Supplementary Fig. 1

A. Food intake (g/day)

B. Body weight (g)

C. EWAT (g)

D. IWAT (g)

E. Liver weight (g)

F. Micrographs: Veh vs. Amx

G. Cholesterol (mg/dl)

H. Triglyceride (mg/dl)
Supplementary Figure 1. Amlexanox reduces body weight and fat mass in mice fed with Western diet. A-F. *Ldlr*<sup>-/-</sup> mice were fed WD for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of WD feeding. **A.** Food intake. **B.** Body weight. **C.** Weight of epididymal white adipose tissue. **D.** Weight of inguinal white adipose tissues. **E.** Liver weight. **F.** H&E staining of liver sections. G-H. *Ldlr*<sup>-/-</sup> mice were fed normal chow diet for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of chow diet feeding. **G.** Fasting serum cholesterol. **H.** Fasting serum triglyceride. Mean ± SEM. *, P<0.05, Student’s unpaired t test.
**Supplementary Figure 2. The effects of amlexanox on circulating levels of total fatty acids.** Lipidomic profiling of plasma from fasted Ldlr<sup>-/-</sup> mice fed WD for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of WD feeding. **A.** Total fatty acids. **B.** Saturated fatty acids. **C.** Unsaturated fatty acids. **D.** Species of saturated fatty acids. **E.** Species of unsaturated fatty acids. Mean ± SEM. *, P<0.05, Student’s unpaired t test.
Supplementary Fig. 3

A

B

C
**Supplementary Figure 3. Amlexanox affects hepatic transcriptome.** Transcriptomic profiling of livers from *Ldlr<sup>−/−</sup>* mice fed WD for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of WD feeding. **A.** MA plot of RNA-seq data. **B, C.** Relative expression values (Z-scaled log<sub>2</sub>(TPM+1)) for genes involved in fatty acid metabolism (B) or inflammation (C).
Supplementary Figure 4. Amlexanox does not affect the number of circulating monocytes in mice fed chow diet. Circulating monocytes in Ldlr−/− mice were fed normal chow diet for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of feeding.
**Supplementary Figure 5. Amlexanox affects transcriptome of aortic vessel.** Transcriptomic profiling of aorta from \textit{Ldlr}^{-/-} mice fed WD for 3 weeks, then orally gavaged with vehicle or amlexanox for 8 weeks with the continuation of WD feeding. **A.** Scatterplot of RNA-seq data. **B.** Gene Set Enrichment Analysis of differentially expressed transcripts related to interferon gamma response, TGF\(\beta\) signaling, P53 pathway and apoptosis in aorta of vehicle or amlexanox treated WD-fed \textit{Ldlr}^{-/-} mice.