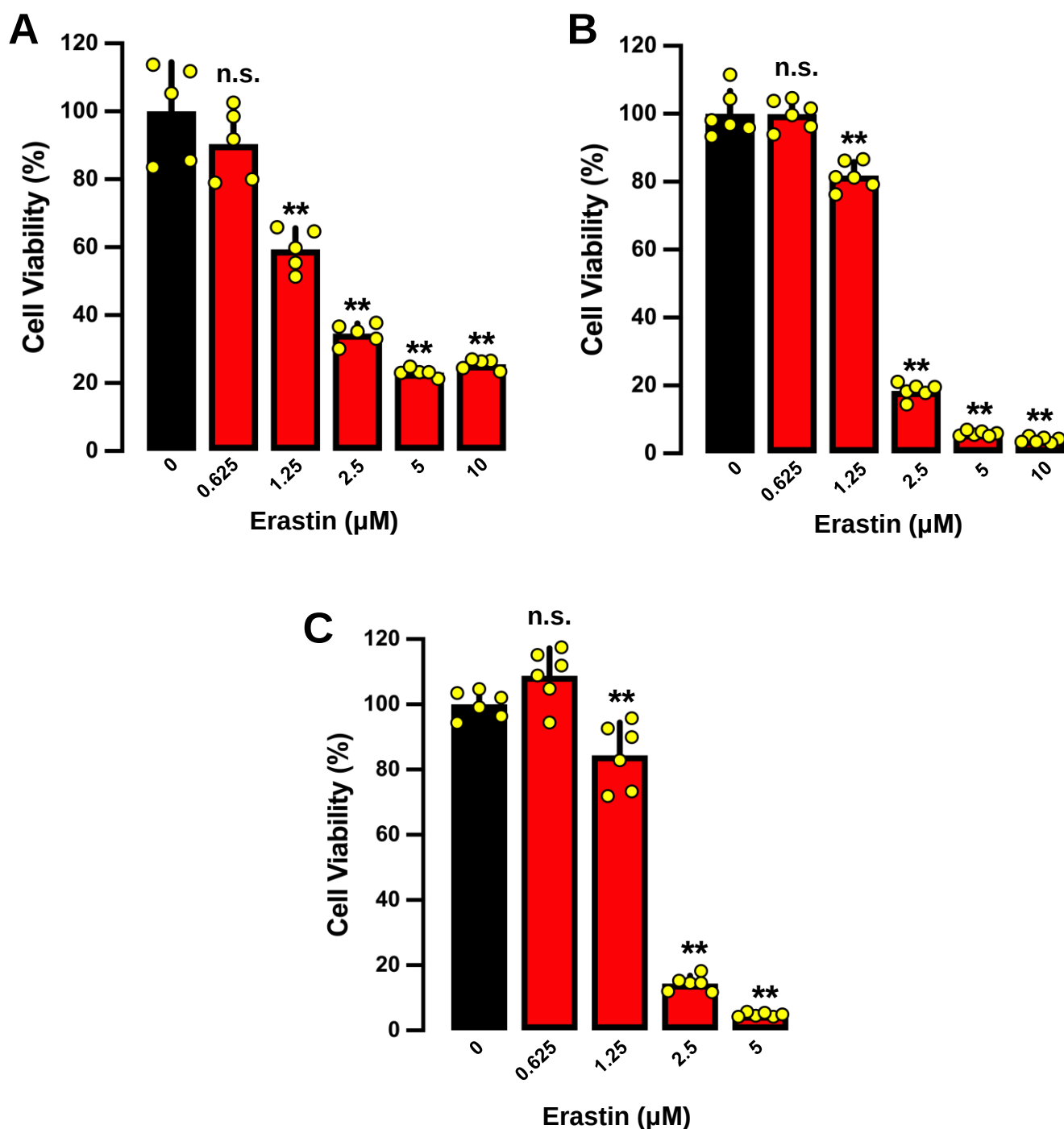


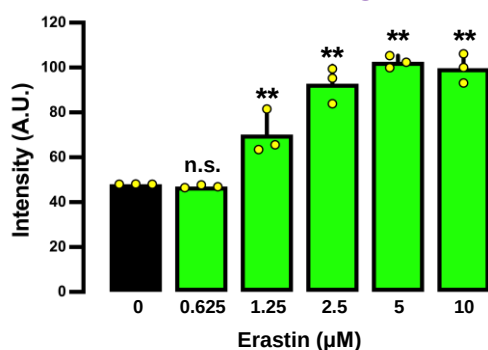
Supplementary Figure S1



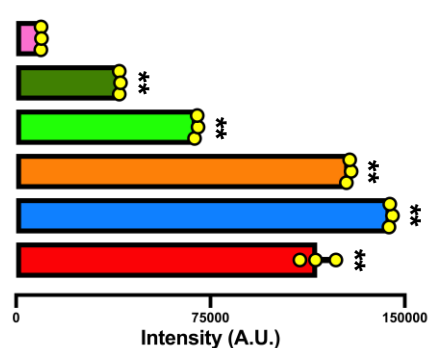
Supplementary Fig. S1. Dose-dependent induction of cell death by erastin in BRL-3A rat hepatocytes. Cells were seeded in 96-well plates at 2000 cells/well, and 12 h later, they were treated with different concentrations of erastin for an additional 24 h. Cell viability was determined by MTT assay ($n = 5$). The data shown in **A**, **B** and **C** were obtained from different experiments at different times. Considerable variations in the sensitivity of the cultured rat hepatocytes to erastin's cytotoxicity were noted. Each value represents the mean $\pm$ S.D. (** $P < 0.01$; n.s. not significant).

Supplementary Figure S2

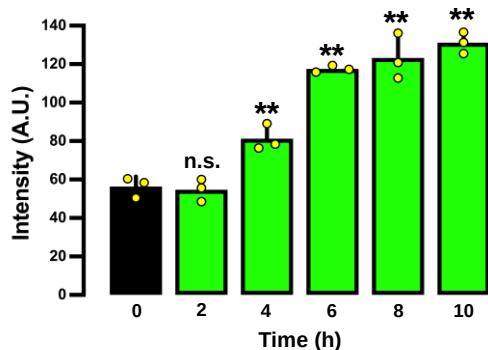
A (quantitative values of Fig. 1B)



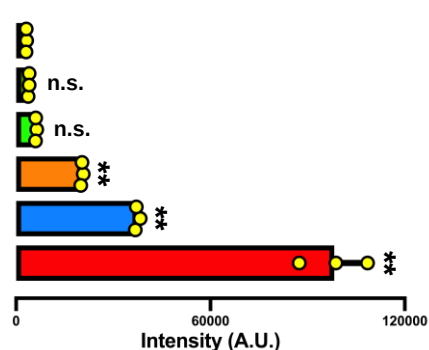
B (quantitative values of Fig. 1C)



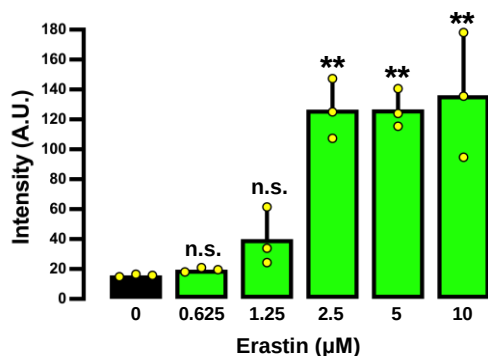
C (quantitative values of Fig. 1D)



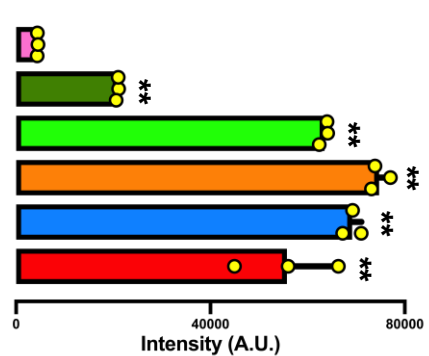
D (quantitative values of Fig. 1E)



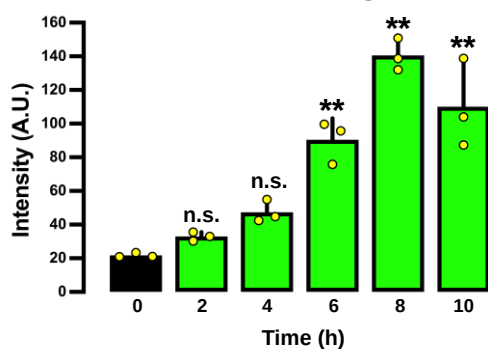
E (quantitative values of Fig. 1F)



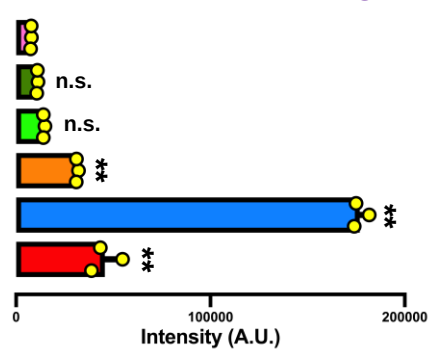
F (quantitative values of Fig. 1G)



G (quantitative values of Fig. 1H)

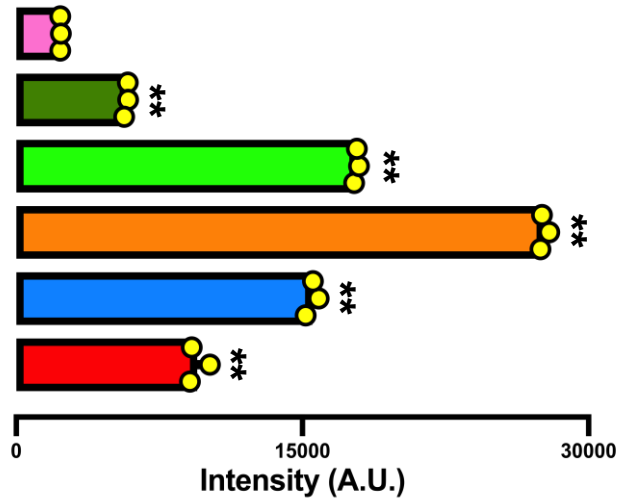


H (quantitative values of Fig. 1I)

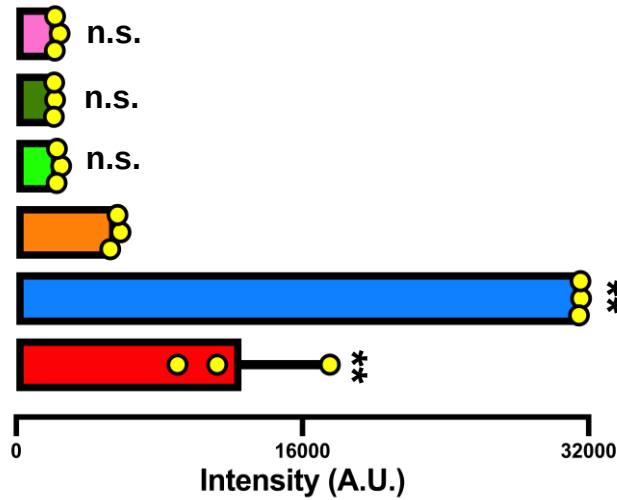


Supplementary Fig. S2. Corresponding quantitative values for the data shown in Fig. 1B–1L. Each value is the mean $\pm$ S.D. ($n=3$). (* $P < 0.05$; ** $P < 0.01$; n.s. not significant).

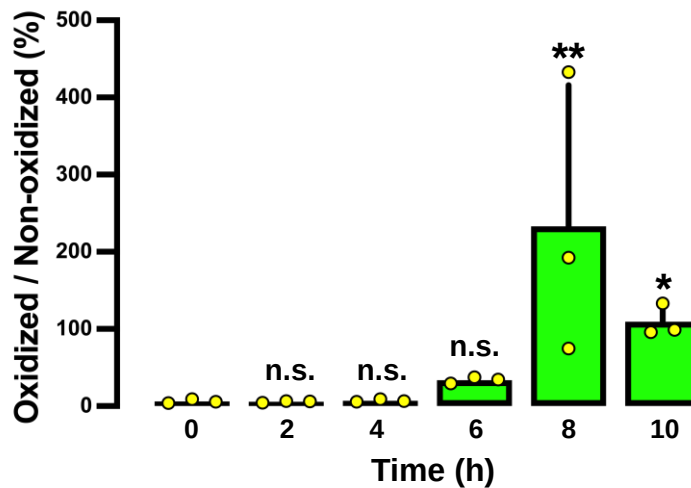
I (quantitative values of Fig. 1J)



J (quantitative values of Fig. 1K)

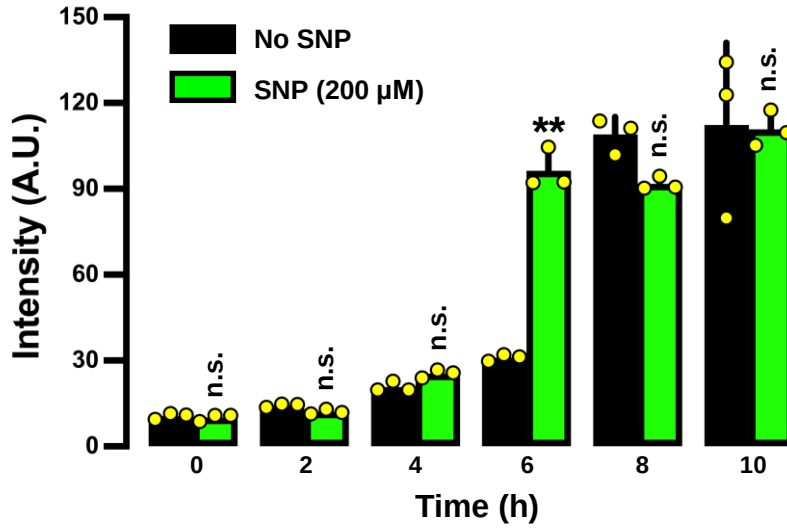


K (quantitative values of Fig. 1L)

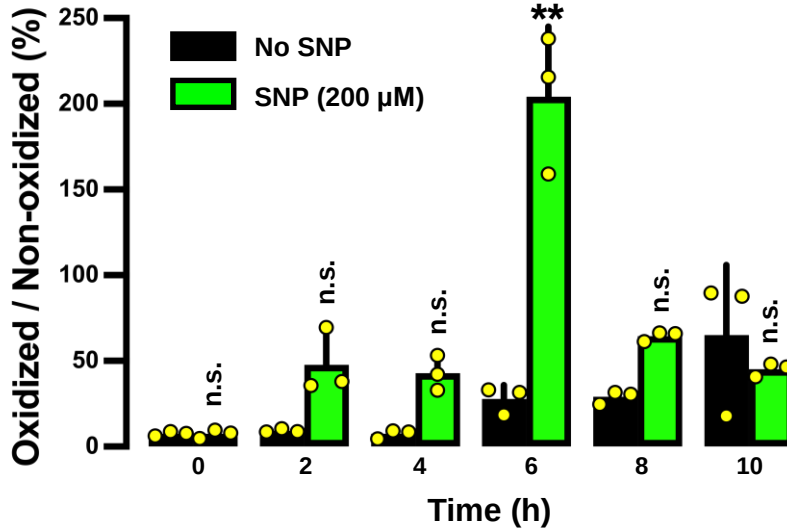


Supplementary Fig. S2 (continued). Corresponding quantitative values for the data shown in Fig. 1B–1L. Each value is the mean $\pm$ S.D. ($n=3$). (* $P < 0.05$; ** $P < 0.01$; n.s. not significant).

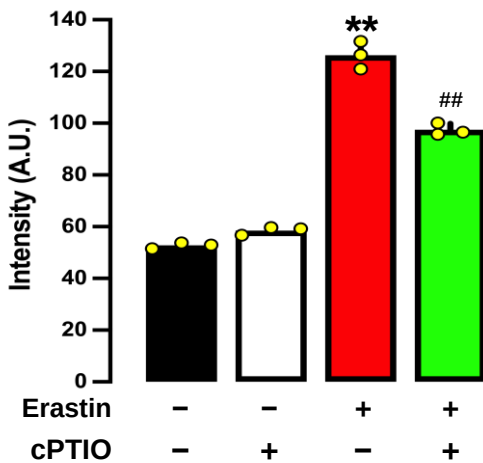
A (quantitative values of Fig. 2E)



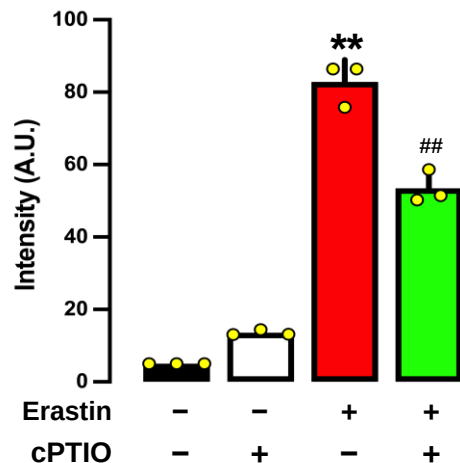
B (quantitative values of Fig. 2F)



C (quantitative values of Fig. 2I)

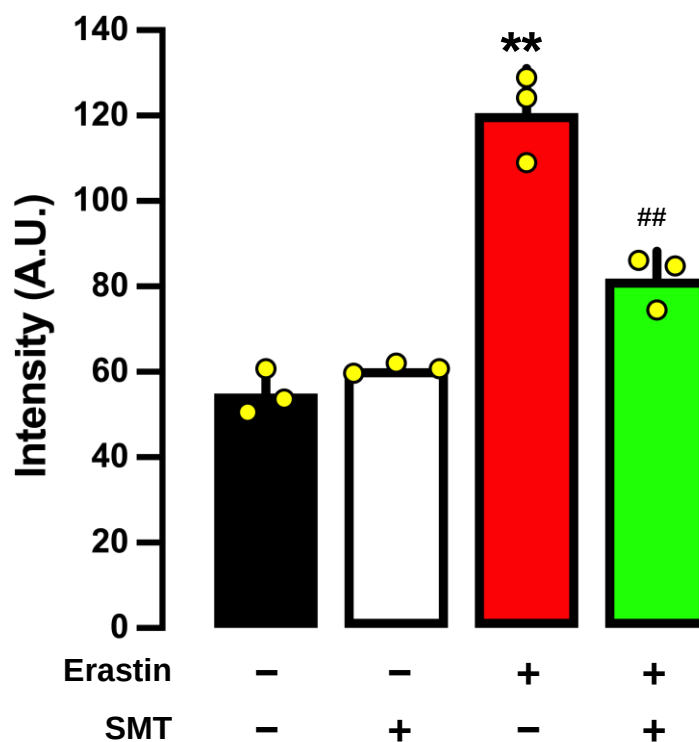


D (quantitative values of Fig. 2K)

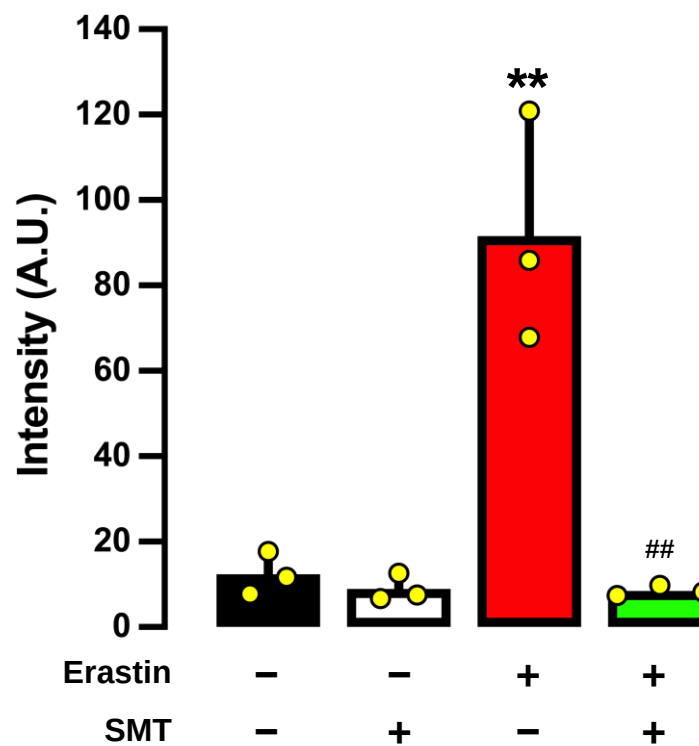


Supplementary Fig. S3. Corresponding quantitative values for the data shown in Fig. 2E, 2F, 2I, 2K. Each value is the mean $\pm$ S.D. (n = 3). (** or ## $P < 0.01$; n.s. not significant).

A (quantitative values of Fig. 3C)



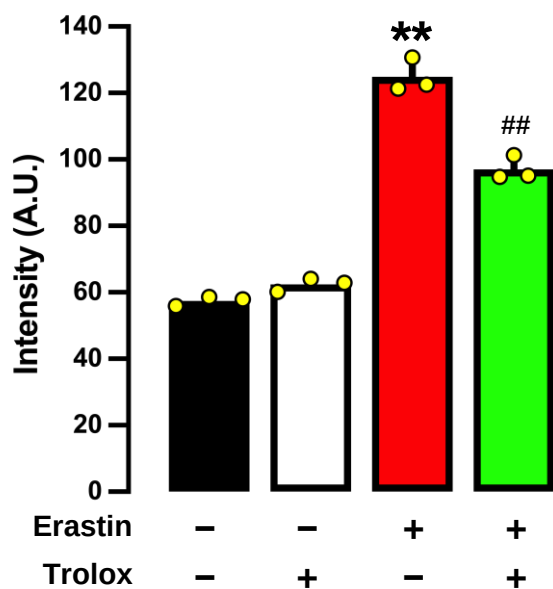
B (quantitative values of Fig. 3E)



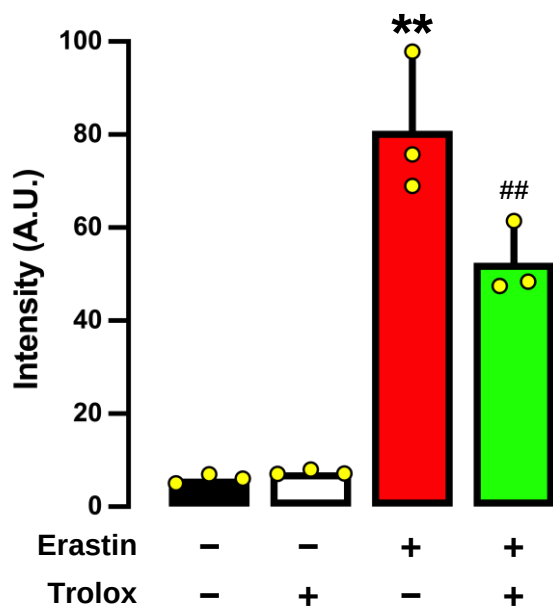
Supplementary Fig. S4. Corresponding quantitative values for the data shown in Fig. 3C, 3E. Each value is the mean $\pm$ S.D. (n=3). (** or ## $P < 0.01$).

Supplementary Figure S5

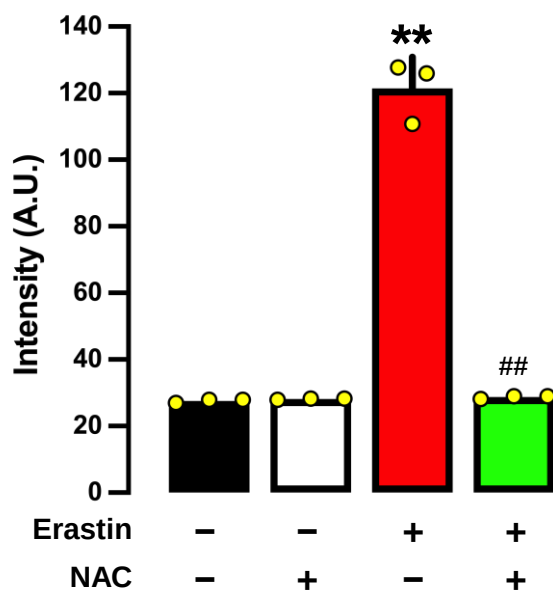
A (quantitative values of Fig. 4C)



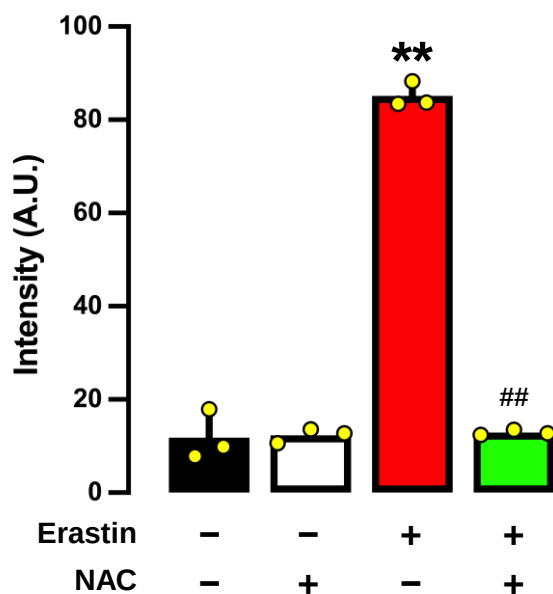
B (quantitative values of Fig. 4E)



C (quantitative values of Fig. 4K)

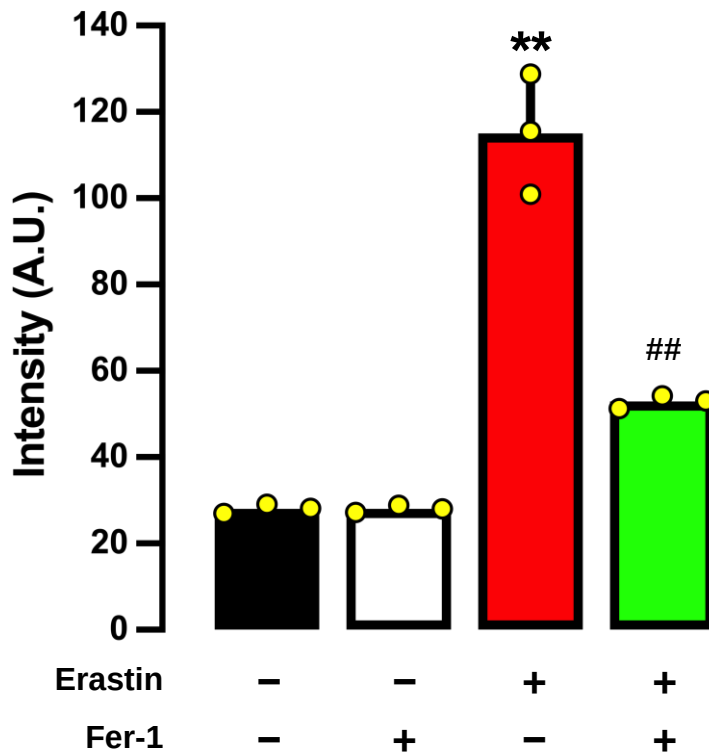


D (quantitative values of Fig. 4M)

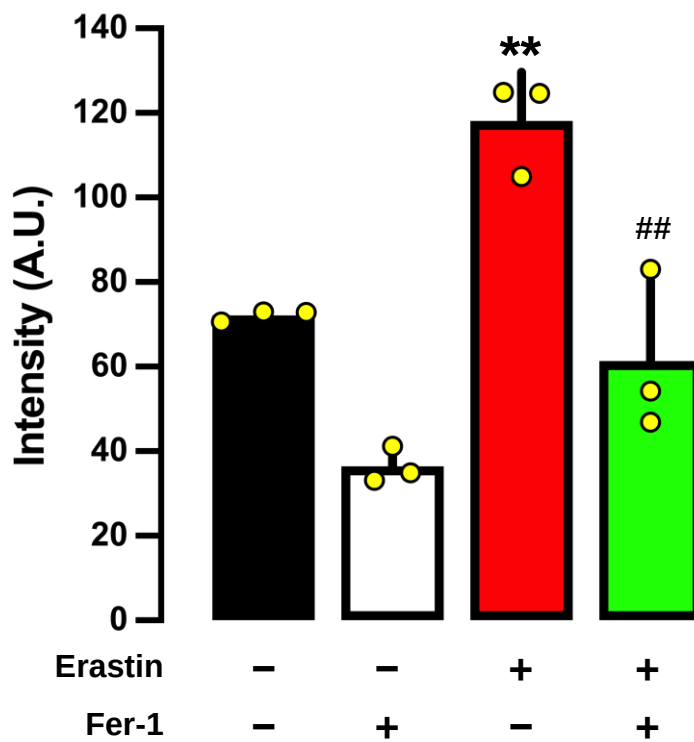


Supplementary Fig. S5. Corresponding quantitative values for the data shown in Fig. 4C, 4E, 4K, 4M. Each value is the mean $\pm$ S.D. (n=3). (** or ## $P < 0.01$).

A (quantitative values of Fig. 5D)

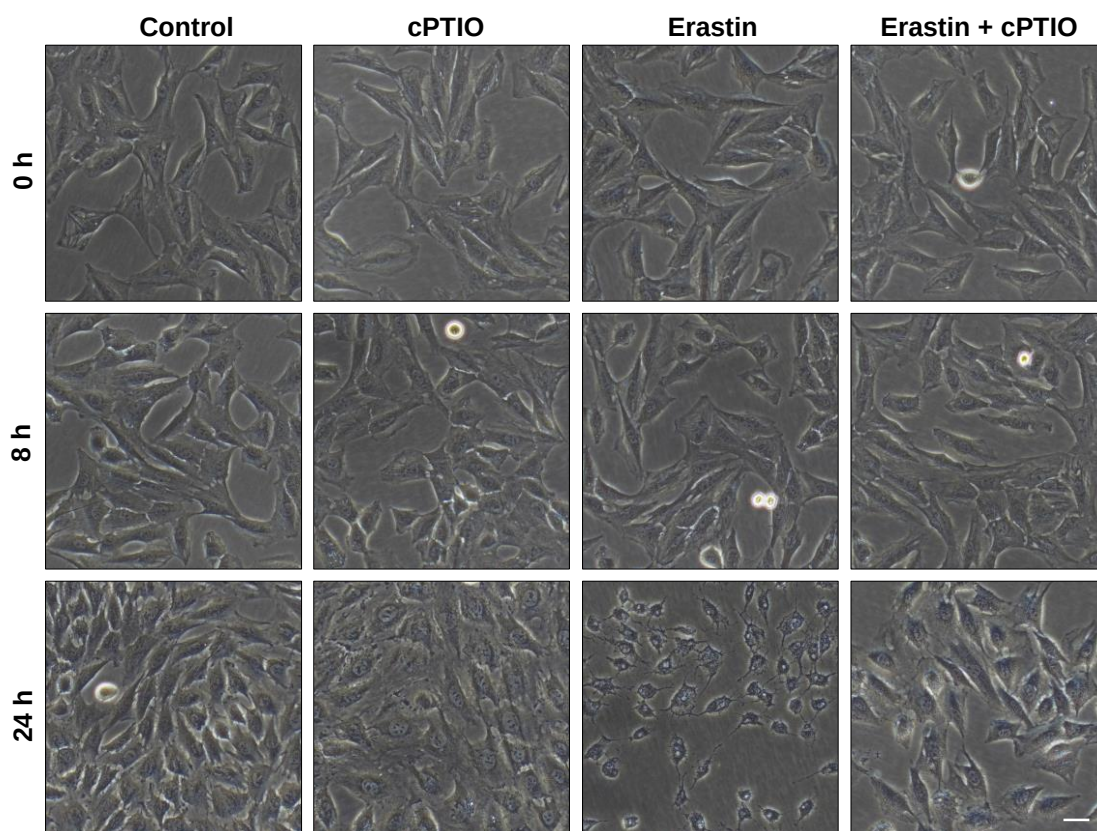


B (quantitative values of Fig. 5F)



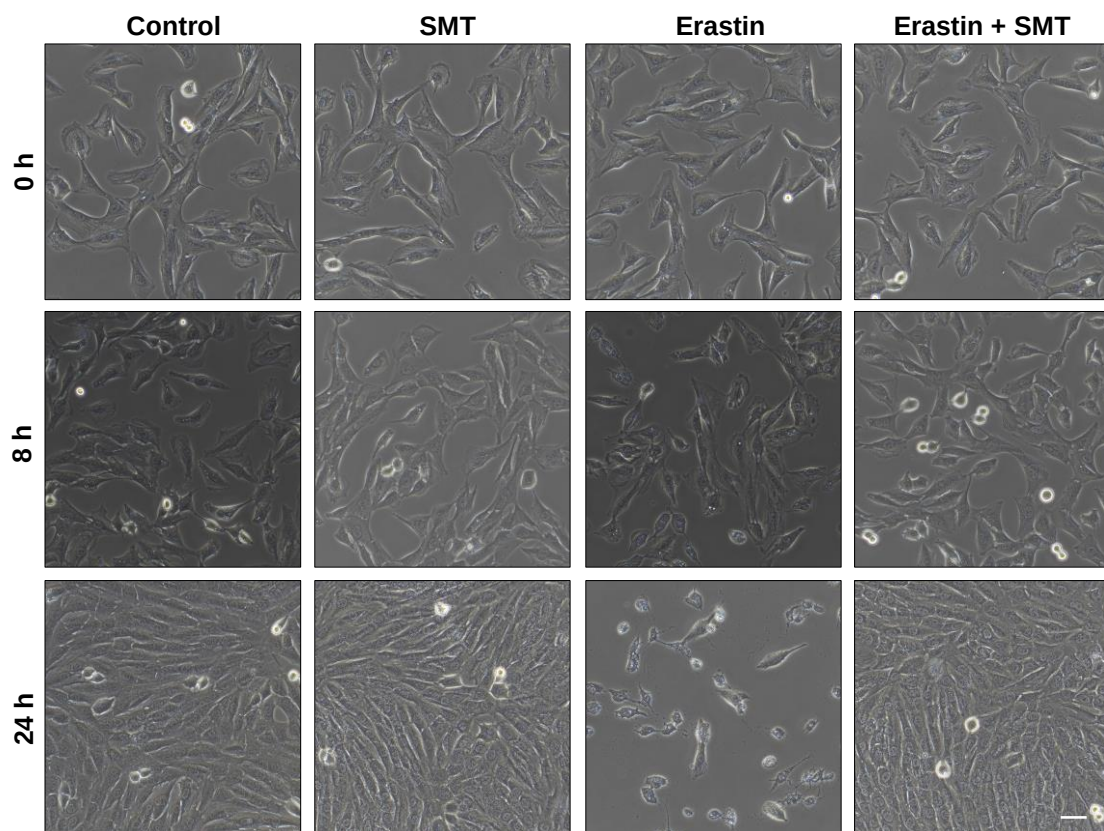
Supplementary Fig. S6. Corresponding quantitative values for the data shown in Fig. 5D, 5F. Each value is the mean $\pm$ S.D. (n = 3). (** or ## $P < 0.01$).

Supplementary Figure S7



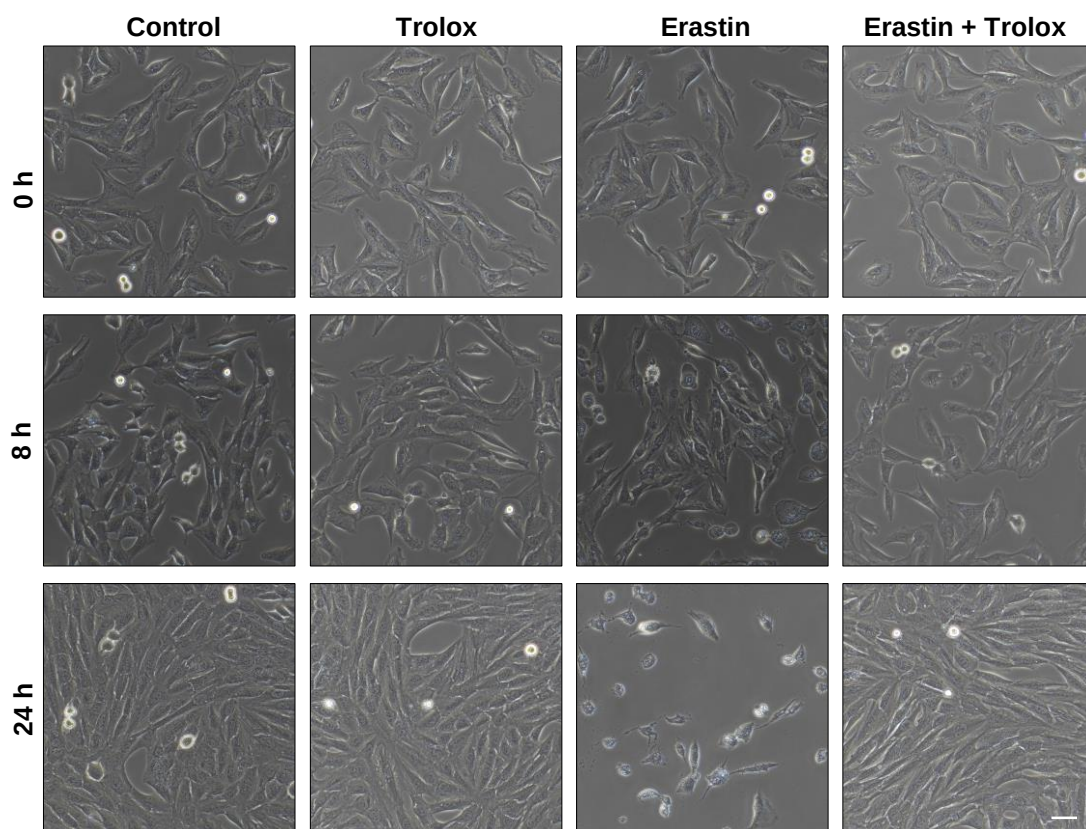
Supplementary Fig. S7. Protective effect of cPTIO against erastin-induced ferroptotic cell death (gross morphological change). Cells were jointly treated with erastin (2.5 μ M) $\pm$ cPTIO (100 μ M) for 24 h, and cellular images were captured with a Nikon Eclipse Ti-U inverted microscope (20 $\times$, scale bar = 30 μ m).

Supplementary Figure S8



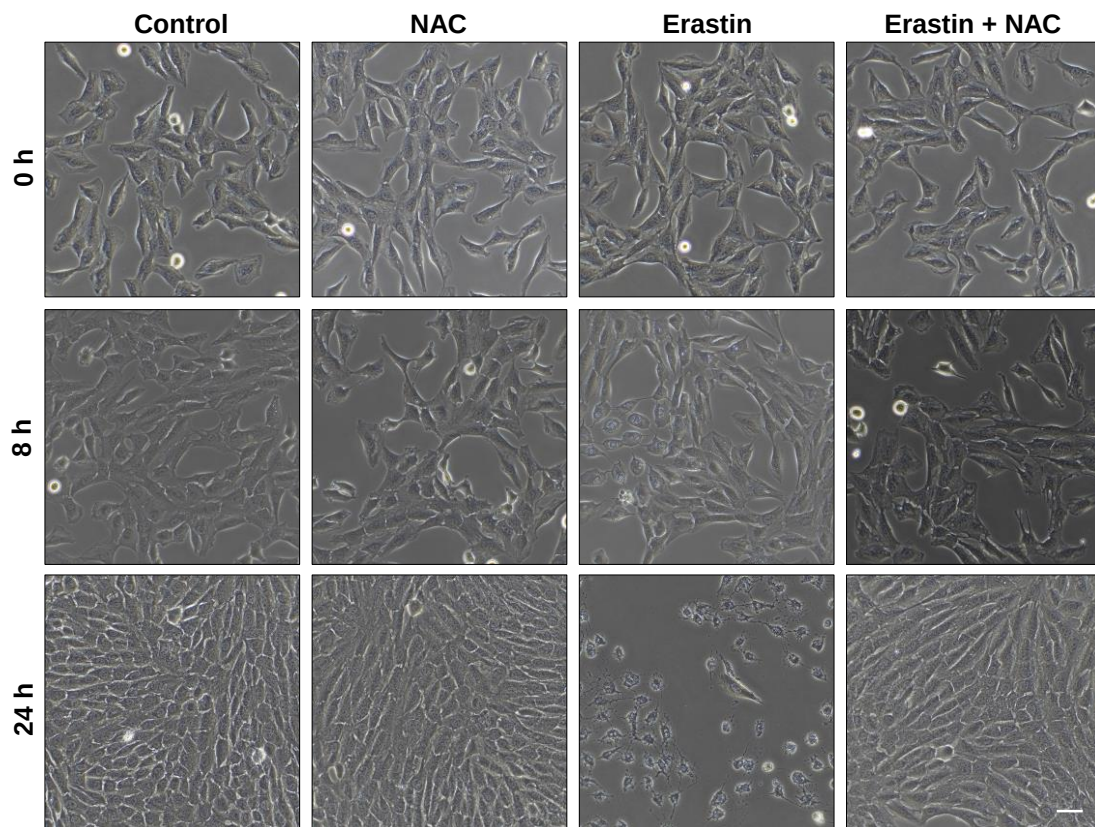
Supplementary Fig. S8. Protective effect of SMT against erastin-induced ferroptotic cell death (gross morphological change). Cells were jointly treated with erastin (2.5 μM) $\pm$ SMT (400 μM) for 24 h, and cellular images were captured with a Nikon Eclipse Ti-U inverted microscope (20 $\times$, scale bar = 30 μm).

Supplementary Figure S9



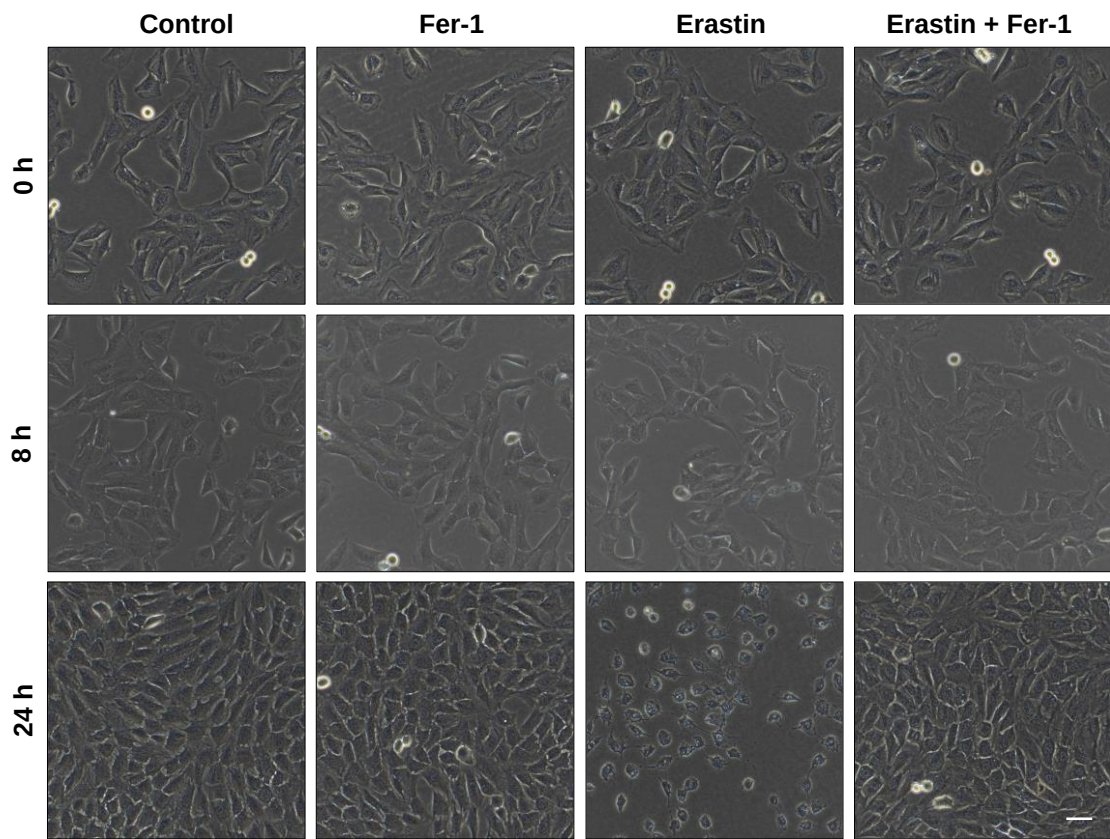
Supplementary Fig. S9. Protective effect of Trolox against erastin-induced ferroptotic cell death (gross morphological change). Cells were jointly treated with erastin ($2.5\ \mu\text{M}$) $\pm$ Trolox ($100\ \mu\text{M}$) for 24 h, and cellular images were captured with a Nikon Eclipse Ti-U inverted microscope ($20\times$, scale bar = $30\ \mu\text{m}$).

Supplementary Figure S10



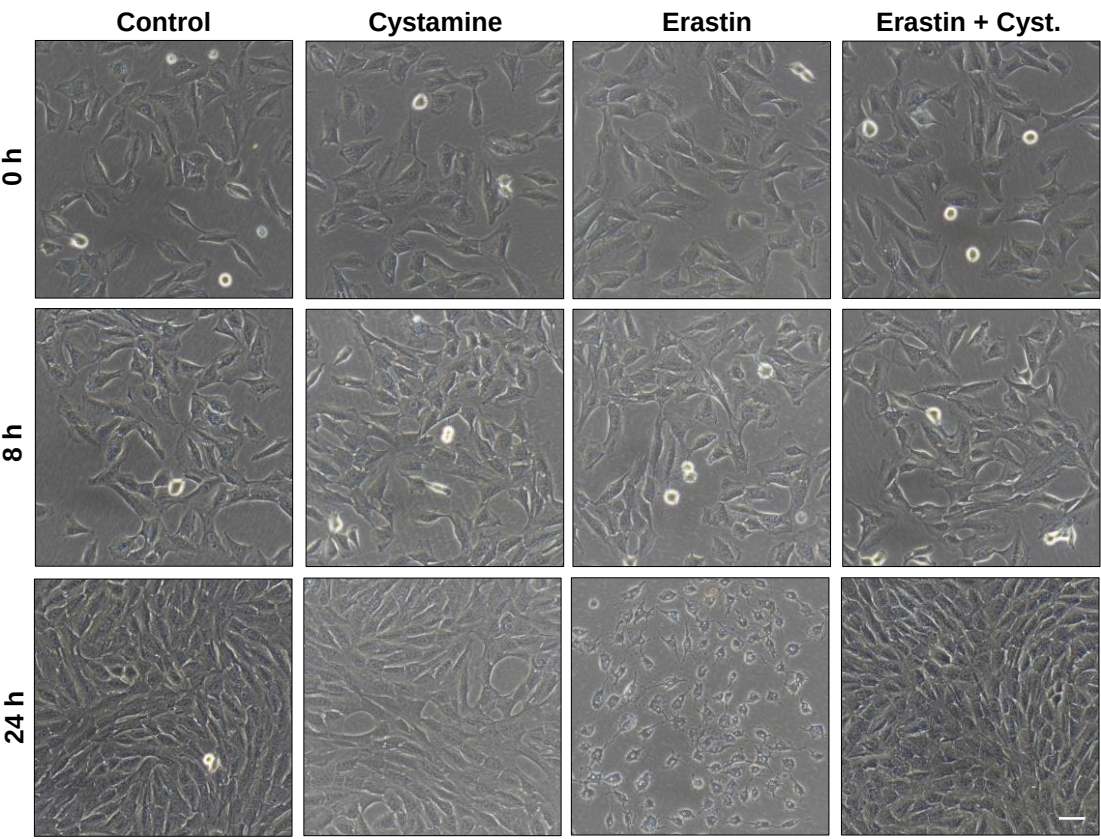
Supplementary Fig. S10. Protective effect of NAC against erastin-induced ferroptotic cell death (gross morphological change). Cells were jointly treated with erastin (2.5 μ M) $\pm$ NAC (400 μ M) for 24 h, and cellular images were captured with a Nikon Eclipse Ti-U inverted microscope (20 $\times$, scale bar = 30 μ m).

Supplementary Figure S11



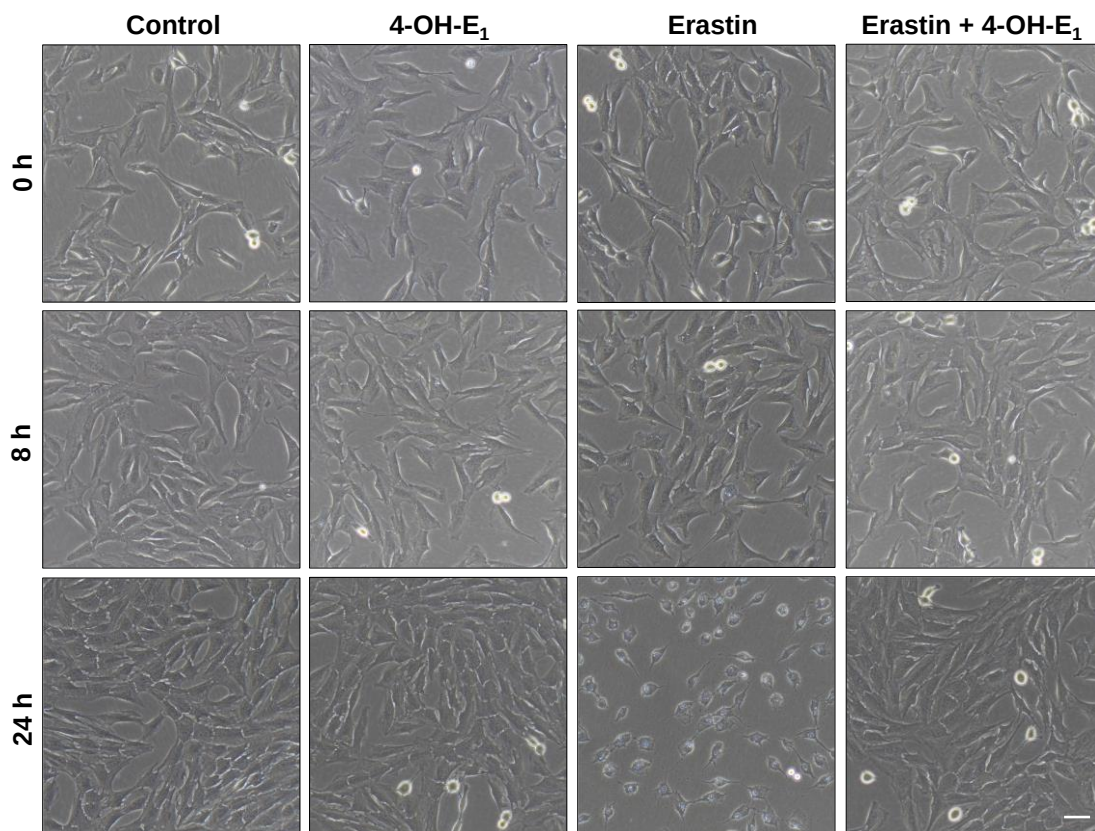
Supplementary Fig. S11. Protective effect of Fer-1 against erastin-induced ferroptotic cell death (gross morphological change). Cells were jointly treated with erastin (2.5 μM) $\pm$ Fer-1 (100 nM) for 24 h, and cellular images were captured with a Nikon Eclipse Ti-U inverted microscope (20 $\times$, scale bar = 30 μm).

Supplementary Figure S12



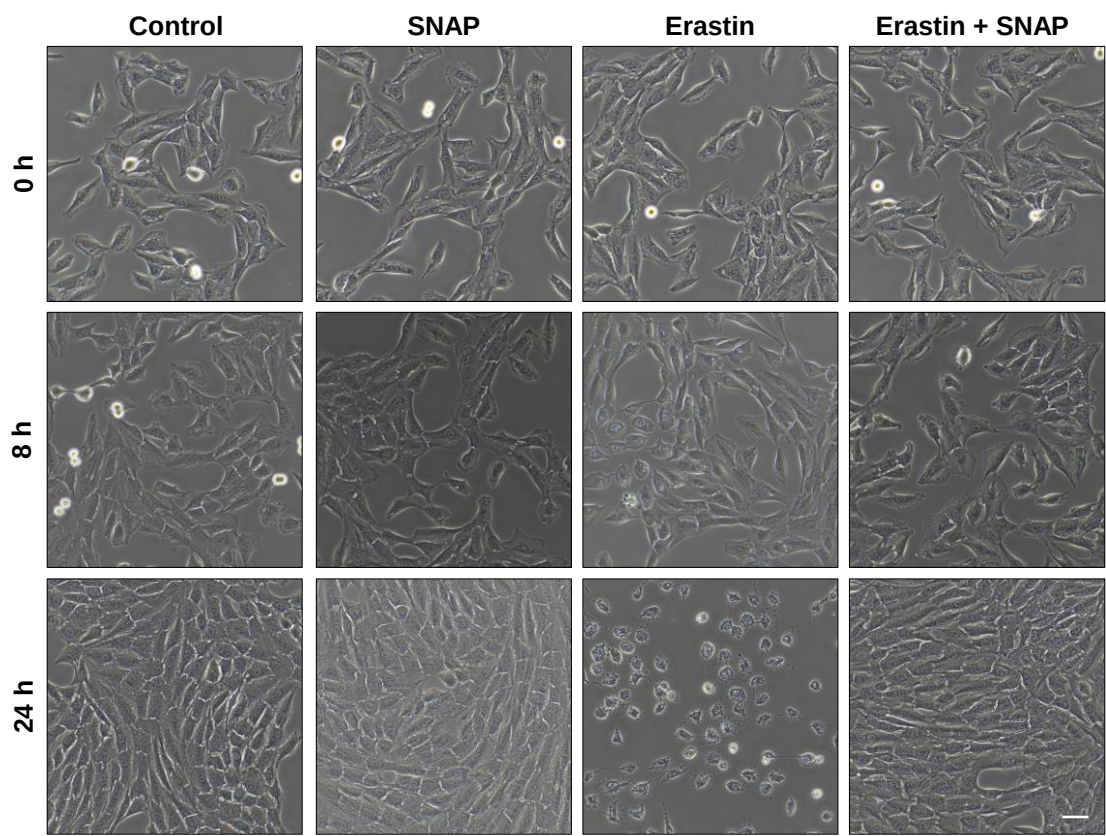
Supplementary Fig. S12. Protective effect of cystamine against erastin-induced ferroptotic cell death (gross morphological change). Cells were jointly treated with erastin (2.5 μ M) $\pm$ cystamine (50 μ M) for 24 h, and cellular images were captured with a Nikon Eclipse Ti-U inverted microscope (20 $\times$, scale bar = 30 μ m).

Supplementary Figure S13



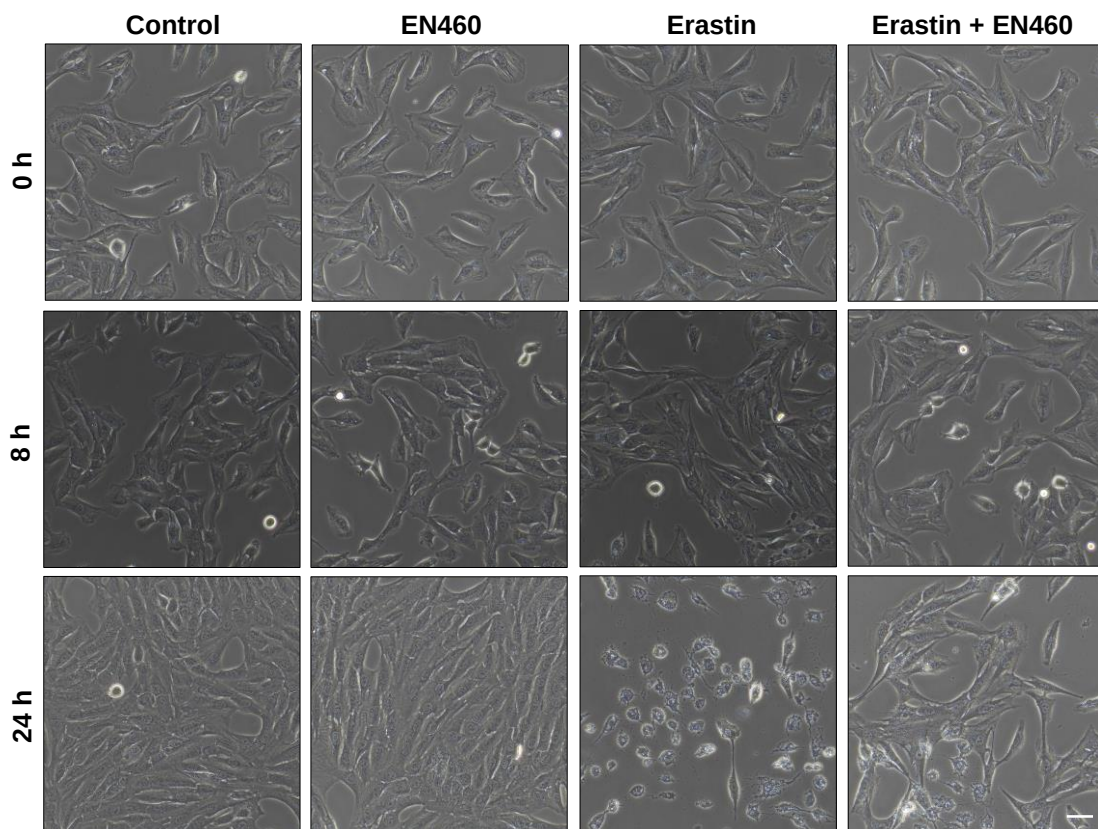
Supplementary Fig. S13. Protective effect of 4-OH-E₁ against erastin-induced ferroptotic cell death (gross morphological change). Cells were jointly treated with erastin (2.5 μ M) $\pm$ 4-OH-E₁ (2.5 μ M) for 24 h, and cellular images were captured with a Nikon Eclipse Ti-U inverted microscope (20 $\times$, scale bar = 30 μ m).

Supplementary Figure S14



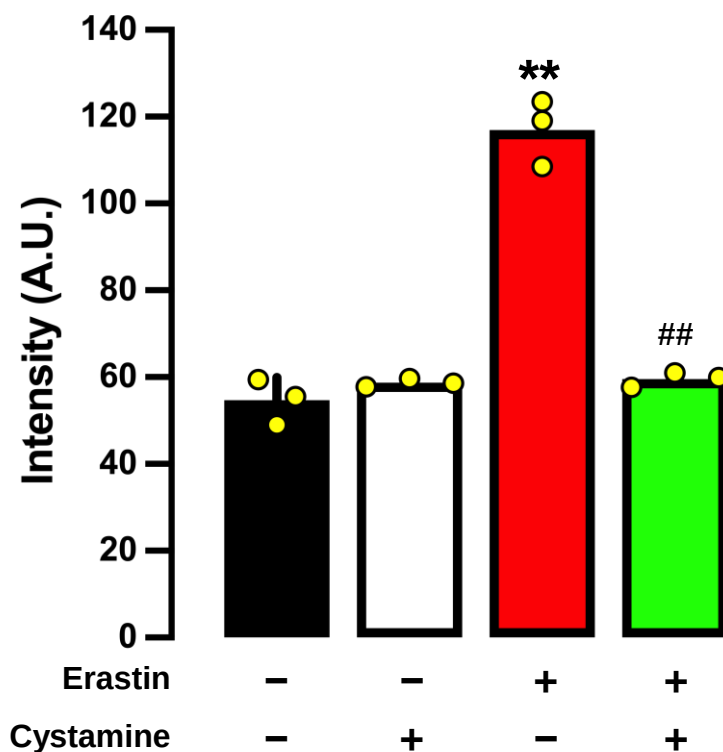
Supplementary Fig. S14. Protective effect of SNAP against erastin-induced ferroptotic cell death (gross morphological change). Cells were jointly treated with erastin (2.5 μ M) $\pm$ SNAP (50 μ M) for 24 h, and cellular images were captured with a Nikon Eclipse Ti-U inverted microscope (20 $\times$, scale bar = 30 μ m).

Supplementary Figure S15

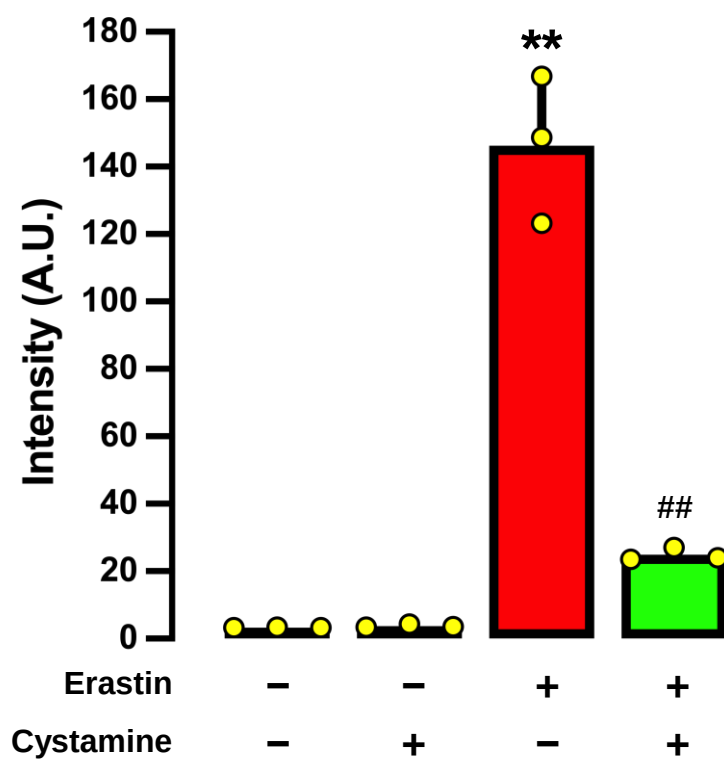


Supplementary Fig. S15. Protective effect of EN460 against erastin-induced ferroptotic cell death (gross morphological change). Cells were jointly treated with erastin (2.5 μM) $\pm$ EN460 (25 μM) for 24 h, and cellular images were captured with a Nikon Eclipse Ti-U inverted microscope (20 $\times$, scale bar = 30 μm).

A (quantitative values of Fig. 7C)

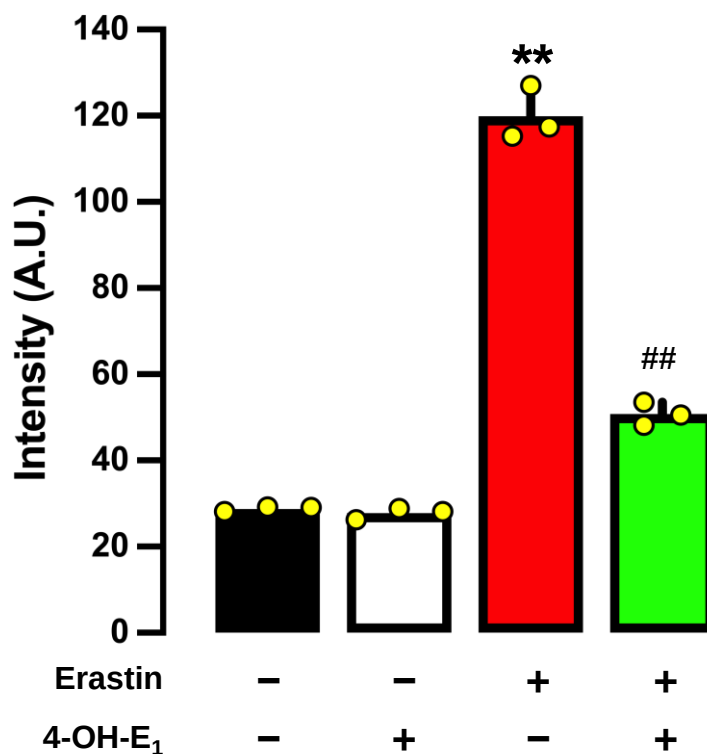


B (quantitative values of Fig. 7E)

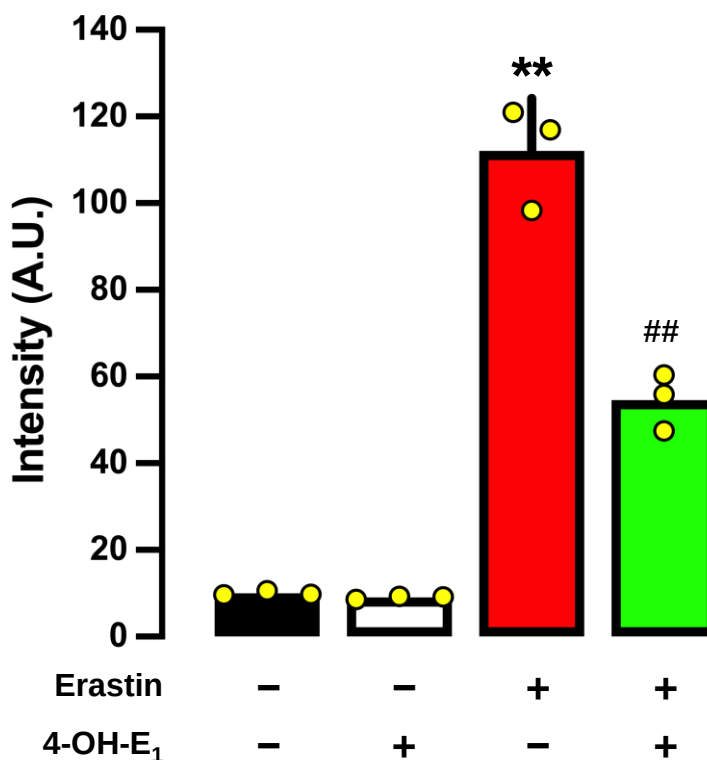


Supplementary Fig. S16. Corresponding quantitative values for the data shown in Fig. 7C, 7E. Each value is the mean $\pm$ S.D. ($n = 3$). (** or ## $P < 0.01$).

A (quantitative values of Fig. 8B)

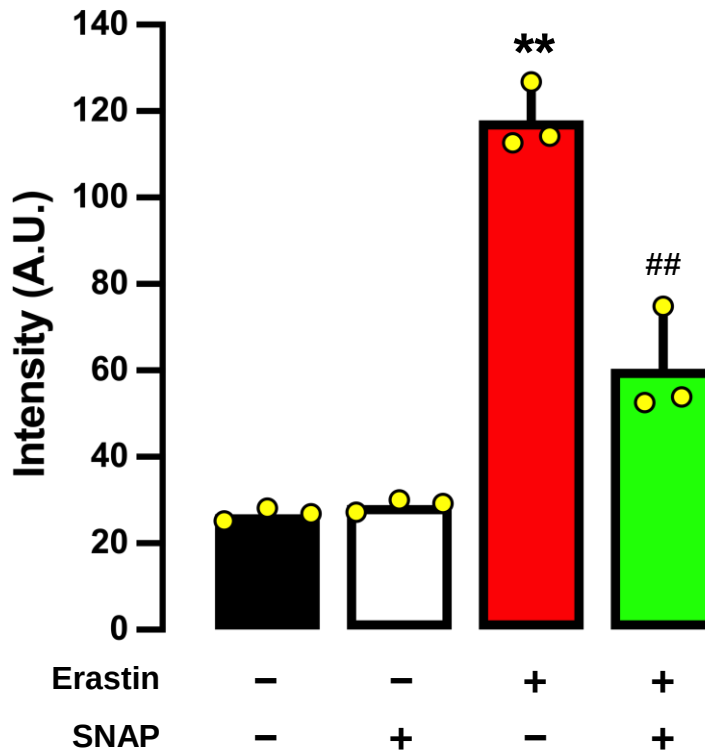


B (quantitative values of Fig. 8D)

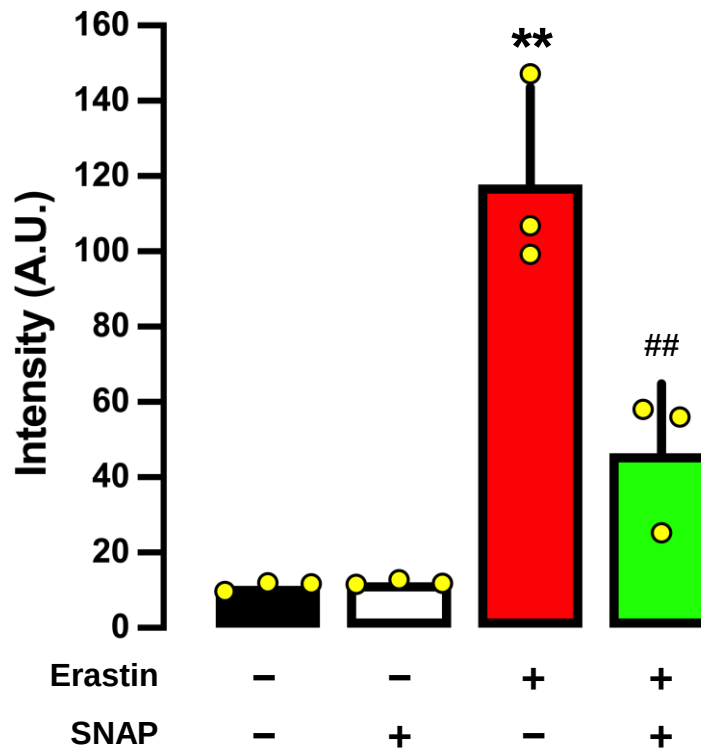


Supplementary Fig. S17. Corresponding quantitative values for the data shown in Fig. 8B, 8D. Each value is the mean $\pm$ S.D. ($n=3$). (** or ## $P < 0.01$).

A (quantitative values of Fig. 9C)

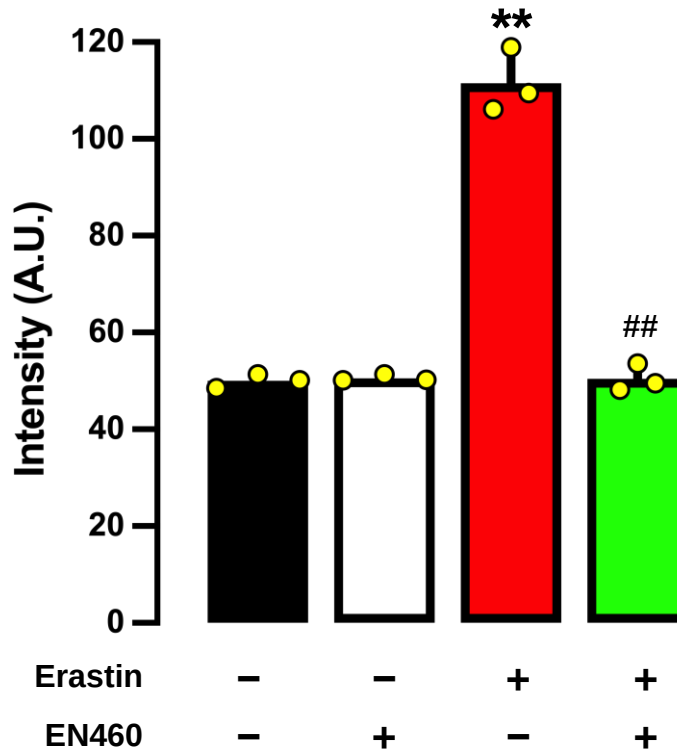


B (quantitative values of Fig. 9E)

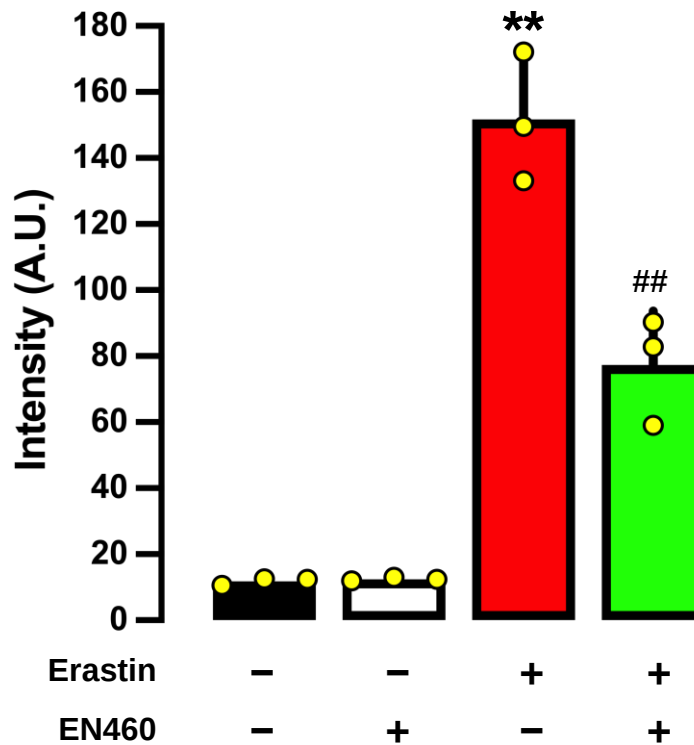


Supplementary Fig. S18. Corresponding quantitative values for the data shown in Fig. 9C, 9E. Each value is the mean $\pm$ S.D. (n = 3). (** or ## $P < 0.01$).

A (quantitative values of Fig. 10C)

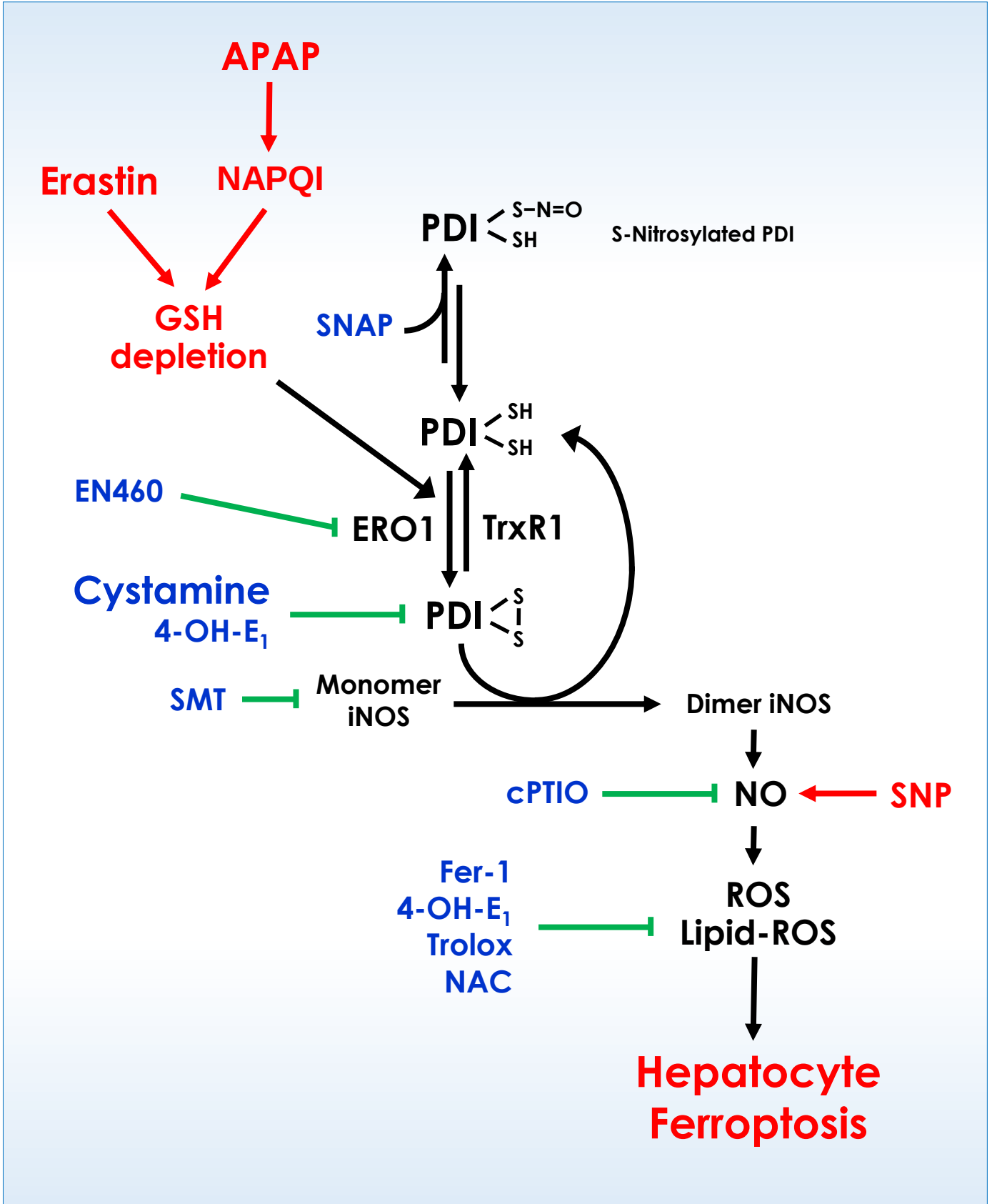


B (quantitative values of Fig. 10E)



Supplementary Fig. S19. Corresponding quantitative values for the data shown in Fig. 10C, 10E. Each value is the mean $\pm$ S.D. (n=3). (** or ## $P < 0.01$).

Supplementary Figure S20



Supplementary Fig. S20. Schematic depiction of the mechanism by which PDI plays a crucial role in mediating erastin- and APAP-induced hepatocyte ferroptosis *in vitro* and *in vivo*. Please refer to the **Discussion** section for detailed explanation.