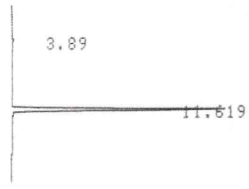
1. *HPLC charts*

1:

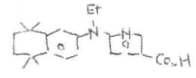


CHROMATOGRAM 1 MEMORIZED

C-R5A CHROMATOPAC
CHANNEL NO 1 FILE 0
SAMPLE NO 0 METHOD 41
REPORT NO 3

PKNO	TIME	AREA	MK	IDNO	CONC	NAME
1	3.89	662			0.7596	
2	11.619	86471			99.2404	
	TOTAL	87133			100	

2:



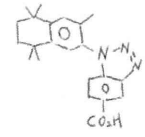
07F05-37
(NEt-TMN)
(AcONH4:MeOH=20:80)

CHROMATOGRAM 1 MEMORIZED

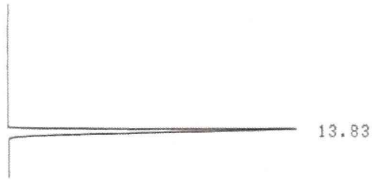
C-R5A CHROMATOPAC
CHANNEL NO 1 FILE 0
SAMPLE NO 0 METHOD 41
REPORT NO 1

PKNO	TIME	AREA	MK	IDNO	CONC	NAME
1	24.918	86773			100	
	TOTAL	86773			100	

4a:



07H06-19
ACONH4 aq. MeOH = 20 : 80



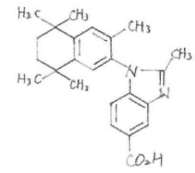
C-R5A CHROMATOPAC

CHANNEL NO	1				FILE	0
SAMPLE NO	0				METHOD	41
REPORT NO	4					

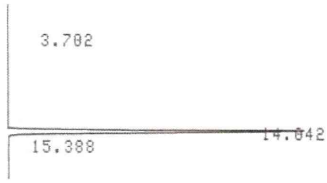
PKNO	TIME	AREA	MK	IDNO	CONC	NAME
1	13.83	3290078			100	
	TOTAL	3290078			100	

4b:

11MHA 1-25 1次目



AcONH4 = MeOH = 20 : 80



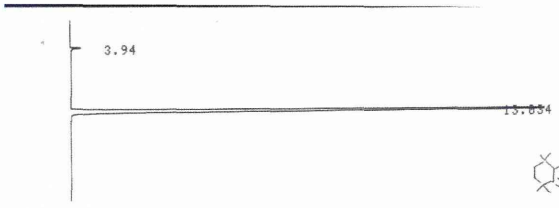
CHROMATOGRAM 1 MEMORIZED

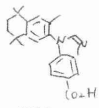
C-R5A CHROMATOPAC

CHANNEL NO	1				FILE	0
SAMPLE NO	0				METHOD	41
REPORT NO	5					

PKNO	TIME	AREA	MK	IDNO	CONC	NAME
1	3.702	535			0.022	
2	14.042	2423895			99.7381	
3	15.388	5829	V		0.2399	
	TOTAL	2430259			100	

6a:





CHROMATOGRAM 1 MEMORIZED

C-R5A CHROMATOPAC
CHANNEL NO 1
SAMPLE NO 0
REPORT NO 2

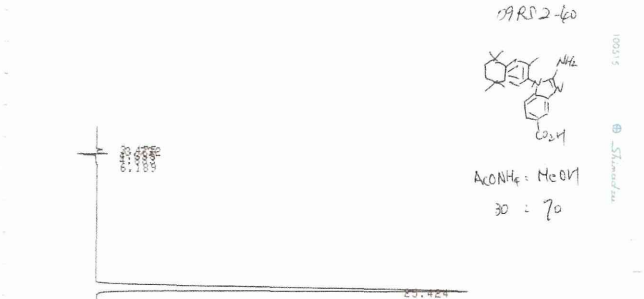
FILE 0
METHOD 41

09RS2-16

酢酸アンモニウム.MeOH
20 : 80

PKNO	TIME	AREA	MK	IDNO	CONC	NAME
1	3.94	3863			1.0982	
2	13.834	347856			98.9018	
TOTAL		351719			100	

6b:



CHROMATOGRAM 1 MEMORIZED

C-R5A CHROMATOPAC
CHANNEL NO 1
SAMPLE NO 0
REPORT NO 2

FILE 0
METHOD 41

PKNO	TIME	AREA	MK	IDNO	CONC	NAME
1	3.475	388			0.0696	
2	3.732	2724	V		0.4884	
3	4.395	6530			1.1709	
4	5.883	13123			2.3532	
5	6.189	411			0.0737	
6	25.424	530861			95.0499	
7	28.072	4423			0.7943	
TOTAL		557666			100	

2. Supplementary Data

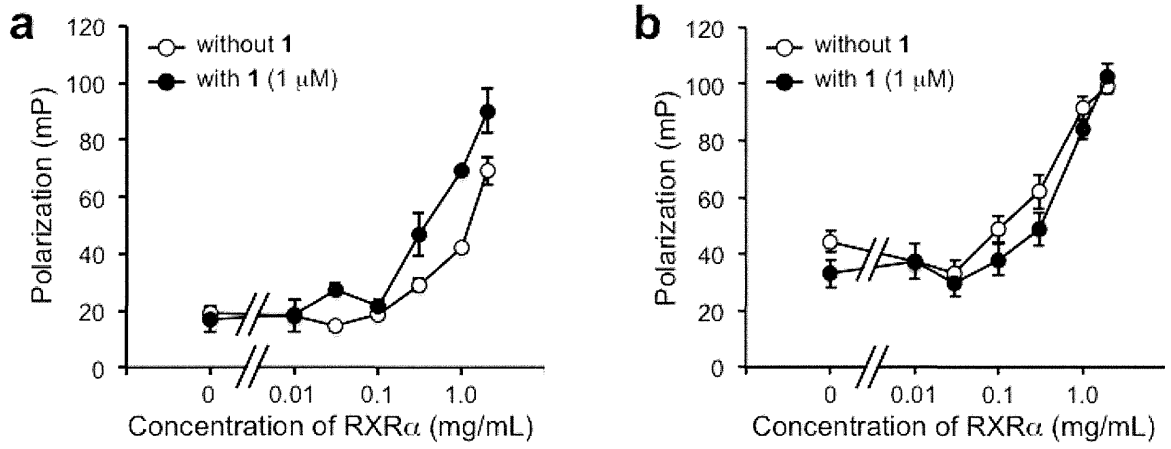


Figure S1. Changes in fluorescence polarization values at various RXR concentrations in the absence (open circles) or presence of 1 μM **1** (closed circles). a) Fluorescein-labeled co-activator peptide D22 (5 nM). b) Fluorescein-labeled co-repressor peptide SMRT-ID2 (5 nM). Fluorescence polarization values, expressed in mP, are the mean ± SEM of measurements obtained from triplicate wells.

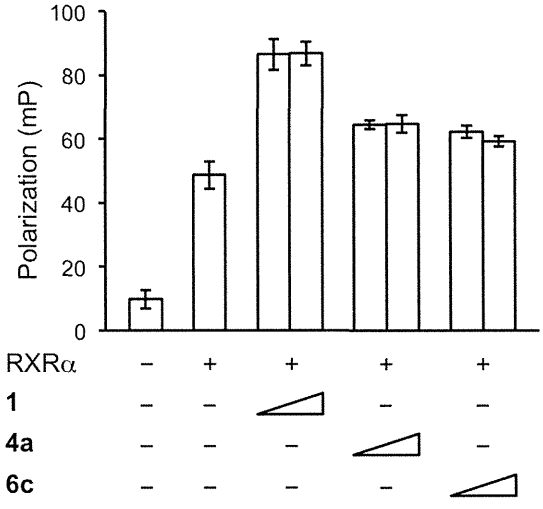


Figure S2. Dose dependency of the effect of RXR agonists at 10 or 33 μM on fluorescence polarization of fluorescein-labeled D22 (5 nM). Fluorescence polarization values, expressed in mP (n = 3–4), are the mean ± SEM. Arrow symbols opposite compound numbers indicate 10 μM (left side/column) and 33 μM (right side/column).

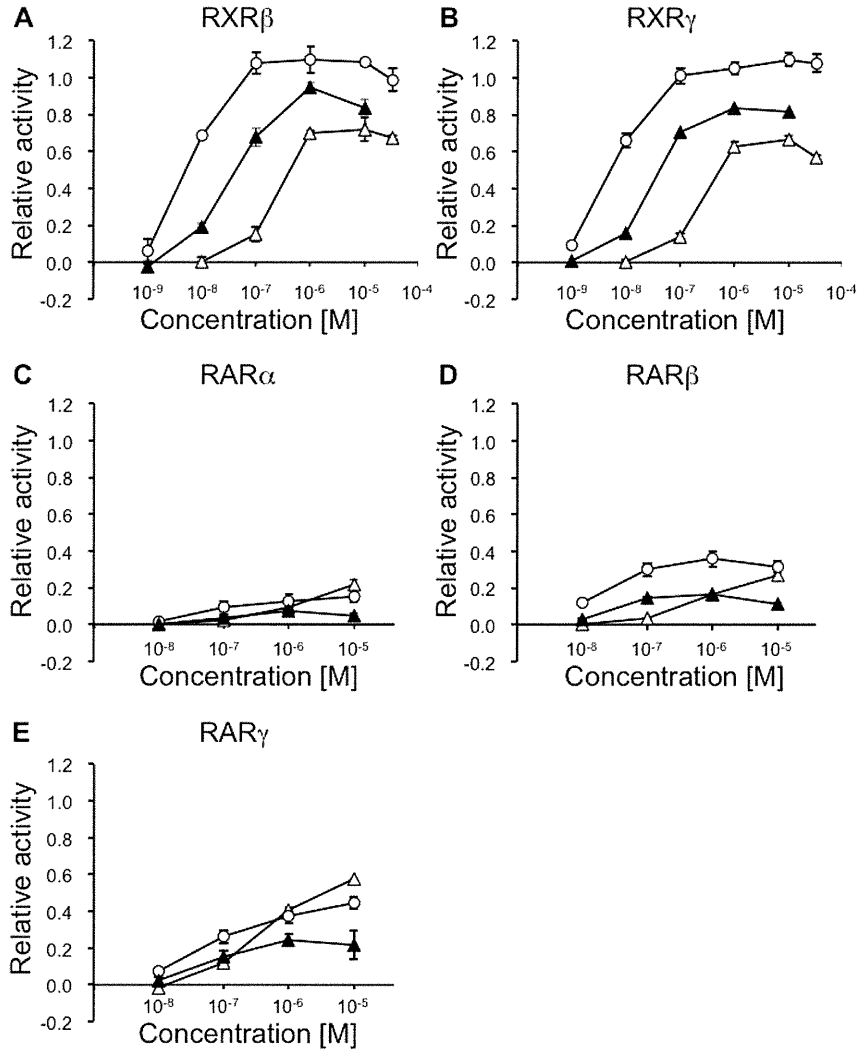


Figure S3. Relative transactivation activities toward RXRβ, RXRγ, RARα, RARβ and RARγ by **2**, **4a** and **6c**. Open circles, triangle and closed triangle indicate **2, 4a** and **6c**, respectively.

A) Relative transactivation data based on the luciferase activity of 1 μM LGD1069 taken as 1.0 toward RXRβ. B) Relative transactivation data based on the luciferase activity of 1 μM LGD1069 taken as 1.0 toward RXRγ. C) Relative transactivation data based on the luciferase activity of 1 μM Am80 (RARα/β selective agonist) taken as 1.0 toward RARα. D) Relative transactivation data based on the luciferase activity of 1 μM Am80 (RARα/β selective agonist) taken as 1.0 toward RARβ. E) Relative transactivation data based on the luciferase activity of 1 μM All-trans retinoic acid (RAR pan agonist) taken as 1.0 toward RARγ.

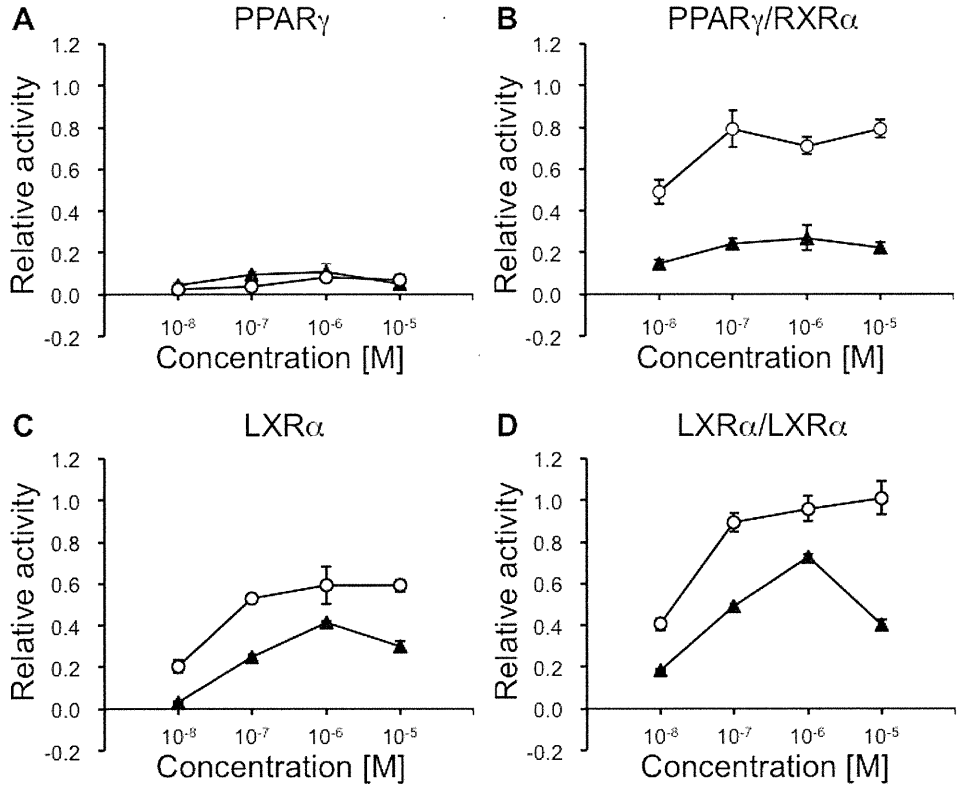


Figure S4. Relative transactivation activities toward PPARγ, PPARγ/RXRα, LXRα and LXRα/RXRα by **2** and **6c**. Open circles and closed triangles indicate **2** and **6c**, respectively. A) Relative transactivation data based on the luciferase activity of 1 μM TIPP703 taken as 1.0 toward PPARγ. B) Relative transactivation data based on the luciferase activity of 1 μM TIPP703 taken as 1.0 toward PPARγ/RXRα. C) Relative transactivation data based on the luciferase activity of 1 μM carba-T0901317 taken as 1.0 toward LXRα. D) Relative transactivation data based on the luciferase activity of 1 μM carba-T0901317 taken as 1.0 toward LXRα/RXRα.

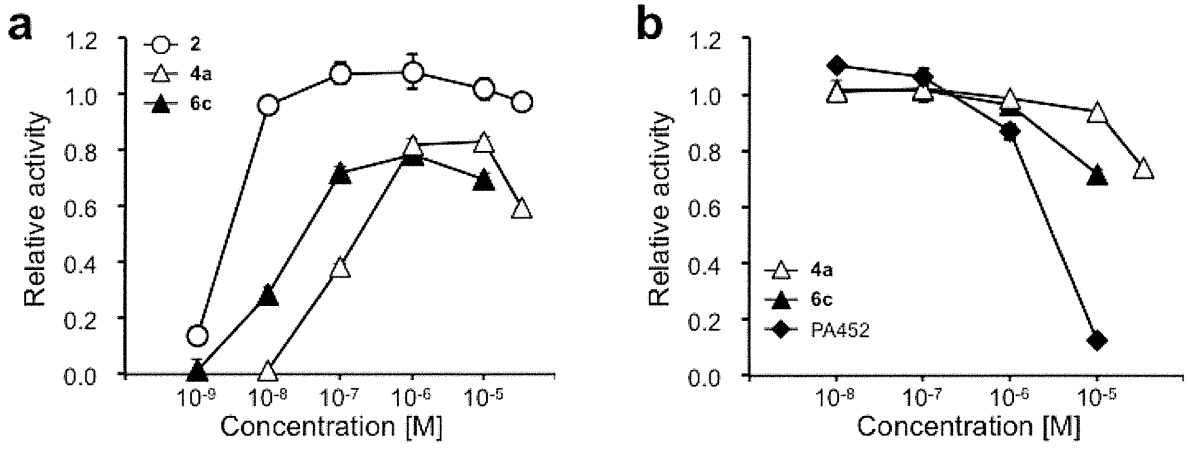


Figure S5. Relative transactivation activities of **2**, **4a** and **6c** toward mouse RXRα. a) Dose-dependence of RXRα agonist activities of **2** (open circles), **4a** (open triangles), and **6c** (closed triangles). b) Dose-dependence of RXRα antagonist activities of **4a** (open triangles), **6c** (closed squares) and RXR antagonist PA452 (closed diamonds) in the presence of 1 μM **1**. COS-1 cells were transfected with three kinds of vectors: mouse RXRα 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. The transactivation activity is shown as relative activity based on the luciferase activity of 1 μM **1** taken as 1.0. Error bars are SEM.

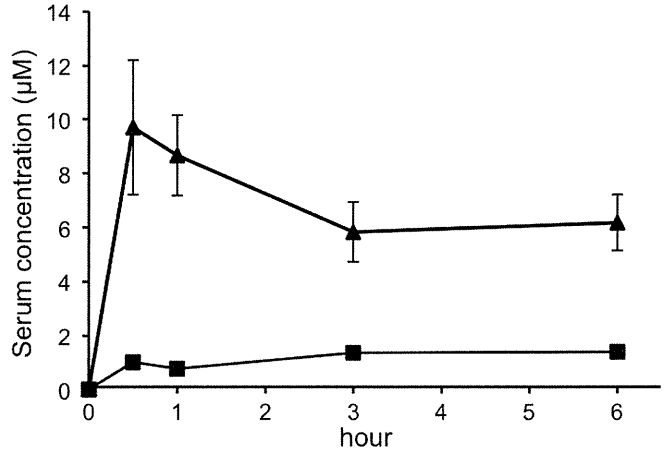


Figure S6. Plasma concentrations of **2** and **6c** in ICR mice after single oral administration of 30 mg/kg. Closed Squares and triangles indicate **2** and **6c**, respectively. The data (n = 5–9) represent the mean ± SEM.

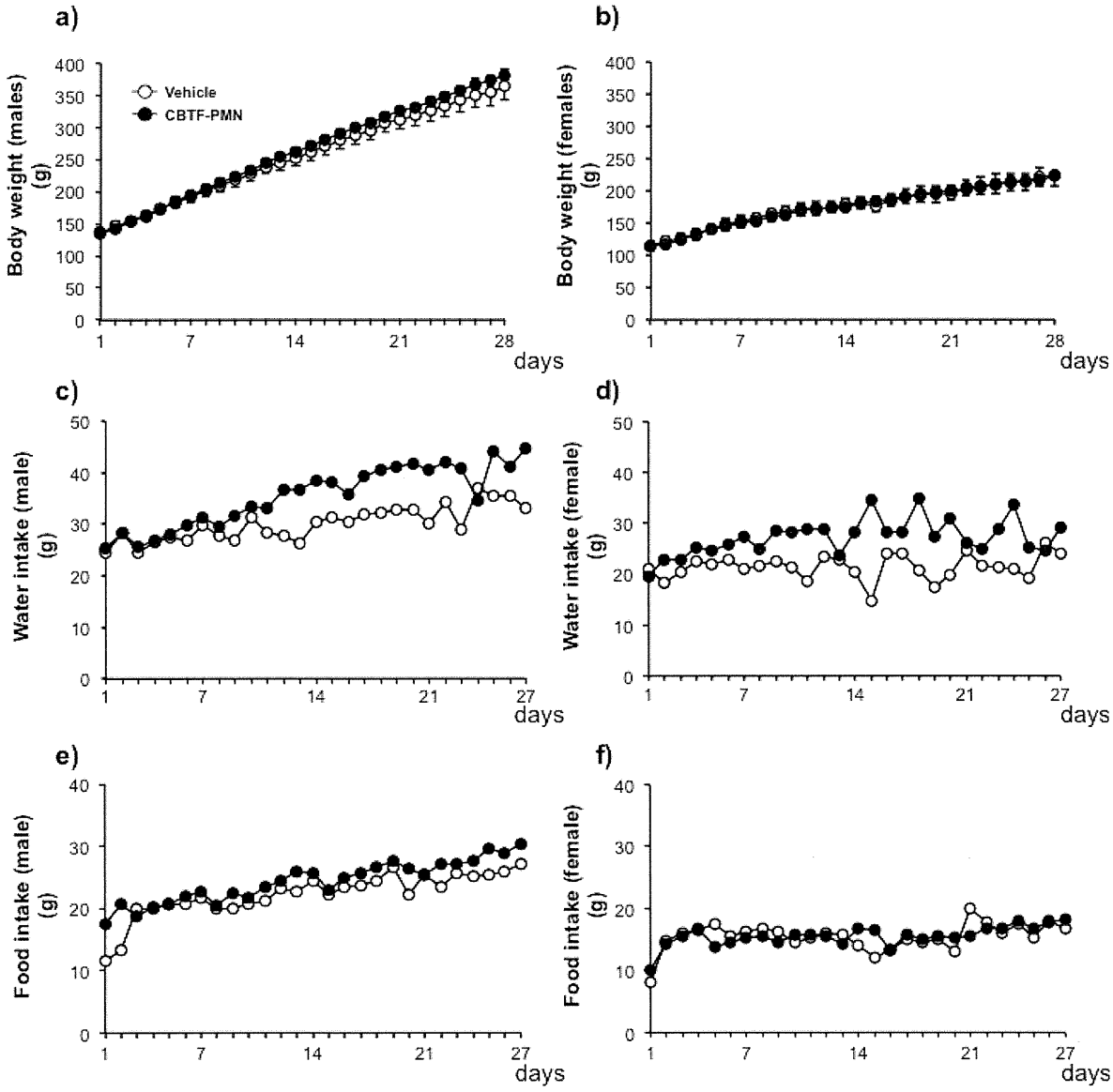


Figure S7. Changes in body weight gain, water intake, and food intake of male or female SD rats treated with oral administration of vehicle or **6c** at 30 mg/kg/day for 28 consecutive days (n = 3–6). a–b) Body weight gain. c–d) Water intake change. e–f) Food intake change. Males: a, c, and e. Females: b, d, and f. Open and closed circles indicate vehicle and **6c** treatment, respectively.

Table S1. Plasma parameters of male ICR mice after oral administration of vehicle, **2**, **4b** or **6c** at 30 mg/kg/day for 7 consecutive days (n = 7–16)

	Vehicle	**2**	**4b**	**6c**
AST (U/I)	54.6 ± 3.8	87.9 ± 18.9**	51.3 ± 3.9	70.1 ± 6.5
ALT (U/I)	22.3 ± 1.5	43.5 ± 6.0**	32.7 ± 6.4*	26.5 ± 2.1
γ-GTP (U/I)	6.1 ± 0.7	7.1 ± 0.3	6.4 ± 0.3	4.5 ± 0.6
ALP (U/I)	281.3 ± 15.7	968.9 ± 115.0**	456.0 ± 51.5*	381.6 ± 58.9
CRE (mg/dL)	D.L.[a]	D.L.	D.L.	D.L.
BUN (mg/dL)	24.1 ± 1.0	26.0 ± 1.8	24.1 ± 2.1	24.8 ± 2.1

a) D.L. means below the detection limit (0.2 mg/dL).

AST : aspartate aminotransferase, ALT : alanine aminotransferase, γ-GTP : γ-glutamyltranspeptidase, ALP : alkaline Phosphatase, CRE : creatinine, BUN : blood urea nitrogen.

Data are mean ± SEM. Statistical analysis was performed by analysis of variance (ANOVA).

Significant differences: * $p < 0.05$ vs. vehicle. ** $p < 0.01$ vs. vehicle.

Table S2. Plasma parameters of male and female SD rats after oral administration of vehicle or **6c** at 30 mg/kg/day for 28 consecutive days (n = 2–6)

	Male			Female		
	Vehicle	**6c**	Reference[a]	Vehicle	**6c**	Reference[a]
AST (U/I)	65.7 ± 6.3	91.7 ± 3.7**	87.0–114.0	69.7 ± 4.8	67.8 ± 2.1	85.0–123.0
ALT (U/I)	30.0 ± 1.7	50.2 ± 2.3**	28.0–40.0	21.7 ± 1.2	37.0 ± 1.2**	25.0–36.0
γ-GTP (U/I)	6.7 ± 0.9	7.0 ± 0.0	0.0–1.0	7.0 ± 0.6	5.8 ± 0.2*	0.0–0.4
ALP (U/I)	703.7 ± 58.6	864.0 ± 94.2	–	382.5 ± 46.5	387.7 ± 31.4	–
CRE (mg/dL)	0.2 ± 0.0	0.2 ± 0.0	0.5–0.6	0.2 ± 0.0	0.2 ± 0.0	0.5–0.6
BUN (mg/dL)	15.5 ± 0.4	14.4 ± 1.4	13.0–16.0	14.5 ± 0.6	15.5 ± 2.0	11.0–16.0
TG (mg/dL)	61.3 ± 9.9	49.0 ± 4.6	61.0–99.0	18.7 ± 4.1	45.2 ± 4.6**	42.0–74.0
TCHO (mg/dL)	50.0 ± 2.5	60.3 ± 4.0	54.0–74.0	57.7 ± 6.9	99.7 ± 6.4**	67.0–87.0

a. These data are taken from the Clinical Laboratory Parameters for Crl:CD(SD) Rats (CRL_Mar, 2006) by Charles River®.

Data are mean ± SEM. Statistical analysis was performed by t-test. Significant differences: * $p < 0.05$ vs. vehicle. ** $p < 0.01$ vs. vehicle.

Table S3. Organ weights of male or female SD rats after oral administration of vehicle or **6c** at 30 mg/kg/day for 28 consecutive days (n = 3–6)

	Male		Female	
	Vehicle	**6c**	Vehicle	**6c**
Weight (g)	339.0 ± 19.1	352.1 ± 7.0	210.2 ± 13.7	206.1 ± 5.4
Brain (g)	1.9 ± 0.1	1.9 ± 0.1	1.7 ± 0.0	1.8 ± 0.0
Liver (g)	10.2 ± 0.8	12.7 ± 0.6*	5.7 ± 0.4	7.6 ± 0.1**
Kidney (g)	2.7 ± 0.1	2.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1
Spleen (g)	0.6 ± 0.0	0.7 ± 0.0*	0.5 ± 0.0	0.5 ± 0.1
Testis (g)	6.1 ± 0.2	6.4 ± 0.2		

Data are mean ± SEM; Statistical analysis was performed by t-test. Significant differences: * $p < 0.05$ vs. vehicle. ** $p < 0.01$ vs. vehicle.