Supplemental Data

Molecular Pharmacology

Anti-obesity effect of a small molecule repressor of RORγ

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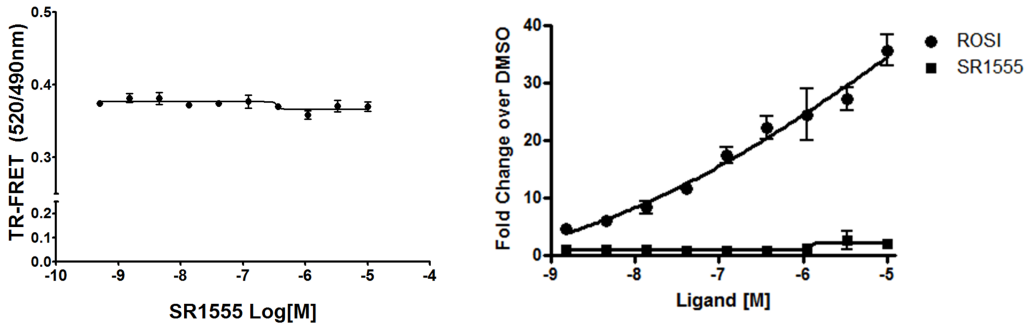
Gene name (*Mus musculus*)	Forward (5'to 3')	Reverse (5'to 3')
aP2 (FABP4)	AAG GTG AAG AGC ATC ATA ACC CT	TCA CGC CTT TCA TAA CAC ATT CC
AdipoQ	TGT TCC TCT TAA TCC TGC CCA	CCA ACC TGC ACA AGT TCC CTT
FGF21	AGC TCT CTA TGG ATC GCC TCA CTT	ACA CAT TGT AAC CGT CCT CCA GCA
RORα	CCA GCT TCC AGT CAG TGG TTA	TGC TCT GGG TCT CGA TGG T
RORγ	CCC GCC ACT CTA TAA GGA ACT CT	AGG GCT GAA GGA AAT AGA AAG TTG T
PPARγ	ACA AGA CTA CCC TTT ACT GAA ATT ACC AT	TGC GAG TGG TCT TCC ATC AC
UCP1	ACT GCC ACA CCT CCA GTC ATT	CTT TGC CTC ACT CAG GAT TGG
PGC1α	CCC TGC CAT TGT TAA GAC C	TGC TGC TGT TCC TGT TTT C
PRDM16	CAG CAC GGT GAA GCC ATT C	GCG TGC ATC CGC TTG TG

Supplemental Figure 1. Primer sequence for Q-PCR analysis

A.

B.



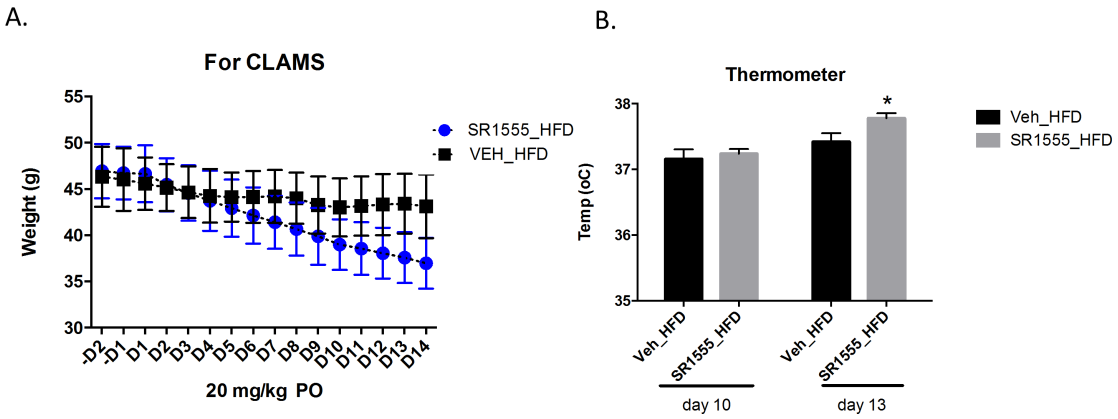
Supplemental Figure 2. PPARG activity (A) LanthaScreen PPARG TR-FRET competitive binding (B)293T cells were cotransfected with Gal4 PPARG along with UAS-luciferase plasmid. The cells were treated for 20hr with indicated concentration of SR1555 or positive control rosiglitazone (ROSI). Relative fold change was determined by normalizing to cells treated with DMSO only (no compound). Each data point was performed in 6 replicates and represented as mean ± SEM, n=6.

Time (hr)	5mg/kg IP [plasma] µM	10mg/kg IP [plasma] µM	20mg/kg PO [plasma] µM
0.25	4.0± 0.1	5.3 ± 0.2	4.4 ± 0.1
0.5	6.3 ± 0.5	8.9 ± 0.7	8.6 ± 0.7
1	6.8 ± 0.6	11.5 ± 0.4	13.6 ± 1.7
2	5.7 ± 0.1	11.6 ± 0.1	16.3 ± 0.1
4	4.1 ± 0.4	8.9 ± 1.0	16.6 ± 2.8
6	2.7 ± 0.6	5.9 ± 3.4	12.4 ± 1.7
8	1.8 ± 0.3	4.3 ± 0.4	9.8 ± 1.7
24	0.1 ± 0.0	0.3 ± 0.1	0.7 ± 0.3

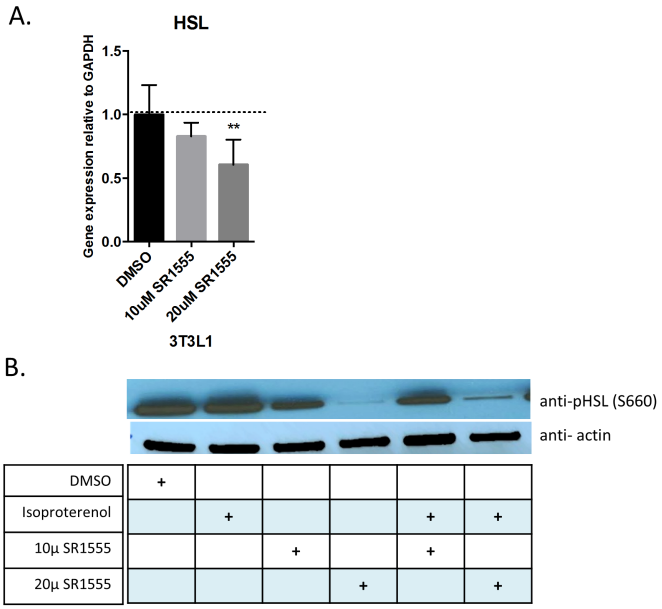
Supplemental Figure 3: *In vivo* plasma drug exposure of SR1555 from bolus administration of compound at 5mg/kg IP, 10mg/kg IP, and 20mg/kg via oral gavage. N=3

Dose	$T_{1/2}$ hr	T_{max} hr	C_{max} µM	AUC_{last} µM*hr	Cl_{obs} ml/min/kg
20mg/kg PO	4.3	3.3	17.0	191	3.8

Supplemental Figure 4: Calculated PK parameters. Plasma concentrations after oral gavage dosing of 20 mg/kg SR1555 were determined and fit to a noncompartimental model in WinNonlin.



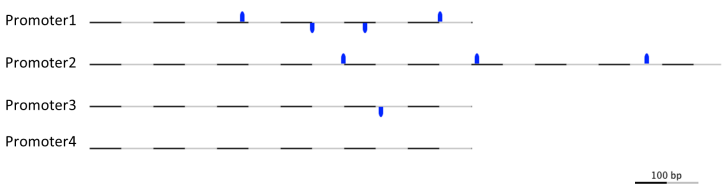
Supplemental Figure 5: DIO mice were administered SR1555 20mg/kg orally 14 days. A) Body weight and B) body temperature at days 10 and 13. Body temperature was recorded with a rectal probe connected to digital thermometer (BA T-12 Microprobe-Thermometer, Physitemp, Clifton, New Jersey, USA).



Supplement Figure 6. HSL activity. Differentiated 3T3L1 cells were incubated with 10µM isoproterenol for 30min to stimulated lipolysis. Relative mRNA level was measured by qPCR (A) and phosphorylated HSL (Ser660) was detected by western blot and actin was used for control (B)

A.

Seq. name	Accession no.	Gene symbol	Start position	End position	Strand	Consensus Sequence
Promoter1	NC_000073	Lipe	238	244	+	ATTTGGG
Promoter1	NC_000073	Lipe	348	354	-	ATCTGGG
Promoter1	NC_000073	Lipe	431	437	-	AAATAGG
Promoter1	NC_000073	Lipe	549	555	+	AAGTGGG
Promoter2	NC_000073	Lipe	397	403	+	AACTGGG
Promoter2	NC_000073	Lipe	607	613	+	AACTAGG
Promoter2	NC_000073	Lipe	874	880	+	AAGTGGG
Promoter3	NC_000073	Lipe	456	462	-	AACTGGG



B.

- >Promoter1|sym=Lipe|taxid=10090|spec=Mus musculus|chr=7|ctg=NC_000073|str=(-)|start=26183628|end=26184229|len=602|comm=Promoter Region
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AGACTCCTTAAGTATTCCTCTGGTATCAGGAGGGGGAAAAGTACTGAACTATAGTGGTACACACCTGTGGTCACAGAATT
TGGGAAATGAAGACAGGAAGAATAGTAGTAGCTTGAGGCCAGCCTGGGCTACATGAGTTTCCCATCTCTGGGGGTAGGGA
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- >Promoter2|sym=Lipe|taxid=10090|spec=Mus musculus|chr=7|ctg=NC_000073|str=(-)|start=26180906|end=26181898|len=993|comm=Promoter Region
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- >Promoter3|sym=Lipe|taxid=10090|spec=Mus musculus|chr=7|ctg=NC_000073|str=(-)|start=26175025|end=26175625|len=601|comm=Promoter Region
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- >Promoter4|sym=Lipe|taxid=10090|spec=Mus musculus|chr=7|ctg=NC_000073|str=(-)|start=26165828|end=26166428|len=601|comm=Promoter Region
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GACTTGAGCAACTCAGAGCCTTCAGACAGCCCCGAGATGTC

Supplemental Figure 7. (A) ROR response elements in the promoter of HSL (B) HSL promoter sequence contained RORE