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RXR Partial Agonist CBt-PMN Exerts Therapeutic Effects on Type 2 Diabetes without the Side Effects of RXR Full Agonists

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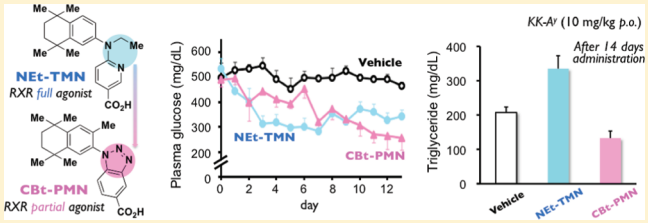
Supporting Information

ABSTRACT: Treating insulin resistance and type 2 diabetes in rodents, currently known retinoid X receptor (RXR) agonists induce significant adverse effects. Here we introduce a novel RXR partial agonist CBt-PMN (**11b**), which shows a potent glucose-lowering effect and improvements of insulin secretion and glucose tolerance without the serious adverse effects caused by RXR full agonists. We suggest that RXR partial agonists may be a new class of antitype 2 diabetes drug candidates.



KEYWORDS: *Nuclear receptors, RXR, partial agonists, type 2 diabetes*

Retinoid X receptors (RXRs) are of interest as nuclear receptors that serve to regulate transcription of genes relevant to diabetes. They function either as homodimers or as heterodimers, for example with peroxisome proliferator-activated receptors (such as PPARγ, the well-known target of thiazolidinedione-type agents to improve insulin resistance) or liver X receptors (LXRs, whose activation induces glucose metabolism and improves glucose tolerance).[1−5] In addition, LXR activation is reported to induce glucokinase expression, which is coregulated with insulin,[6] and to promote insulin secretion via stimulation of pancreatic islets.[7] So-called permissive RXR-heterodimers, such as PPAR/RXR and LXR/RXR, can be activated by RXR agonists alone.[8] Therefore, RXR agonists seem to be promising candidates for improving both insulin resistance and glucose tolerance. Several RXR agonists **1**−**4** (Figure 1) have been evaluated for the treatment of insulin resistance and type 2 diabetes in rodents.[9] However, all of them induce significant adverse effects, such as blood triglyceride (TG) elevation,[10] weight gain,[11] hepatomegaly,[12] and hypothyroidism.[13]

On the basis of a report that structurally different RXR agonists show different patterns of activation of RXR-heterodimers,[14] we previously examined the feasibility of separating the blood glucose-lowering action of RXR agonists from the adverse effects. For this purpose, we administered RXR agonists NEt-TMN (**5**),[15] NEt-3IB (**6a**), and NEt-3IP (**6b**)[16] (Figure 1), which similarly activate RXR, but differently activate PPAR/RXR and LXR/RXR,[17] to KK-A^{y} type 2 diabetes model mice, and we examined the relationship of the RXR-heterodimeric activation pattern to the antihyperglycemic effect and adverse effects such as hepatomegaly and TG elevation.[18] We found that **6a** has a less potent TG-elevating activity and hepatomegaly than the other RXR agonists examined, though all of them showed similar blood glucose-lowering action on repeated administration. This result suggested that it might be possible to separate the therapeutic effects from the side effects of RXR agonists. However, even **6a** shows significant TG-elevation and hepatomegaly. Since all RXR agonists that have been reported to show serious side effects are RXR full agonists that potently activate RXR, we hypothesized that there is a

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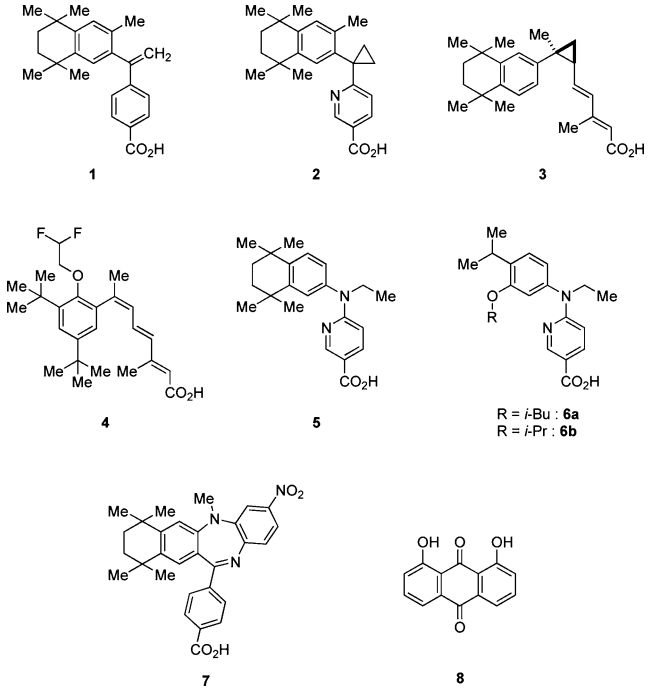

Figure 1. Chemical structures of known RXR ligands.

threshold difference between the therapeutic effects and adverse effects of RXR activation. Therefore, we decided to focus on RXR partial agonists, which would activate RXR only moderately or whose transcriptional efficacy would be limited. We further considered that this idea might be consistent with reports that RXR antagonists HX531 (**7**)[19] and danthron (**8**)[20] (Figure 1) show blood glucose-lowering effects in type 2 diabetes model mice, because partial antagonists are also thought to behave as partial agonists.

To test our hypothesis, we aimed to synthesize RXR partial agonists by modifying the representative RXR agonist structure, focusing on restriction of the molecular flexibility by linking the hydrophobic or acidic domain and the linking domains to form a new ring moiety (Figure 2). Screening of the synthesized

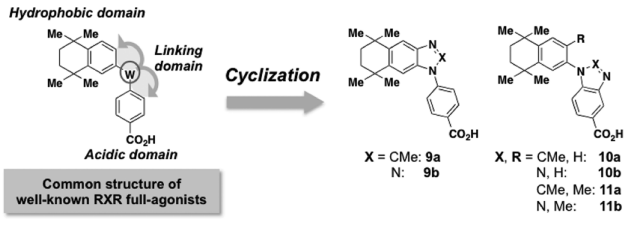

Figure 2. Molecular design strategy for creating RXR partial agonists.

compounds identified CBt-PMN (**11b**) as a novel RXR partial agonist. Studies in mice and rats showed that **11b** did not induce the side effects typically caused by RXR full agonists, while oral administration to KK-A^y mice, a widely used model of type 2 diabetes, resulted in a potent glucose-lowering effect and improved insulin secretion and glucose tolerance. These results indicate that RXR partial agonists may be a new class of antitype 2 diabetes drug candidates without the serious adverse effects shown by RXR full agonists. In this article, we describe the molecular design strategy and the results of the in vitro and in vivo experiments, and we discuss the mechanism of action of **11b**.

In general, representative RXR agonists consist of a hydrophobic domain including 1,1,4,4-tetramethyltetralin, an acidic domain bearing benzoic acid, nicotinic acid, or pyrimidinecarboxylic acid, and a linking domain connecting these domains, as shown in Figure 2. Our design strategy to

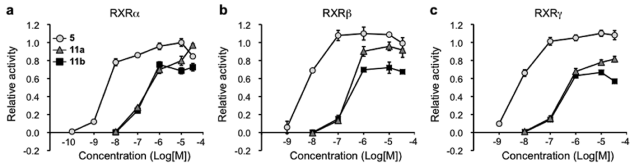

Figure 3. Results of reporter gene assays of **5**, **11a**, and **11b**. COS-1 cells were transfected with three kinds of vectors consisting of a RXR receptor subtype, a luciferase reporter gene under the control of the appropriate RXR response element (CRBPII-tk-Luc), and secreted alkaline phosphatase (SEAP) gene as a background. (a) RXRα, (b) RXRβ, and (c) RXRγ, based on the luciferase activity of 1 μM **1** (RXR full agonist) taken as 1.0. Circles, triangles, and squares indicate **5**, **11a**, and **11b**, respectively. The data (n = 3) represent the mean ± sem. Data for NEt-TMN were taken from ref 18, because these experiments were performed at the same time.

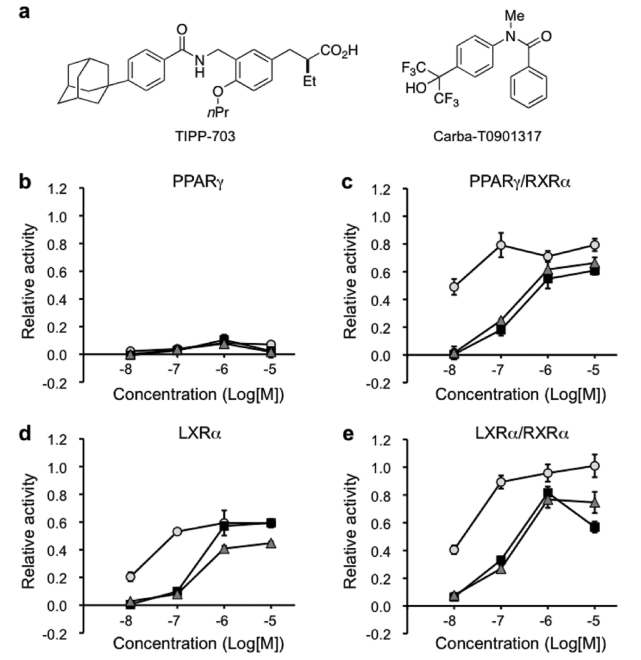

Figure 4. Relative transactivation activities of **5**, **11a**, and **11b** toward PPARγ, PPARγ/RXRα, LXRα, and LXRα/RXRα. COS-1 cells were transfected with four kinds of vectors, consisting of RXRα, a partner receptor (PPARγ or LXRα), the partner response element (tk-PPREx3-Luc for PPARγ or tk-rBARx3-Luc for LXRα), and secreted alkaline phosphatase (SEAP) gene as a background. (a) Chemical structures of TIPP703[21] (PPAR pan-agonist) and carba-T0901317[22] (LXR pan-agonist). (b) Relative transactivation data for PPARγ, based on the luciferase activity of 1 μM TIPP703 taken as 1.0. (c) Relative transactivation data for PPARγ/RXRα, based on the luciferase activity of 1 μM TIPP703 taken as 1.0. (d) Relative transactivation data for LXRα, based on the luciferase activity of 1 μM carba-T0901317 (LXR pan-agonist) taken as 1.0. (e) Relative transactivation data for LXRα/RXRα, based on the luciferase activity of 1 μM carba-T0901317 taken as 1.0. TIPP703 or carba-T0901317 at 1 μM give each E_{max} value. Circles, triangles, and squares indicate **5**, **11a**, and **11b**, respectively. The data (n = 3–6) represent the mean ± sem.

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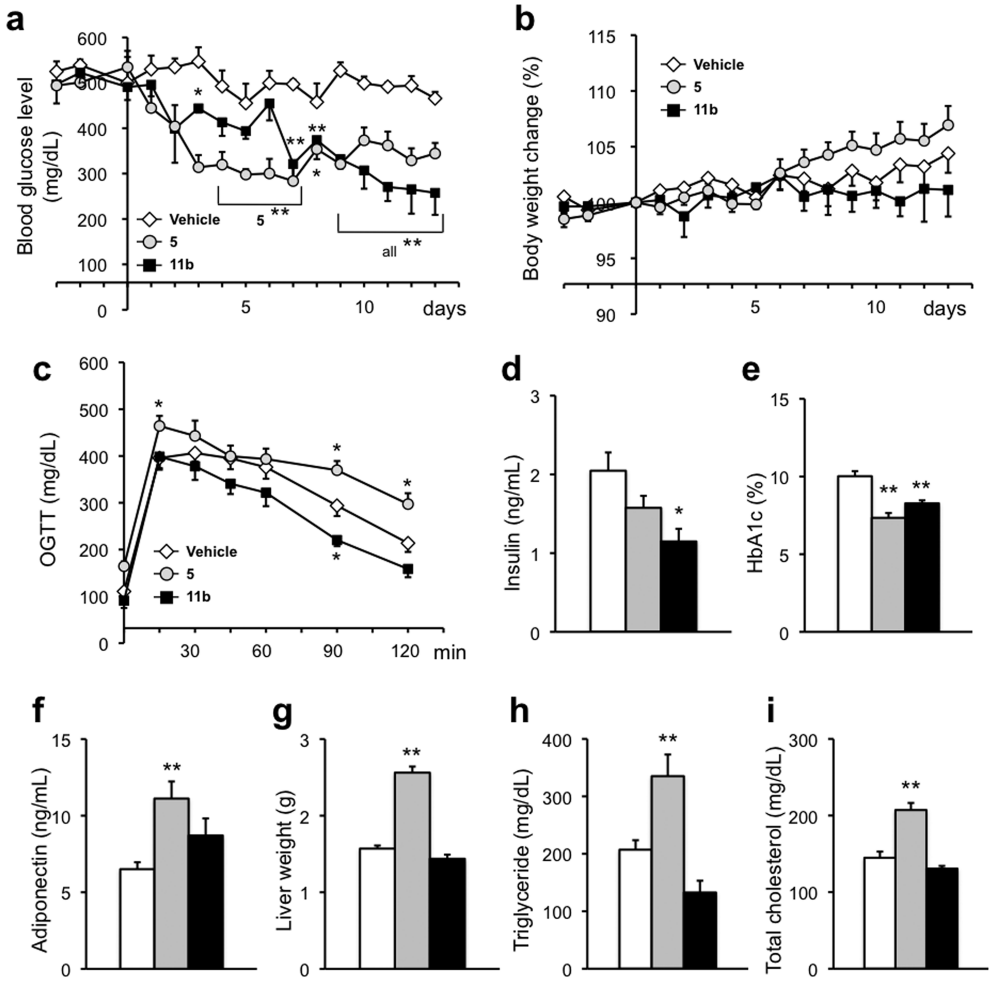

Figure 5. Evaluation of antitype 2 diabetes effects of repeated oral administration of **5** or **11b** at 10 mg/kg/day to male KK-A^y mice for 14 consecutive days. (a) Time course of blood glucose levels. (b) Time course of body weight change. (c) Results of oral glucose tolerance tests (OGTT) in KK-A^y mice treated with vehicle and compounds. (d) Effects of compounds on serum insulin levels. (e) Effects of compounds on serum HbA1c levels. (f) Effects of compounds on adiponectin levels. (g–i) Effects of compounds on liver weight, serum triglyceride, and total cholesterol, respectively. The white, gray, and black bars indicate vehicle, **5**, and **11b** treatment, respectively. The data (n = 3–7) represent the mean ± sem. Data for vehicle control and **5** were taken from ref 18, because these experiments were performed at the same time. Statistical analysis was performed by analysis of variance (ANOVA). Significant differences: * $p < 0.05$ vs vehicle. ** $p < 0.01$ vs vehicle.

obtain RXR partial agonistic activity was to form a ring between the hydrophobic or acidic domain and the linking domain to decrease the molecular flexibility.

Compounds were synthesized as illustrated in Schemes S1 and S2 (see Supporting Information) and evaluated by measuring their RXR-agonistic activities in reporter-gene assays. Although the compounds possessing ring structures between the hydrophobic and the linking domains did not show RXR agonistic activities, compounds **11a** and **11b**, in which the ring was formed between the acidic and the linking domains, did show agonistic activity (Supporting Information Table S2). Interestingly, while **11a**, possessing a 2-methylimidazole structure, showed full agonistic activity, **11b**, possessing a triazole structure, showed only partial agonistic activity toward RXRα (EC_{50} = 143 nM, E_{max} = 75%) (Figure 3a and Supporting Information Table S2). The RXR partial agonist activity of **11b** is thought to be due to not only the closed ring structure but also other factors, including the polarity/positions of the nitrogen atoms. Moreover, **11b** behaved similarly toward other RXR subtypes (Figure 3b,c). The RXR agonistic activity of the full agonist LGD1069 (**1**) at 1 μM was reduced in the presence of increasing concentrations of **11b**, indicating that **11b** acts as a partial antagonist (Supporting Information Figure S1). In addition, **11b** showed moderate RAR activation (Supporting Information Figure S2). These results support the idea that **11b** acts as a RXR partial agonist.

The activities of **11a** and **11b** toward PPARγ/RXRα and LXRα/RXRα were next examined, with RXR full agonist **5** as a positive control.[18] None of the compounds showed PPARγ activity, but compounds **11a** and **11b** showed similar PPARγ/RXRα activation, though they were both less potent than **5** (Figure 4b,c). Compounds **11a** and **11b** also activated both LXRα and LXRα/RXRα less potently than **5** (Figure 4d,e). Since these compounds showed both PPARγ/RXRα and LXRα/RXRα agonistic activities in vitro, we next examined their in vivo activities.

First, it was confirmed that oral single administration of each compound at 30 mg/kg resulted in a serum concentration over 1 μM in ICR male mice (Supporting Information Figure S3). Then, changes in body weight, hepatomegaly, and serum triglyceride (TG) elevation were assessed when each compound was administered orally to ICR mice at 30 mg/

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kg/day for 7 days (Supporting Information Figure S4). The mice given the RXR full agonists **5** and **11a** showed greater body weight gain than did the vehicle control group, and the increase was significant in the case of **5**. In contrast, the group treated with **11b** showed similar body weight change to the control group (Supporting Information Figure S4a). Liver weight was increased significantly by both **5** and **11a**, but not by **11b**, compared to the control group (Supporting Information Figure S4b). Compound **11b** also did not increase serum TG and total cholesterol values compared to the control group, whereas **5** significantly increased the TG level (Supporting Information Figure S4c,d). Further, when **11b** was administered orally to male and female SD rats at 30 mg/kg/day for 28 days, no significant difference in body weight change, water intake, or food intake was observed, compared with the vehicle control (Supporting Information Figure S5). The testes of animals treated with **11b** were slightly enlarged, but the other agents had no such effect (Supporting Information Table S4). As for serum constituents, although some significant differences from the vehicle were observed, the data were within the ranges considered normal by the suppliers (Charles River, Ltd.) (Supporting Information Table S5). Thus, it seems unlikely that the RXR partial agonist **11b** would cause the side effects associated with RXR full agonists.

Next, we examined the antitype 2 diabetes activity in male KK-A^y mice. Compound **5** or **11b** was orally administered at 10 mg/kg/day for 14 days. The average blood glucose level in vehicle-treated mice was about 500 mg/dL, while the level in **5**-treated mice was reduced to about 300 mg/dL from day 3 after the start of administration, showing a significant blood glucose-lowering effect. Compound **11b** also showed a significant blood glucose-lowering effect, although the lag time was longer than that in the case of **5** (Figure 5a). Moreover, **11b** significantly reduced serum insulin concentration (Figure 5d) and HbA1c (hemoglobin A1c, which is correlated with blood glucose levels over a period of time) (Figure 5e) and produced an improvement in the oral glucose tolerance test (OGTT) (Figure 5c), showing significant antitype 2 diabetes effects. Since **11b** improved insulin resistance in KK-A^y mice, we quantitated adiponectin, which is reported to be associated with insulin resistance, and found that **5** increased adiponectin significantly, whereas **11b** did so only moderately (Figure 5f). Since a low adiponectin level is related to insulin resistance, adiponetin elevation by RXR agonists may be correlated with their antitype 2 diabetes effects.

We also evaluated adverse effects in male KK-A^y mice treated with RXR full agonist **5** or RXR partial agonist **11b**. Examination of body weight change, liver weight, serum TG, and total cholesterol revealed that while **5** induced significant increases similar to those seen in ICR mice, **11b** did not alter these parameters in comparison with the vehicle (Figure 5b,g–i). Thus, **11b** appears to have a favorable profile of therapeutic and side effects. The reason why **11b** showed antitype 2 diabetes effects at 10 mg/kg *p.o.* but did not produce significant side effects even when orally administered at 30 mg/kg/day, which provides a serum concentration sufficient to produce the E_{max}, is considered to be its RXR partial agonist character, though other factors such as differences in timing or mechanism of action may also be involved.

To address the mechanism of the antitype 2 diabetes activity of **11b**, we examined changes in the expression levels of genes associated with glucose/lipid metabolism in the liver of KK-A^y mice by means of RT-PCR (Figure 6). It is reported that RXR

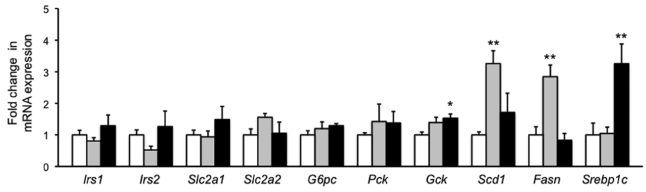

Figure 6. Fold changes in mRNA expression of *Irs1* (a), *Irs2* (b), *Slc2a1* (c), *Slc2a2* (d), *G6pc* (e), *Pck* (f), *Gck* (g), *Scd1* (h), *Fasn* (i), and *Srebp1c* (j) in the liver tissue of male KK-A^y mice treated with vehicle, **5**, or **11b** at 10 mg/kg/day for 14 consecutive days. These measurements were performed using the same mice as in the case of Figure 5. The white, gray, and black bars indicate vehicle, **5**, and **11b** treatment, respectively. The data (n = 3–7) represent the mean ± sem. Statistical analysis was performed by analysis of variance (ANOVA). Significant differences: * $p < 0.05$ vs vehicle. ** $p < 0.01$ vs vehicle.

agonists increase *Slc2a1* (GLUT1) and *Slc2a2* (GLUT2), thereby inducing an increase of liver glucose intake.[23] *Gck* expression is also increased by RXR agonists.[23] Other changes include suppression of *G6p* and *Pck* expression, and increase in expression of *Gck* (related to glycolysis), *Scd1*, *Fasn*, and *Srebp1c*, which are associated with increased lipid synthesis induced by LXR agonists.[6] We also examined changes in expression of *Irs1* and *Irs2*. Neither **5** nor **11b** influenced gene expression of *Irs1*, *Irs2*, *Slc2a1*, *Slc2a2*, *G6pc*, and *Pck*. However, **11b** increased *Gck* expression significantly, indicating that one of the mechanisms of the glucose-lowering effect of **11b** is induction of glycolysis via *Gck*. While **5** markedly increased the gene expression of *Scd1* and *Fasn*, **11b** did not. Since *Scd1* and *Fasn* are associated with lipid synthesis, this result may explain the lack of serum TG elevation by **11b**.

Expression of *Gck*, *Scd1*, and *Fasn* is regulated by *Srebp1c*,[24−26] but **5** had no effect on the expression of *Srebp1c*. It has been reported that *Sreb1c* expression in liver is suppressed by adiponectin.[27] Therefore, the reason why **5** had no effect on *Srebp1c* expression may be that it induced a significant increase of adiponectin, as shown in Figure 6. On the other hand, the partial agonist **11b** activates RXR only moderately, and this may be sufficient to induce expression of *Srebp1c*, which lowers blood glucose, without causing overexpression of *Scd1* and *Fasn*, which induce lipid synthesis. These results are consistent with our hypothesis that there is a threshold difference between the therapeutic and adverse effects of RXR activation. Although an appropriate low dosage of a RXR full agonist may show similar beneficial effects to a RXR partial agonist **11b**, in the case of the overdose medical malpractice, RXR full agonists can cause several adverse effects. Therefore, RXR partial agonists will be more attractive antitype 2 diabetes drug candidates than RXR full agonists.

In summary, we hypothesized that there are different thresholds for the therapeutic effects and side effects of RXR activation. Therefore, we aimed to synthesize RXR partial agonists by reducing the molecular flexibility of the representative RXR agonist structure. As we had hoped, ring formation between the acidic and linking domains with a triazole structure afforded a RXR partial agonist **11b**. This compound showed a significant antitype 2 diabetes effect in KK-A^y diabetic model mice but did not induce the side effects associated with RXR full agonists in ICR mice or SD rats. Compound **11b** did not induce expression of genes associated with lipid synthesis, whereas the full agonist **5** did induce expression of these genes. These results support our hypothesis

of a threshold difference for the therapeutic and side effects of RXR agonists. We believe that RXR partial agonists such as **11b** represent a promising class of candidate antitype 2 diabetes agents.

■ ASSOCIATED CONTENT

Supporting Information

General information, synthetic procedures, combustion analysis data, HPLC charts, luciferase reporter gene assay, and in vivo experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

H.K. conceived and designed the project. N.Y., R.S., and M.H. synthesized compounds. F.O., S.Y., and Y.O. performed reporter gene assays. M.M. prepared plasmids. K.K., M.N., and C.F. performed in vivo experiments with ICR mice and SD rats. A.T. performed HPLC analysis. Y.Y. and H.Y. performed in vivo experiments with KK-A^{y} mice. C.F., S.U., A.M., M.N., and T.O. performed PCR analysis. The manuscript was written by H.K. and F.O.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

RXR, retinoid X receptor; PPAR, peroxisome proliferator-activated receptors; LXR, liver X receptor; RAR, retinoic acid receptor; TG, triglyceride; RT-PCR, reverse transcriptase polymerase chain reaction; *Irs*, insulin receptor substrate; GLUT, glucose transporter; *G6p*, glucose-6-phosphatase; *Pck*, phosphoenolpyruvate carboxykinase; *Gck*, glucokinase; *Scd1*, stearoyl-CoA desaturase 1; *Fasn*, fatty acid synthase; *Srebp1c*, sterol regulatory element-binding protein 1c

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