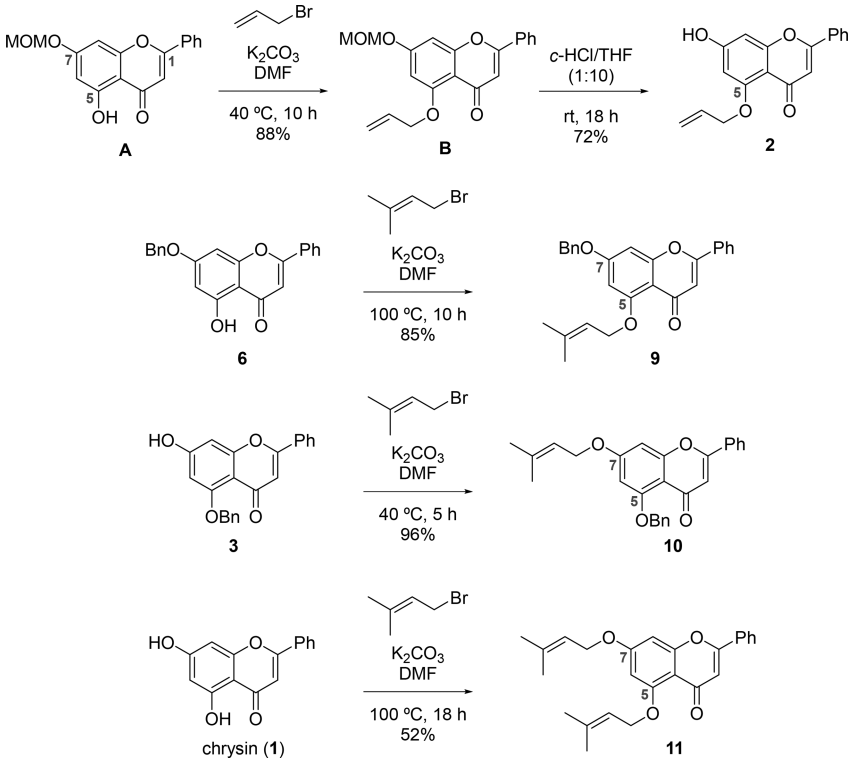
Scheme 1. Preparation of Novel Chrysin Derivatives



activate cofactors or pan-PPAR modulators have been studied.[19]

In a preliminary phenotype-based screening using the adipogenesis model of human bone marrow mesenchymal stem cells (hBM-MSCs),[20] chrysin (5,7-dihydroxyflavone, **1**), a natural flavonoid, was identified as an adiponectin-secretion-promoting compound.[21] Chrysin was first isolated from the plant *Passiflora coerulea* and has traditionally been used as a sedative that directly affects benzodiazepine receptors.[22,23] Notably, the effects of chrysin on PPARγ functions were associated with improvements of the age-related lipid abnormalities in animal models.[24] Although chrysin increased adiponectin biosynthesis during adipogenesis in hBM-MSCs via PPARγ activation, its pharmacological mechanism has not been clearly elucidated at the molecular level. In addition, the effect of chrysin on adiponectin production was not potent enough to clinically develop it as a therapeutic drug for diverse human metabolic diseases. In this study, we synthesized novel chrysin derivatives to develop more potent adiponectin secretion-inducing activity. We confirmed that chrysin (**1**) was directly bound to PPARγ in a concentration-dependent manner. Among the synthetic chrysin derivatives (**2**−**11**), the newly synthesized prenylated derivatives (compounds **10** and **11**) exhibited improved PPARγ binding and adiponectin secretion-inducing activity.

To design novel chrysin derivatives with potent adiponectin secretion-inducing activity, the X-ray crystal structure of the PPARγ ligand-binding domain (LBD) complexed with a flavonoid luteolin was analyzed (Supplementary Figure S1).[25] In general, PPARγ ligands interact with PPARγ LBD in the Y-shape ligand-binding pocket (LBP) around the helix (H)3 with three arms (Figure S1B). Both hydrophobic and polar residues are located in Arm I near H12. Arms II and III, which extend from Arm I in parallel with H3, are mainly composed of hydrophobic residues. An interaction with β-sheets near Arms II and III is one common structural feature of PPARγ partial agonists. In the flavonoid-preferable crystal structure of the PPARγ LBD, the C5 and C7 hydroxyl groups of luteolin were located on the LBP entrance near the β-sheets (Figure S1C). To increase the hydrophobic interactions of chrysin derivatives with the hydrophobic Arms II and III, the C5 and/or C7 positions of compound **1** were primarily chosen to modify with hydrophobic methyl, benzyl, or prenyl groups.

The preparation procedures of the synthetic chrysin derivatives (**2**, **9**, **10**, and **11**) are described in Scheme 1. Other chrysin derivatives (**3**−**8**) were prepared as previously described.[26] Chrysin 5-allyl ether (**2**) was prepared from chrysin 7-methoxymethyl (MOM) ether (**A**)[26] by allylation with allyl bromide, followed by deprotection of the MOM group in the resulting chrysin 5-allyl-7-MOM ether (**B**) with a 63% yield for the two steps. The prenylation of chrysin 7-benzylether (**6**)[27] and chrysin 5-benzylether (**3**)[26] with 3,3-dimethylally bromide (prenyl bromide) and K_2CO_3 in dimethylformamide (DMF) gave rise to chrysin 5-prenyl-7-benzylether (**9**, 85%) and chrysin 5-benzyl-7-prenylether (**10**, 96%), respectively. Finally, the bis-prenylation of commercially available chrysin (**1**) with prenyl bromide afforded chrysin 5,7-bisprenylether (**11**) at a 52% yield.

In the pharmacological analyses, we first evaluated the effects of compound **1** and its derivatives **2**−**11** on adiponectin biosynthesis during adipogenesis in hBM-MSCs (Figure 1A). In hBM-MSCs, the compounds or positive control drugs, pioglitazone and telmisartan, were cotreated with adipogenesis-inducing medium containing insulin, dexamethasone, and 3-isobutyl-1-methylxanthine (IDX condition). During adipogenesis in hBM-MSCs, compounds **1**−**6** and **8**−**11** significantly promoted adiponectin biosynthesis at 10 μM compared with the vehicle-treated control (Figure 1B). Compound **1**

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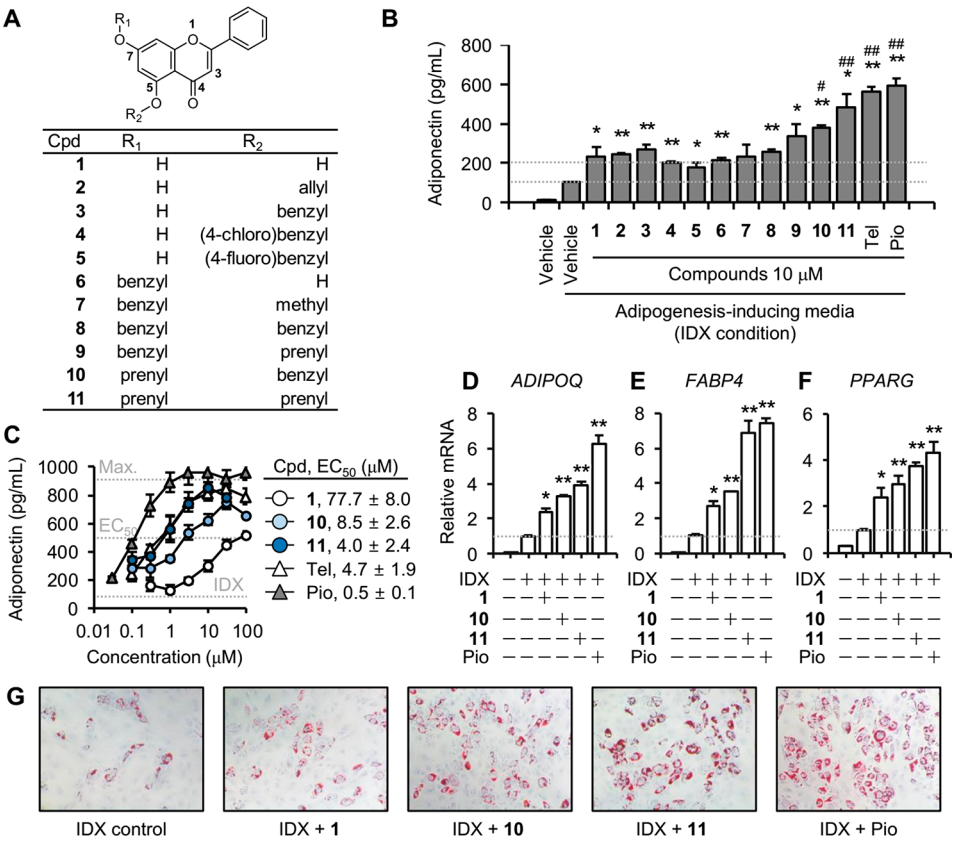

Cpd	R_1	R_2
1	H	H
2	H	allyl
3	H	benzyl
4	H	(4-chloro)benzyl
5	H	(4-fluoro)benzyl
6	benzyl	H
7	benzyl	methyl
8	benzyl	benzyl
9	benzyl	prenyl
10	prenyl	benzyl
11	prenyl	prenyl

Figure 1. Adiponectin secretion-inducing activity of chrysin derivatives (**2**−**11**). (A) Chemical structures of compounds **1**−**11**. (B) Adiponectin-inducing activity was evaluated by treating 10 μM of compounds **1**−**11** or positive control drugs telmisartan (Tel) and pioglitazone (Pio) to hBM-MSCs under the IDX condition. After the adipogenic induction, adiponectin concentrations in culture supernatants were measured by enzyme-linked immunosorbent assay (ELISA). (C) The concentration-dependent effects were determined for compounds **1**, **10**, and **11**. The maximum adiponectin secretion-inducing activity of pioglitazone was set to the 100% response. Effects of chrysin derivatives on the mRNA expression of adiponectin (*ADIPOQ*) (D), fatty acid binding protein 4 (*FABP4*) (E), and PPARγ (*PPARG*) (F). (G) Lipid droplets were visualized with Oil red O staining in differentiated hBM-MSCs. Values represent mean ± standard deviation (N = 3, one-way ANOVA followed by Welch two-sample t test; $^{*}P < 0.05$ and $^{**}P < 0.01$ compared with the IDX control, $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ compared with compound **1**).

increased adiponectin secretion 2.3-fold compared with the IDX condition. The adiponectin secretion-inducing activity of compounds **2**−**6** and **8**−**9** was similar to that of compound **1**. Notably, the prenylation at the 5- or 7-hydroxyl moiety of compound **1** significantly improved the adiponectin secretion-inducing activity. Compounds **9**, **10**, and **11** significantly upregulated adiponectin secretion by 3.3-, 3.8-, and 4.8-fold, respectively, compared with the IDX condition. Compound **10** with a 7-hydroxy prenyl group was more potent than compound **9** whose 5-hydroxyl moiety was prenylated (Figure 1B).

Next, we chose the top two most potent adiponectin secretion-inducing compounds, **10** and **11**, to evaluate their concentration-dependent and phenotypic effects. In the concentration-effect analysis, the adiponectin secretion-inducing activity of chrysin (**1**) reached a half-maximal effect at a concentration near 100 μM when 100% activity was set to the maximum adiponectin secretion-inducing activity of pioglitazone (Figure 1C). In contrast, the half-maximal effective concentration (EC_{50}) values of compounds **10** and **11** were determined to be 8.5 and 4.0 μM, respectively (Figure 1C). As PPARγ partial agonist telmisartan did,[28] compounds **10** and **11** could not reach 100% efficacy, thereby suggesting PPARγ partial agonism of chrysin derivatives. Compounds **10** and **11** showed improved adiponectin-secretion inducing activity by 9−19-fold compared with compound **1**. When the gene transcription of quantitative biomarkers of adipogenesis, adiponectin, fatty acid binding protein 4 (FABP4), and PPARγ were evaluated,[29,30] compounds **10** and **11** more potently upregulated the mRNA levels of adiponectin, FAPB4, and PPARγ than the IDX control and compound **1** (Figures 1D−F). In the phenotypic analysis for differentiated adipocytes, compounds **1**, **10**, and **11** significantly increased the number and size of lipid droplets, which is a major phenotypic change induced by PPARγ agonists, compared with the vehicle control during adipogensis in hBM-MSCs (Figure 1G). These outcomes induced by chrysin derivatives were also observed in hBM-MSCs treated with pioglitazone, a clinically available adiponectin secretion-inducing compound (Figure 1D−G).

The effect of compound **1** on PPARγ activation has been reported in fluorescence- or luminescence-based reporter gene assays.[31] To confirm whether compound **1** and chrysin derivatives directly bind to PPARγ, a time-resolved fluorescence resonance energy transfer (TR-FRET)-based competitive binding assay was performed (Figure 2). Both compounds **10** and **11** significantly replaced the fluorescence-labeled ligand by over 50% at a concentration of 10 μM, like other PPARγ ligands (Figure 2A). When the inhibition constant (K_i) against PPARγ was determined in the

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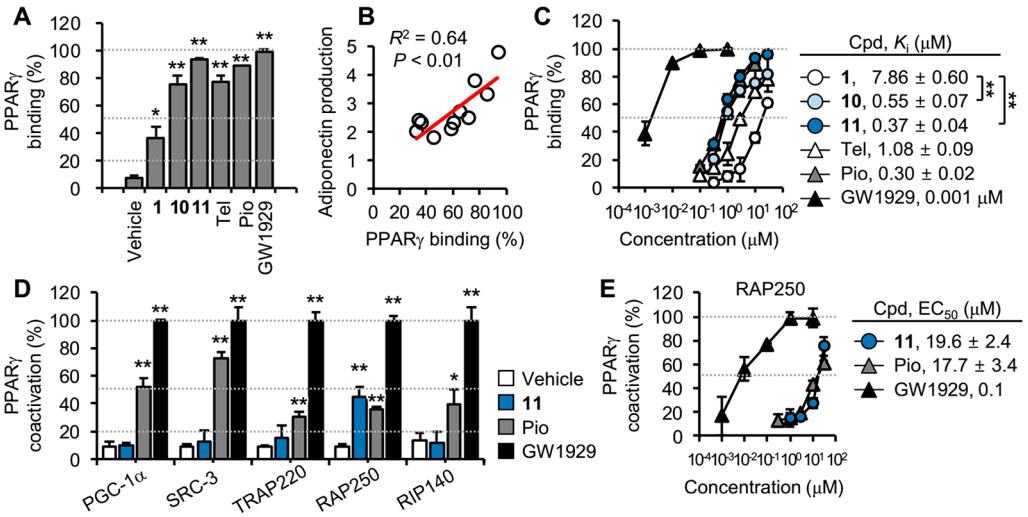

Figure 2. PPARγ agonist properties of compounds **10** and **11**. (A) TR-FRET-based competitive binding assay for PPARγ was conducted for compounds **1**, **10**, and **11** (10 μM). As positive ligand controls, PPARγ partial agonist telmisartan (Tel) and PPARγ full agonists pioglitazone (Pio) and GW1929 were used (10 μM). (B) Concentration-effect analysis of compounds **10** and **11** for PPARγ binding was performed. Cheng and Prusoff analysis was conducted to determine the K_i values. (C) TR-FRET-based coactivator recruitment assay for PPARγ was performed for 10 μM of compound **11**, with 10 μM of Pio and GW1929 as positive controls. The level of coactivator recruitment by ligand-bound PPARγ was evaluated against coactivators PGC-1α, SRC-3, TRAP220, RAP250, and RIP140. (D) Concentration-effect analysis of compounds **11** on RAP250 recruitment upon PPARγ binding. Values represent mean ± standard deviation ($N = 3$, one-way ANOVA followed by Welch two-sample t test; $^*P < 0.05$ and $^{**}P < 0.01$ compared with vehicle control).

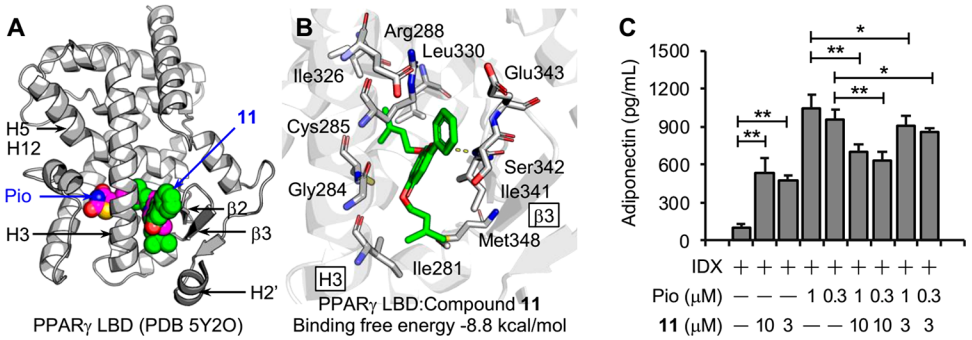

Figure 3. PPARγ partial agonism of compound **11**. (A) Overlaid binding models of compound **11** and PPARγ full agonist pioglitazone (Pio) in the PPARγ LBD. (B) Detailed binding model of compound **11**. Residues closely contact (within 3.5 Å) with compound **11** were labeled, and a suggested hydrogen bond was presented in a yellow dash. (C) Effects of compound **11** on adiponectin biosynthesis when cotreated with Pio. Values represent mean ± standard deviation ($N = 3$, one-way ANOVA followed by Welch two-sample t test; $^*P < 0.05$ and $^{**}P < 0.01$).

concentration-effect analysis, the K_i values of compounds **1**, **10**, and **11** were 7.86, 0.55, and 0.37 μM, respectively (Figure 2B). The PPARγ binding affinities of compounds **10** and **11** were significantly improved by 14−20-fold over that of compound **1**. Notably, their PPARγ binding affinities were comparable with those of the currently prescribed PPARγ full agonist pioglitazone (K_i, 0.30 μM) and PPARγ partial agonist telmisartan (K_i, 1.08 μM), whereas their affinities were far weaker than that of GW1929, *N*-(2-benzoylphenyl)-*O*-[2-(methyl-2-pyridinylamino)ethyl]-L-tyrosine hydrate (K_i, 0.001 μM). For PPARα and PPARδ, chrysin derivatives did not exhibit over 50% binding at up to a concentration of 10 μM (Supplementary Table S1). Therefore, chrysin derivatives functioned as selective PPARγ ligands. Notably, their adiponectin secretion-inducting activity was significantly correlated to the PPARγ binding affinities (Figure 2B), thereby supporting that the PPARγ was mainly responsible for the adiponectin secretion-inducing activity of chrysin derivatives.

The recruitment of coactivator proteins to ligand-bound PPARγ is essential to the transcriptional activation of PPARγ target genes.[13] Thus, compound **11**-induced coactivator recruitment to the PPARγ LBD was investigated by the TR-FRET-based nuclear receptor coactivator assay using the coactivator peptides for PPARγ, PPARγ coactivator-1 alpha (PGC-1α), steroid receptor coactivator-3 (SRC-3), thyroid hormone receptor-associated protein 220 kDa (TRAP220), nuclear receptor-activating protein 250 (RAP250), and receptor-interacting protein 140 (RIP140) (Figure 2C, Table S2). As expected, PPARγ full agonists GW1929 and pioglitazone recruited all coactivator peptides to the ligand-bound PPARγ LBD (Figure 2C). In contrast, the compound **11**-bound PPARγ LBD only significantly recruited the coactivator peptide RAP250 at 10 μM (Figure 2C), thereby also supporting the PPARγ partial agonist characteristics of compound **11**.[32] When the concentration-dependent effect of the RAP250 coactivator recruitment was analyzed, the EC_{50} values of compound **11** and pioglitazone were determined to

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be 19.6 and 17.7 μM, respectively (Figure 2D). In this regard, the prenylated chrysin derivatives could activate PPARγ functions by recruiting RAP250, and their effects on PPARγ were significantly improved compared with those of compound **1**.

Unlike the PPARγ full agonists pioglitazone and GW1929, compound **11** potently recruited only one of the investigated coactivators to the PPARγ LBD, thereby suggesting that compound **11** might function as a PPARγ partial agonist.[33] To elucidate the potential binding mode of the prenylated chrysin derivative compound **11** in the PPARγ LBP, a molecular modeling study was conducted (Figure 3). For the activation of PPARγ, partial and full agonists bind at distinct sites in the PPARγ LBP.[33,34] PPARγ full agonists form hydrogen bonds near the H12 with residues, such as Tyr473 (H12), His323 (H5), and His449 (H12), to stabilize H12 and facilitate coactivator binding, which leads to transcriptional activation. In contrast, PPARγ partial agonists mainly position near β-sheets rather than H12 and partially stabilize H12 via conformational changes.[33,34] When the energy-optimized binding models were compared between pioglitazone and compound **11** in the PPARγ LBP, compound **11** was preferentially located between H3 and the β-sheets (Figure 3A). The prenyl moieties of compound **11** could hydrophobically interact with Ile281, Gly284, Cys285, and Arg288 of H3 and Ile341, Ser342, and Glu343 of the β-sheet (Figure 3B). Notably, compound **11** could form a hydrogen bond with Ser342 through the 1-oxygen atom. As revealed by the combined hydrogen/deuterium exchange analysis with X-ray crystallography study, the Ser342 residue plays an important role in PPARγ activation by partial agonists.[34] Thus, these results indicate that compound **11** may function as a partial agonist of PPARγ. To further experimentally validate the suggested PPARγ partial agonism of compound **11** in the optimized docking model, a competition experiment for adiponectin secretion-inducing activity was performed by cotreating hBM-MSCs during adipogenesis with pioglitazone and compound **11** (Figure 3C). Monotreatment with compound **11** or pioglitazone significantly promoted adiponectin secretion compared with the IDX control. When compound **11** was cotreated with pioglitazone, the adiponectin secretion-inducing activity of pioglitazone was significantly inhibited by compound **11** (Figure 3C). The adiponectin secretion in the 0.3 and 1 μM pioglitazone groups was reduced by 36.1% and 38.2%, respectively, in hBM-MSCs cotreated with the 10 μM compound **11** (Figure 3C).

In this study, we demonstrated that chrysin (**1**) promotes adiponectin biosynthesis during adipogenesis in hBM-MSCs and also directly binds to the PPARγ LBD. In the structure–activity study with synthetic chrysin derivatives (**2**–**11**), the 7-prenylated chrysin derivatives (**10** and **11**) were identified as more potent adiponectin secretion-inducing and PPARγ-binding compounds than chrysin (**1**). Notably, the activity of compounds **10** and **11** was as potent as that of pioglitazone and telmisartan. In contrast to pioglitazone, compound **11** selectively recruited the coactivator peptide for RAP250 to ligand-bound PPARγ. The selective coactivator recruitment and competitive inhibition of pioglitazone-promoted adiponectin synthesis supported that compound **11** was a PPARγ partial agonist. Currently, PPARγ partial agonists are expected to have fewer adverse effects, such as fluid retention, liver injury, and heart failure, compared with TZD-class PPARγ full agonists, while maintaining beneficial metabolic outcomes.[19,35] In this regard, compound **11** represents a novel PPARγ partial agonist pharmacophore with therapeutic potential for treating various metabolic diseases associated with hypoadiponectinemia. Further research on prenylated chrysin derivatives will be directed to pharmacologically elucidate the therapeutic benefits in human diseases related to hypoadiponectinemia.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.2c00511.

Experimental procedures for preparation of synthetic chrysin derivatives and biological evaluation, ^{1}H and ^{13}C NMR spectra, and HRMS results of new compounds (PDF)

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Author Contributions

#These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

hBM-MSC, human bone marrow mesenchymal stem cell; PPAR, peroxisome proliferator-activated receptor; NAFLD, nonalcoholic fatty liver disease; LBD, ligand-binding domain; LBP, ligand-binding pocket; ELISA, enzyme-linked immunosorbent assay; EC_{50}, half-maximal effective concentration; FABP4, fatty acid binding protein 4; TR-FRET, time-resolved fluorescence resonance energy transfer; PGC-1α, PPARγ coactivator-1 alpha; SRC-3, steroid receptor coactivator-3; TRAP220, thyroid hormone receptor-associated protein 220 kDa; RAP250, nuclear receptor-activating protein 250; RIP140, receptor-interacting protein 140

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