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**APPENDIX 1**. **Transcriptional activity of PPARs by CG301269 treatment.** ***A-B***. Mouse (***A***) or human (***B***) PPARα expression vector, RXRα expression vector, DR-1 reporter vector and β-gal expression vector were transfected. 1 μM of WY14643 (WY), rosiglitazone (Rosi), GW501516 (GW) or various concentration of CG301269 (CG269; 0.001, 0.01, 0.1 and 1 μM) was treated for 24 hours. Reporter assays was performed as described in **RESEARCH DESIGN AND METHODS**. Each bar represents mean ± S.D. of duplicates. **P* <0.05 vs. (-), ***P* <0.01 vs. (-). ***C-D.*** HEK293 cells overexpressing mouse PPARδ (***C***) or LXR (***D)*** were treated with 1 μM of WY, Rosi, GW, CG301269 or T0901317 (T1317:LXR ligand) for 24 h and analyzed transcriptional activities. Each bar represents mean ± S.D. of duplicates. $^{\#}P$ <0.01 vs. (-). ***E-F***. Mammalian one-hybrid assay. HEK293 cells were transfected with mouse with GAL4-PPARα LBD (***E***) or GAL4-PPARγ LBD (***F***) expression vector and UAS-luciferase vector. After transfection, cells were treated with various concentration of CG301269 for 24 hours and relative transcriptional activities of fusion protein were analyzed. Each line represents means ± S.D. of duplicates. The $EC_{50}$ of CB301269 was denoted. -■-, CG301269; -○-, WY 14643; -◊-, rosiglitazone.

**APPENDIX 2**. Structural formula and electrostatic potential surface illustration of two ligands, (***A***) CG301269 (molecular volume = 337.5 $Å^3$) and (***B***) Ligand-3FEI, 3FEJ (molecular volume = 320.4 $Å^3$). Red and blue colors in electrostatic potential surface illustrations indicate strong negative and positive charge, respectively.

**APPENDIX 3. CG301269 alters trypsin digestion patterns of PPARα and PPARγ.** Trypsin digestion assay was conducted as previous paper (Camp et al., *Diabetes* 49:539-546, 2000) with minor modifications. Briefly, $^{35}$S-Met-labeled, *in vitro* translated mouse PPARα (A) and PPARγ (B) proteins were incubated with or without indicated PPAR agonists (1 μM) in 100 mM Tris buffer (pH 8.0) at RT for 30 min with gentle shaking. Next, except for the first lane, trypsin (10 μg/ml, Sigma) was added and incubated for 10 min. Trypsin digestion reaction was aborted by addition of 5x SDS sampling buffer and separated in 10% SDS-PAGE gel. Labeled PPARs were visualized by image analysis (FLA-7000, Fuji, Japan). * represent altered patterns appeared upon CG269 treatment.

**APPENDIX 4. CG301269 activates PPARα in 3T3-F442A adipocytes.** ***A.*** Differentiated 3T3-F442A adipocytes were incubated with indicated with PPAR agonists for 24 hours. Relative gene expression was analyzed by use of qRT-PCR and normalized with GAPDH. Each bar represents mean ± S.D. of duplicates. □, (-); ◘, WY (1 μM); ▨, Rosi (1 μM); ▩, CG269 (0.5 μM); ▥, CG269 (1 μM); ■, CG269 (5 μM). * *P*<0.05 vs. (-); # *P*<0.01 vs. (-). ***B.*** Differentiated 3T3-F442A adipocytes were incubated with 10 μM of WY, Rosi, or CG269 for 24 hours. Fatty acid oxidation assay was performed as described in **RESEARCH DESIGN AND METHODS**. Each bar represents mean ± S.D. of triplicates. * *P*<0.05 vs. (-); # *P*<0.01 vs. (-).

**APPENDIX 5. CG301269 stimulates the expression of PPARγ target genes.** ***A-B***. 3T3-L1 (***A***) and 3T3-F442A (***B***) adipocytes were incubated with indicated PPAR agonists for 24 hours. ***C***. white adipose tissues (gonadal fat) were dissected from the mice after 4 weeks of treatment. Total RNA was isolated from 3T3-L1 (***A***) and 3T3-F442A (***B***) adipocytes as well as WAT (***C***). Relative expression level of PPARγ target genes was examined as described in Fig. 2. Each bar represents mean ± S.D. of duplicates. ***A-B.*** □, (-); ◘, WY (1 μM); ▨, Rosi (1 μM); ▩, CG269 (0.5 μM); ▥, CG269 (1 μM); ■, CG269 (5 μM). * *P*<0.05 vs. (-); # P<0.01 vs. (-). ***C.*** □, vehicle; ◘, WY; ▨, Rosi; ■, CG269. ***D.*** 3T3-L1

adipocytes were transfected with GFP siRNA or PPARγ siRNA. Cells were treated with indicated PPARγ agonists (1 μM) for 24 hours and relative gene expression was measured by use of qRT-PCR. Each bar represents mean ± S.D. of triplicates. □, GFP siRNA; ■, PPARγ siRNA. * $P$<0.05 vs. GFP siRNA (-); # $P$<0.01 vs. GFP siRNA (-); ¶ $P$<0.05 vs. GFP siRNA + Rosi or CG269.

**APPENDIX 6. Investigation of differentially expressed genes upon CG301269 by microarray analysis.** 3T3-L1 adipocytes were treated with vehicle, rosiglitazone (1 μM) or CG301269 (0.5 or 5 μM) for 24 hours. Rosiglitazone-treated cells were used as the positive control. Changes in gene expression were determined by microarray analysis using Affymix GeneChip. ***A***. Genes with a False Discovery Rate (FDR, $P$<0.05) and fold changes (≥ ± 1.5 fold) were selected as the differentially expressed genes (DEGs). Upregulated or downregulated DEGs were noted. ***B.*** Hierarchical clustering. ***C.*** For functional grouping, DEGs were analyzed using DAVID web tool (http://david.abcc.ncifcrf.gov/home.jsp). Total 246 genes were differentially expressed and relative to vehicle control, the numbers of DEGs induced by CG301269 (5 μM) and rosiglitazone were 170 and 218, respectively. Of 170 DEGs, 91 genes and 79 genes were upregulated and downregulated by CG301269 (5 μM), respectively. Specifically, 7 DEGs were unique to CG301269, which are related to lipid, one carbon and protein metabolism as well as immune responses [**phosphomevalonate kinase (*Pmvk*), methylene tetrahydrofolate dehydrogenase (NADP$^+$ dependent) 1-like (*Mthfd1l*), isoleucine-tRNA synthetase (*Iars*), 1-acylglycerol-3-phosphateO-acyltransferase3 (*Agpt3*), predicted gene 14733 (*GM14733*), GRAM domain containing 1B (*Gramd1b*) and complement factor D (*Cfd*)**]. 163 DEGs were common to both CG301269 (5 μM) and rosiglitazone, which include genes involved in fatty acid metabolism and inflammatory response [for example, **hydroxyacyl-Coenzyme A dehydrogenase (*Hadhb*), resistin (*Rten*), chemokine ligand 12 (*CxCL12*), and inteferone gamma inducible protein 30 (*Ifi30*)**]. As indicated in diagram of functional grouping (***C***), DEGs are associated with metabolic process (25%), inflammatory/immune responses (5%), oxidation/reduction (3%), signal transduction (12%), cell growth/apoptosis (9%), transcription (5%) and others (40%). The partial lists of genes with biological significance were as follows; ***fatty acid metabolism,*** **acyl-CoA thioesterase 2, and aldehyde dehydrogenase 9 subfamily A1; *PPAR signaling pathway*, stearoyl-coenzyme A desaturase 3, oxidized low density lipoprotein (lectin-like) receptor 1, and glycerol kinase; *inflammatory/immune responses*, chemokine (C-X-C motif) ligand 12, interferon gamma inducible protein 30, orosomucoid 1, resistin, and complement factor D (adipsin); *oxidation/reduction*, carbonyl reductase 3 dehydrogenase/reductase (SDR family) member 9 aldehyde dehydrogenase 9, and subfamily A1 oxidoreductase NAD-binding domain containing 1 .**

**APPENDIX 7. CG301269 suppresses the expression of pro-inflammatory genes in 3T3-F442A adipocytes.** Differentiated 3T3-F442A adipocytes were pre-incubated with indicated PPAR agonists for overnight and cells were treated with 1 ng/ml of TNFα for 3 hours. Relative expression of inflammatory genes was evaluated by use of qRT-PCR and normalized with GAPDH. Each bar represents mean ± S.D. of duplicates. □, (-);▤, TNFα 1 ng/ml; ◘, WY 1 μM/TNFα; ▨ Rosi 1 μM/TNFα; ▥, CG269 1 μM/TNFα; ■, CG269 5 μM/TNFα. * $P$<0.05 vs. (-); ** $P$<0.01 vs. (-); # $P$<0.05 vs. TNFα; ¶ $P$<0.05 vs. TNFα.

**APPENDIX 8. CG301269 does not influence food intake in *db/db* mice.** Average daily food intake of PPAR agonist-treated *db/db* mice was calculated and shown as graph. Each bar represents mean ± S.D.

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**APPENDIX 9. CG301269 decreases expression of hepatic lipogenic genes in *db/db* mice.** Relative gene expression of each gene in liver was determined as described in Fig. 6*C*. Each bar represents mean ± S.D. ☐, Veh; ⊠, WY; ▨, Rosi; ■, CG269. * $P<0.05$ vs. Veh; # $P<0.01$ vs. Veh.

**APPENDIX 10. CG301269 does not affect liver size in *db/db* mice.** Macroscopic pictures of liver size and shape from *db/db* mice treated as in Fig. 4***A*** were shown.

**Supplementary Table 1. Docking scores of molecular reported as fine ligand of PPARα and PPARγ.**

| PDB ID | 3FEI (for PPARα) | 3FEJ (for PPARγ) |
|---|---|---|
| Ligand-3FEI,3FEJ | 127.82[a](*100*[b]) | 167.58(*100*) |
| WY14643 | 56.46(*44.2*) | 84.7(*50.5*) |
| Rosiglitazone | 59.5(*46.5*) | 138.42(*82.6*) |
| CG301269 | 133.83(*104.7*) | 162.01(*96.7*) |

[a] Calculated values of –PMF (Potential of Mean Force). [b] Relative values to Ligand-3FEI, 3FEJ.
Protein crystal reference : Chemmedchem 4: 951-956 (2009)

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**Supplementary Table 2. qRT-PCR primer sequences**

| *Gene* | *5' sequence* | *3' sequence* |
|---|---|---|
| ACO | TGTTAAGAAGAGTGCCACCAT | ATCCATCTCTTCATAACCAAATTT |
| Acrp30 | TTGCAAGCTCTCCTGTTCCT | TCTCCAGGAGTGCCATCTCT |
| ADD1 | AATGGTCCAGGCAAGTTCTGGGT | TCCCTCTCAGCTGTGGTGGTGAA |
| aP2 | AAGAAGTGGGAGTGGGCTTT | GCTCTTCACCTTCCTGTCGT |
| CD11b | GACTCAGTGAGCCCCATCAT | AGATCGTCTTGGCAGATGCT |
| CD11c | GAGGATTTCAGCATCCCAGA | CACCTGCTCCTGACACTCAA |
| CD36 | GAGCAACTGGTGGATGGTTT | GCAGAATCAAGGGAGAGCAC |
| CD68 | TTCTGCTGTGGAAATGCAAG | AGAGGGGCTGGTAGGTTGAT |
| COX2 | AGAAGGAAATGGCTGCAGAA | GCTCGGCTTCCAGTATTGAG |
| CPT1 | ACTCCTGGAAGAAGAAGTTCAT | AGTATCTTTGACAGCTGGGAC |
| F4/80 | GCTGCACCTCTGTGCCTTT | CAGGTATGCCATGATGCTTG |
| FAS | GCTGCGGAAACTTCAGGAAAT | AGAGACGTGTCACTCCTGGACTT |
| FATP | ATGCGGGCTCCTGGAGCAGGACAGCC | CTGCGTGTCAGGCAGGATGCTCTCAGGCCC |
| FGF21 | CTGGGGGTCTACCAAGCATA | GCTTTGACACCCAGGATTTG |
| G6Pase | GAGTCTTGTCAGGCATTGCT | GGTACATGCTGGAGTTGAGG |
| G6PD | CCTACCATCTGGTGGCTGTT | CATTCATGTGGCTGTTGAGG |
| GAPDH | TGCACCACCAACTGCTTAG | GGATGCAGGGATGATGTTC |
| IL1β | TGCAGAGTTCCCCAACTGGTACATC | GTGCTGCCCTAATGTCCCCTTGAATC |
| IL6 | AGTTGCCTTCTTGGGACTGA | TCCACGATTTCCCAGAGAAC |
| iNOS | AATCTTGGAGCGAGTTGTGG | CAGGAAGTAGGTGAGGGCTTG |
| LPL | ATGGAGAGCAAAGCCCTGG | AGTCCTCTCTCTGCAATCAC |
| mCAD | AGGTTTCAAGATCGCAATGG | CTCCTTGGTGCTCCACTAGC |
| MCP1 | AGGTCCCTGTCATGCTTCTG | TCTGGACCCATTCCTTCTTG |
| PEPCK | AAAAGCCTTTGGTCAACAAC | AAACTTCATCCAGGCAATGT |
| PPARα | TCTTCACGATGCTGTCCTCCT | CTATGTTTAGAAGGCCAGGC |
| PPARγ | TTGCTGAACGTGAAGCCCATCGAGG | GTCCTTGTAGATCTCCTGGAGCAG |
| PPARδ | GCTGCTGCAGAAGATGGCA | CACTGCATCATGTGGGCATG |
| TNFα | GCCACCACGCTCTTCTGCCT | GGCTGATGGTGTGGGTGAGG |

**Supplementary Table 3. CG301269 does not cause cardiac pathology.**

| Variables | Veh (n = 6) | CG301269 (n = 7) | *P* value |
|---|---|---|---|
| BW (g) | 26.2±2.0 | 26.4±1.7 | n.s |
| Heart (g) | 0.12±0.01 | 0.12±0.01 | n.s |
| Lung (g) | 0.15±0.02 | 0.14±0.01 | n.s |
| Heart/BW (mg/g) | 4.8±0. 27 | 4.8±0.57 | n.s |
| Lung/BW (mg/g) | 5.8±0.12 | 5.8±0.34 | n.s |

C57BL/6 mice subjected to myocardial I/R surgery were injected with vehicle or CG301269 (50 mg/kg, once a day) for 4 weeks and mice were sacrificed The weights of the total heart and lung were normalized to the body weight and used as an index of ventricular hypertrophy and pulmonary congestion, respectively.