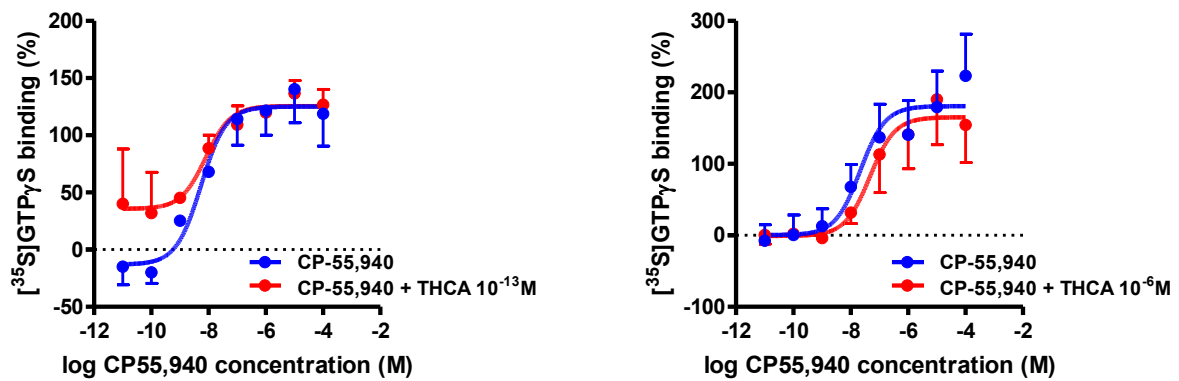


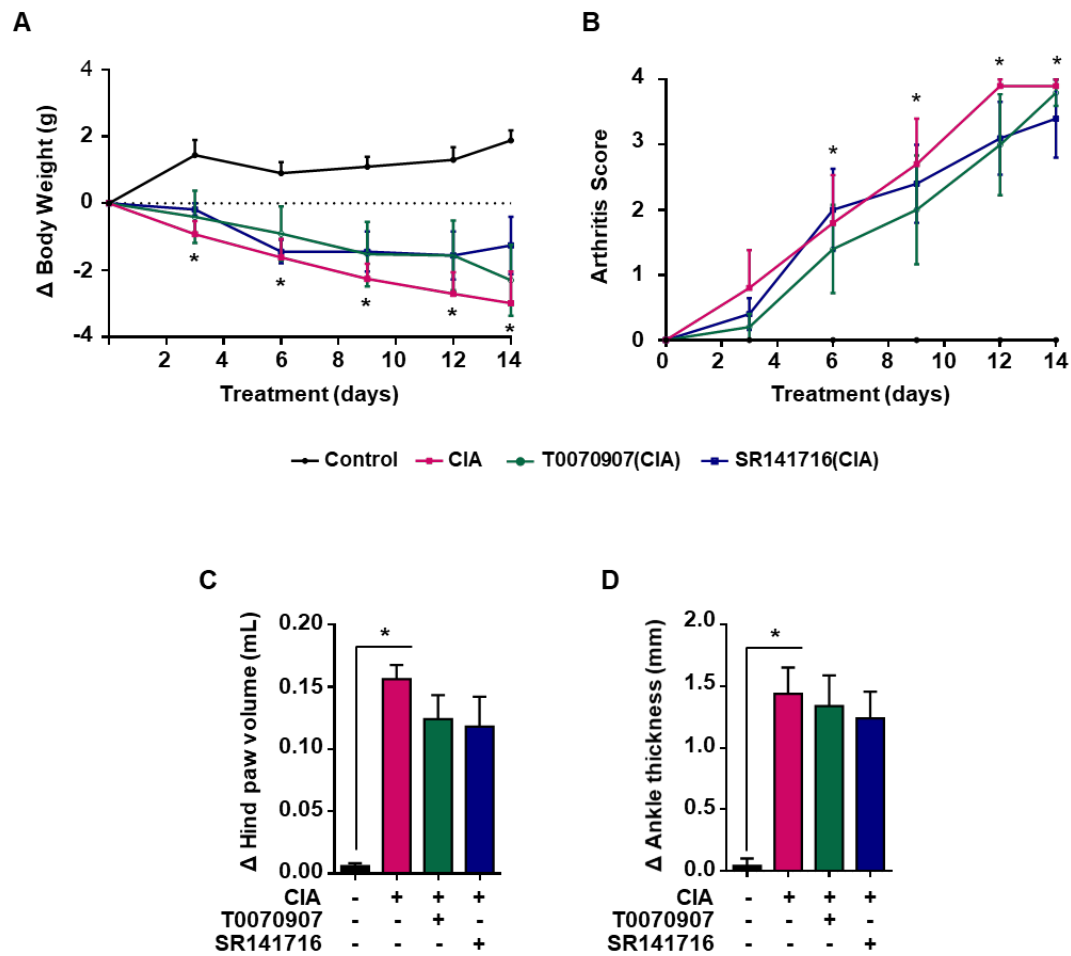
## SUPPORTING INFORMATION

Supplemental Table 1: The primer sequences for the quantitative real-time PCR were:

Gene	Forward (5' → 3')	Reverse (5' → 3')
<b>m-TNF<math>\alpha</math></b>	CTACTCCCAGGTTCTCTTCAA	GCAGAGAGGAGGTTGACTTTC
<b>m-ICAM1</b>	GTGGCGGGAAAGTTCTG	CGTCTTGCAGGTCATCTTAGGAG
<b>m-CXCL16</b>	CGTTGTCCATTCTTTATCAGGTTCC	TTGCGCTCAAAGCAGTCCA
<b>m-ADAMTS5</b>	GGCATCATTCATGTGACACC	CGAGTACTCAGGCCCAAATG
<b>m-IL-17</b>	TTCATGTGGTGGTCCAGCTTTC	CCTCAGACTACCTCAACCGTTC
<b>m-MMP-13</b>	CTTGATGCCATTACCAGTC	GGTTGGGAAGTTCTGGCCA
<b>m-iNOS</b>	AACGGAGAACGTTGGATTTG	CAGCACAAGGGGTTTTCTTC
<b>m-COX-2</b>	TGAGCAACTATTCCAAACCAGC	GCACGTAGTCTTCGATCACTATC
<b>m-RANKL</b>	ATGATGGAAGGCTCATGGTTGG	CAGCATTGATGGTGAGGTGTG
<b>m-IL-1<math>\beta</math></b>	CTCCACCTCAATGGACAGAA	GCCGTCTTTCATTACACAGG
<b>m-IL-6</b>	GTATGAACAACGATGATGCACTTG	ATGGTACTCCAGAAGACCAGAGGA
<b>m-MCP-1</b>	AAGTCCCTGTCATGCTTCTG	TCTGGACCCATTCCTTCTTG
<b>m-GAPDH</b>	TGGCAAAGTGGAGATTGTTGCC	AAGATGGTGATGGGCTTCCCG

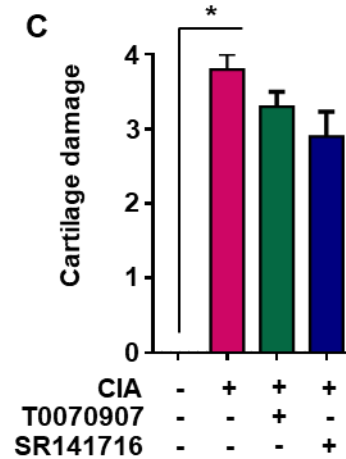
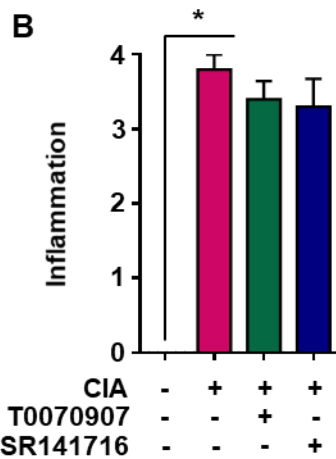
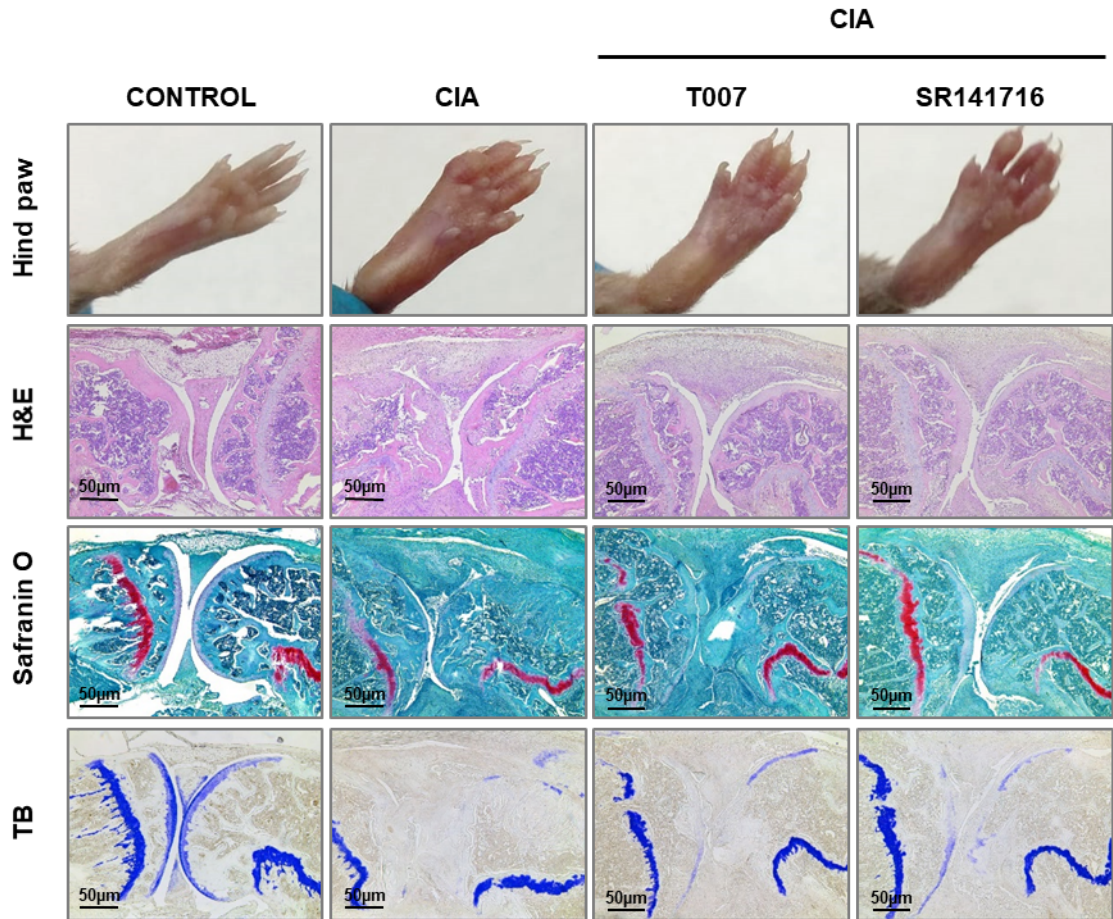


**Figure S1.**  $[^{35}\text{S}]\text{-GTP}\gamma\text{S}$  binding stimulated by CP-55,940 ( $10^{-4}$ - $10^{-11}$ M) in the absence or presence of  $\Delta^9\text{-THCA-A}$  ( $10^{-13}$  or  $10^{-6}$ M). Data were expressed as mean  $\pm$  SEM of at least three experiments performed in triplicate for each point, and were assessed by a two-way ANOVA followed by Bonferroni's posthoc test to compare CP-55,940 +  $\Delta^9\text{-THCA-A}$  vs. CP-55,940 alone

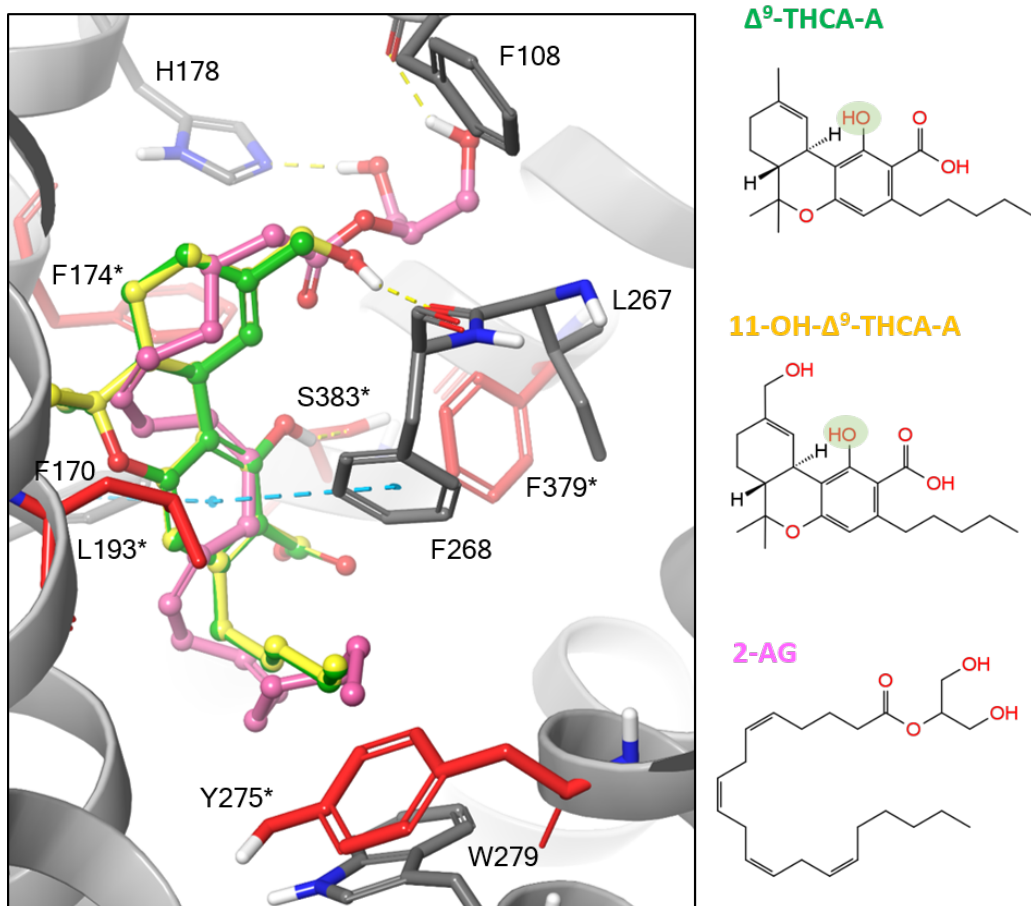


**Figure S2.** Effect of administration of CB<sub>1</sub> and PPAR<sub>γ</sub> antagonists in a CIA model. (A) Cumulative body weight change and (B) clinical scores in control mice, CIA-induced mice and treated mice during the treatment; values are referenced at the beginning of treatment (taken as 0). Measurement of paw swelling using a (C) plethysmometer and a (D) caliper at the end of the two-week treatment period. Data are means ± SEM (n= 5 mice per group). For (A, B) \*p<0.05 CIA mice vs. control mice; for (C, D) \*p<0.05.

A



**Figure S3.** Effect of CB<sub>1</sub> and PPAR<sub>γ</sub> antagonists on knee joints of the hind limbs in CIA mice. (A) Representative hind paw images and joint sections with H&E, safranin O and toluidine blue staining (Original magnification 40X). (B) Scoring of histological inflammation was determined using the criteria described in material and methods. (C) Cartilage damage was evaluated based on safranin O and toluidine blue staining according to the criteria described in materials and methods. Data are presented as mean ± SEM (n=5). \*p<0.05.



**Figure S4.** Rigid (receptor) top docking results of  $\Delta^9$ -THCA-A, 11-OH- $\Delta^9$ -THCA-A and 2-AG to the orthosteric site of CB<sub>1</sub> X-RAY structure PDB 5XR8. Residues interacting with ligands are shown and important residues identified by mutagenesis experiments are depicted in red sticks and labeled with an asterisk. Color coding for  $\Delta^9$ -THCA-A, 11-OH- $\Delta^9$ -THCA-A and 2-AG are in green, yellow and pink, respectively