## Supplementary materials:



**Figure S1.** RAW264.7 cells were treated with indicated reagents for 24 hours. The gene expression of *NFATc1* was detected by real-time PCR. The results are expressed using delta-delta Ct method. *GAPDH* was used as an endogenous control to normalize each sample. Data were expressed as mean  $\pm$  SD. \*p <0.05.



**Figure S2.** Bone marrow macrophages (BMMs) were cultured on 10 cm dish with M-CSF (10 ng/mL) and RANKL (50 ng/mL) for 7 days to generate mature OCs. The mature OCs were resuspended in 15 mL tube after trypsinization and seeded onto Osteo-Assay Surface 96-well plates and cultured in triplicate with indicated reagents and M-CSF (10 ng/mL) for 2 days. Data are expressed as mean ± SE.



from day 1 to day 2.

BMMs were treated Dox and/or Febu from day 5 to day 10.

**Figure S3. (A)** Bone marrow macrophages (BMMs) were cultured in quadruplicates with M-CSF (10 ng/mL) and RANKL (50 ng/mL) for 10 days. Cells were treated with Febuxostat (Febu) at 60  $\mu$ M from day 1 to 2 or from day 5 to 10. TRAP-positive cells containing three or more nuclei per well were counted. Data are expressed as mean  $\pm$  SD. \*p <0.05. Representative photos are shown. Original magnification, ×100. Bar, 100  $\mu$ m. **(B)** BMMs were cultured in triplicates with M-CSF (10 ng/mL) and RANKL (25 ng/mL) in the presence or absence of Dox (0.1  $\mu$ M) or Febu (60  $\mu$ M) for the initial 2 days. Then, the culture medium was changed and the cells were cultured M-CSF (10 ng/mL) and RANKL (25 ng/mL) for the additional 8 days (left). BMMs were cultured in triplicates with M-CSF (10 ng/mL) and RANKL (25 ng/mL). At day 5, Dox (0.1  $\mu$ M) and/or Febu (60  $\mu$ M) was added and cultured for 5 days. TRAP-positive cells containing three or more nuclei per well were counted at day 10. Data are expressed as mean  $\pm$  SD. \*p <0.05.



**Figure S4.** MM.1S and RPMI 8226 cells were pre-treated with H2DCFDA reagent at 10  $\mu$ M for 30 minute. Cells were washed and re-suspended in culture media, and then the cells were treated with Dox (3.0  $\mu$ M) for 2 hours. Cells were washed and re-suspended in PBS. ROS production in MM cells was detected with microplate reader SpectraMax i3 (Molecular Devices, California, USA). Data are expressed as mean ± SD. \*p <0.05.



**Figure S5.** BMMs were cultured with M-CSF (10 ng/mL) and RANKL (50 ng/mL) to generate mature OCs. Then, culture medium was changed and the OCs were cultured in triplicates with the indicated doses of Dox for 48 hours. TRAP-positive multinucleated cells containing three or more nuclei per well were counted (left). Intact OCs were also counted by F-actin ring staining on glass bottom 96-well plates. Representative photos are shown (right). Results are expressed as mean  $\pm$  SD.



**Figure S6.** The mature OCs generated from BMMs were cultured with the indicated reagents for 24 hours. Cell lysates were collected, and PIM2 protein levels were analyzed by Western blotting.  $\beta$  -actin served as a loading control. The band sizes of PIM2 was densitometrically compared to those of a control after normalization to those of  $\beta$ -actin.

# Figure 1E



## Figure 3B



