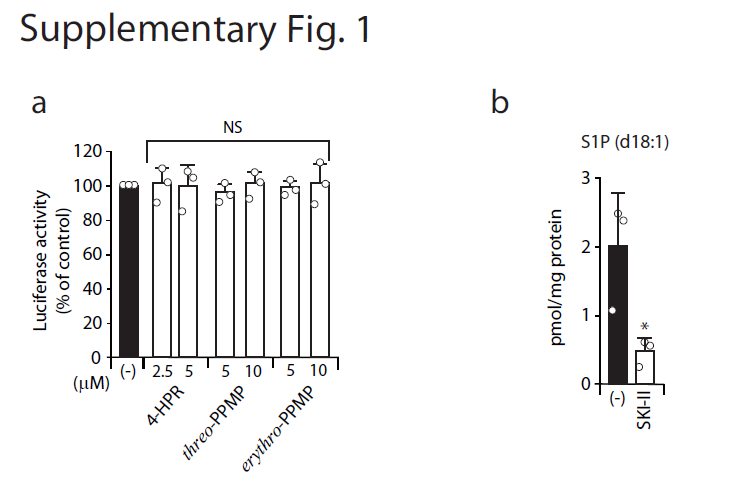
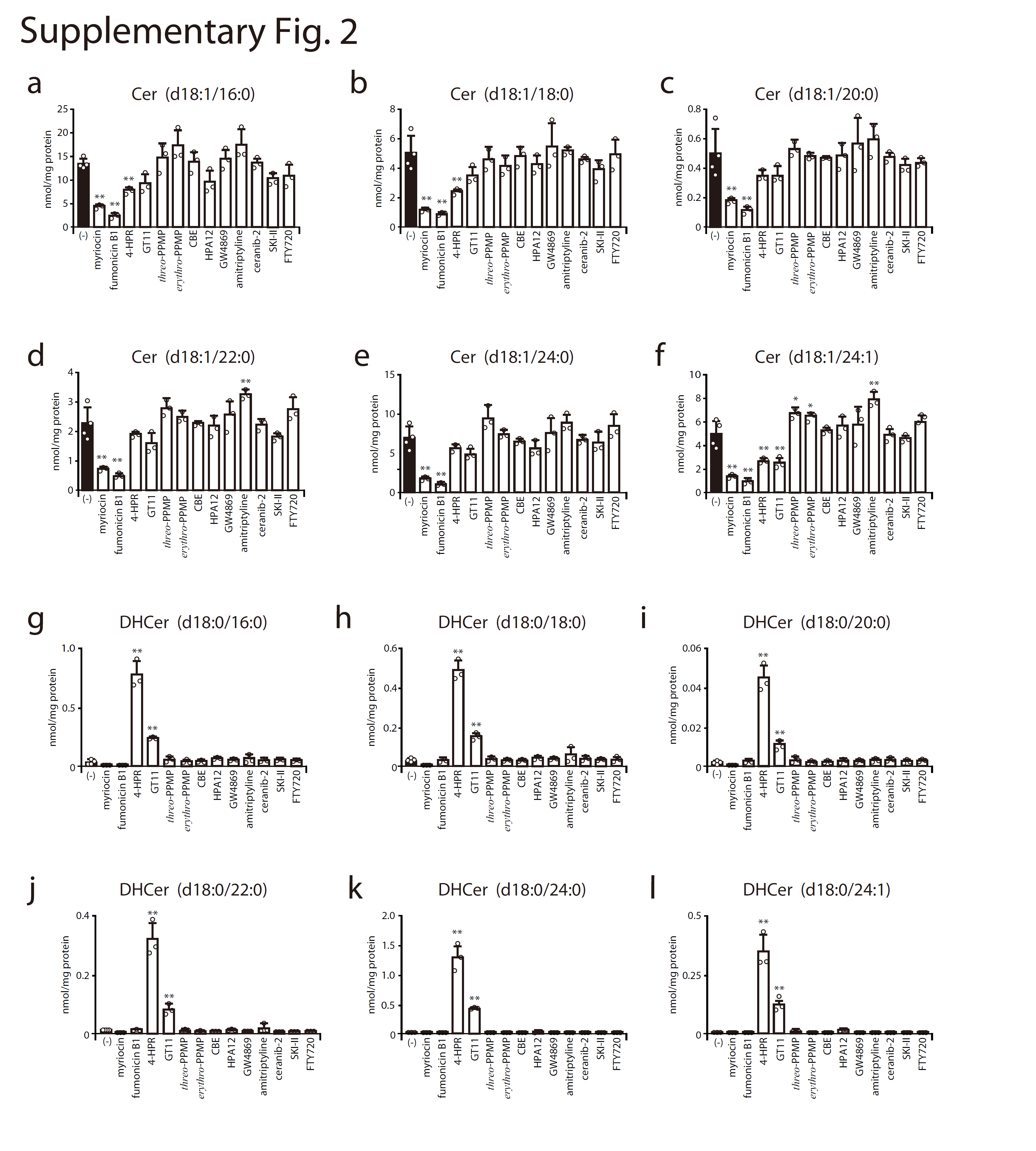
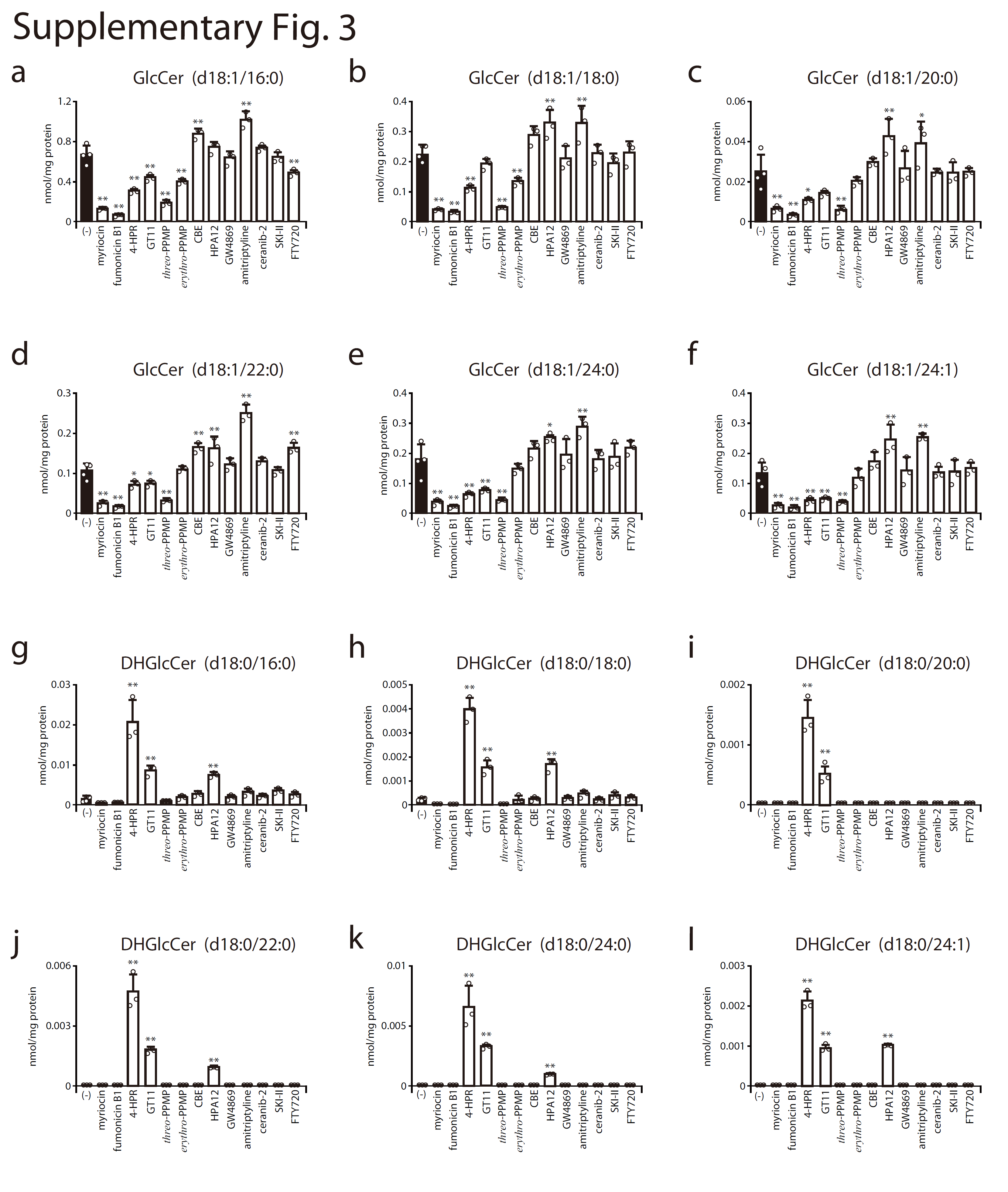
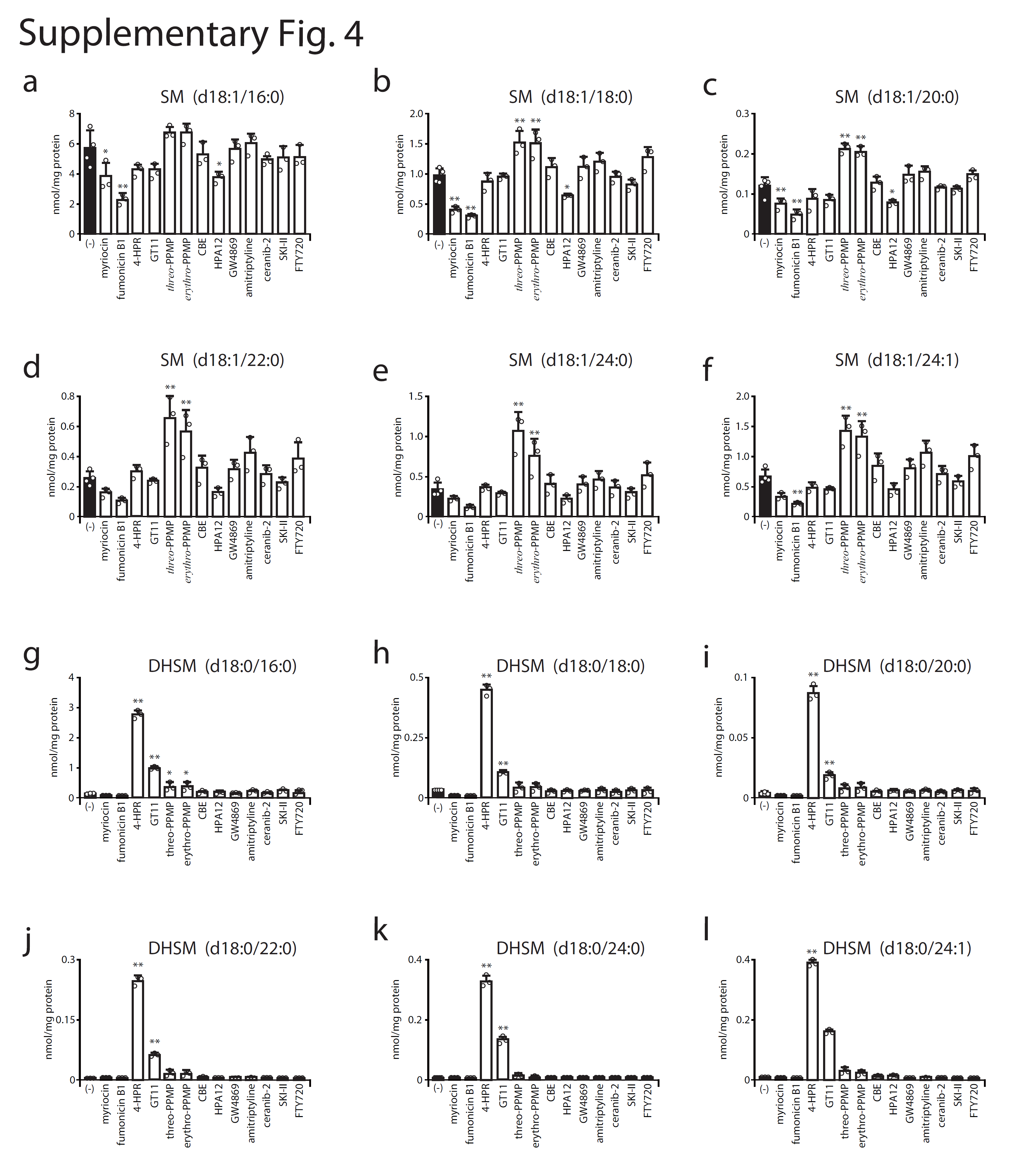
**Supplementary figures**



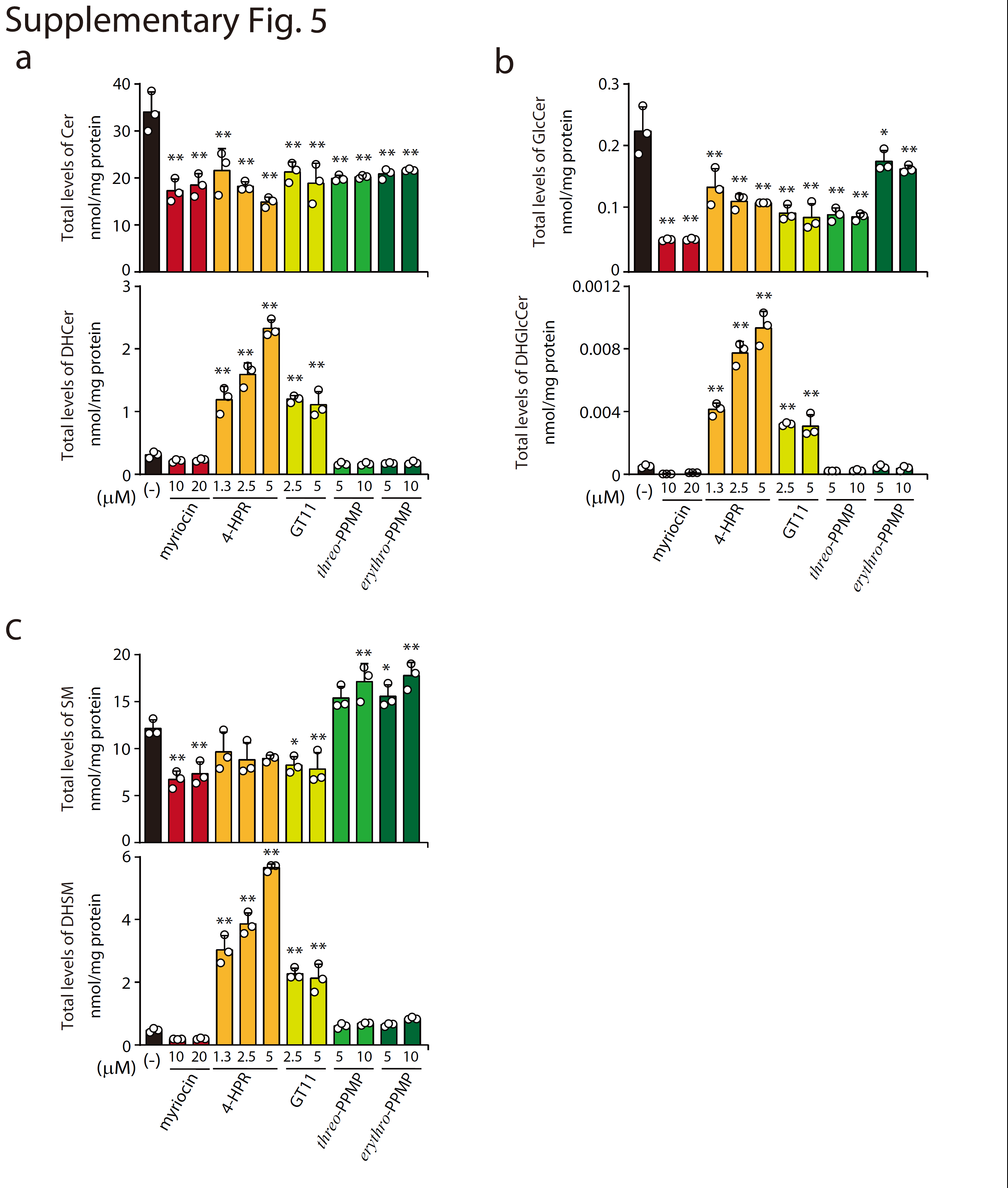
**Supplementary Fig. 1 | Effect of compounds on *Renilla* luciferase activity and** **SKase inhibitor SKI-II on cellular sphingosine-1-phosphate (S1P) level. (a)** HEK293FT cells expressing dual split protein (DSP)1-7 and DSP8-11 were treated for 2 days with the indicated concentrations of the compounds. Cells were resuspended in 6 M EnduRen, a substrate for *Renilla* luciferase, and incubated at 37 °C for 4 h. Luciferase activity was measured using the SpectraMax i3x Microplate Reader. Statistical significance was determined by one-way ANOVA followed by the Dunnett test for multiple comparisons when compared with vehicle/dimethyl sulfoxide (DMSO)-treated cells. **(b)** Effect of SKase inhibitor SKI-II on cellular S1P levels.293FT/ACE2/TMPRSS2/DSP1-7 cells were treated for 2 days with 10M SKI-II. Cellular levels of S1P were quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis according to Saigusa et al. Simultaneous quantitation of sphingoid bases and their phosphates was performed on biological samples by LC/electrospray ionization tandem MS. *Anal. Bioanal. Chem.* 403, 1897-1905 (2012). Statistical significance was determined by the Student’s *t* test. \* *p* < 0.05. Abbreviations: 4-HPR, *N*-(4-hydroxyphenyl)retinamide;NS, not significant

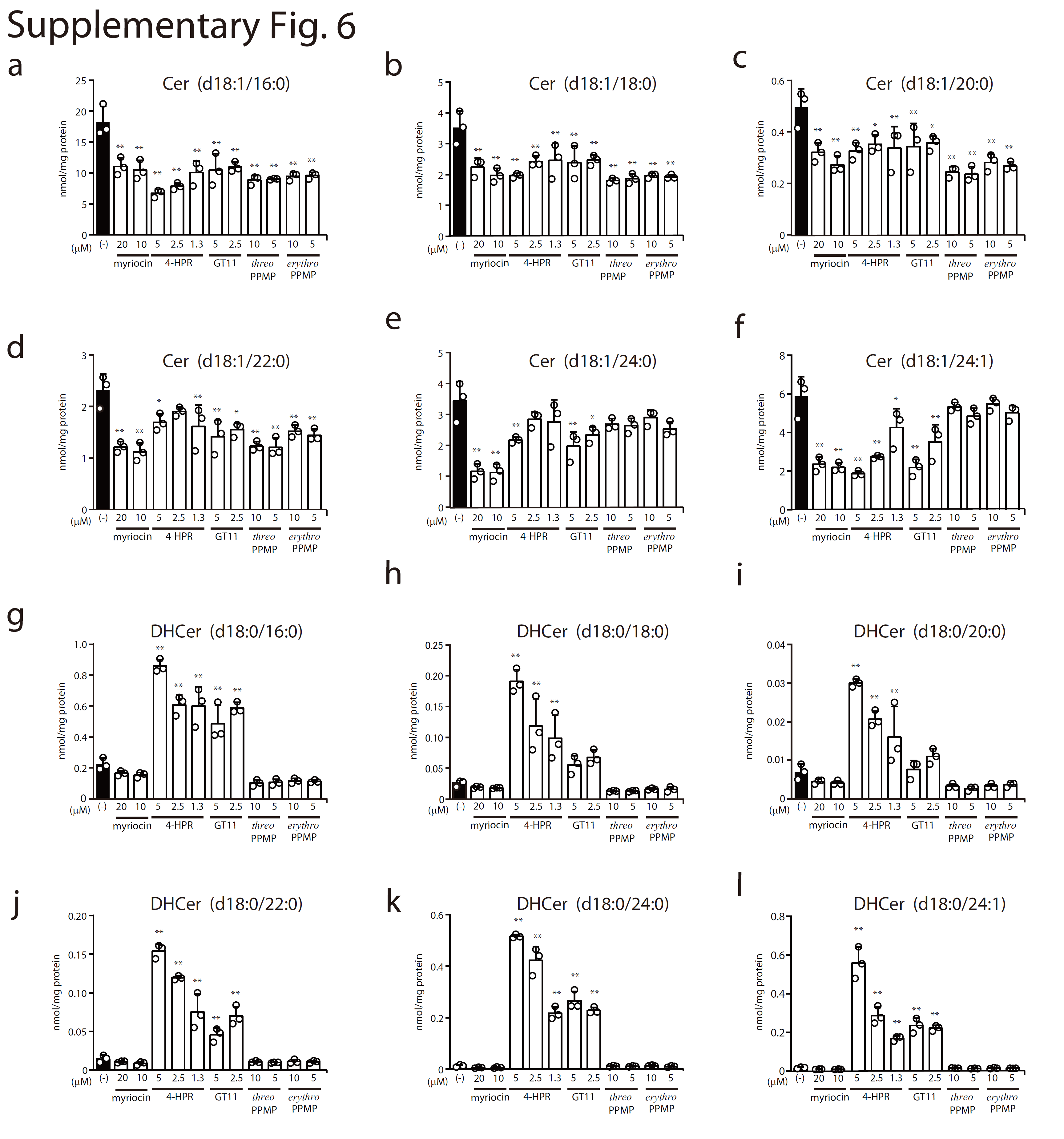


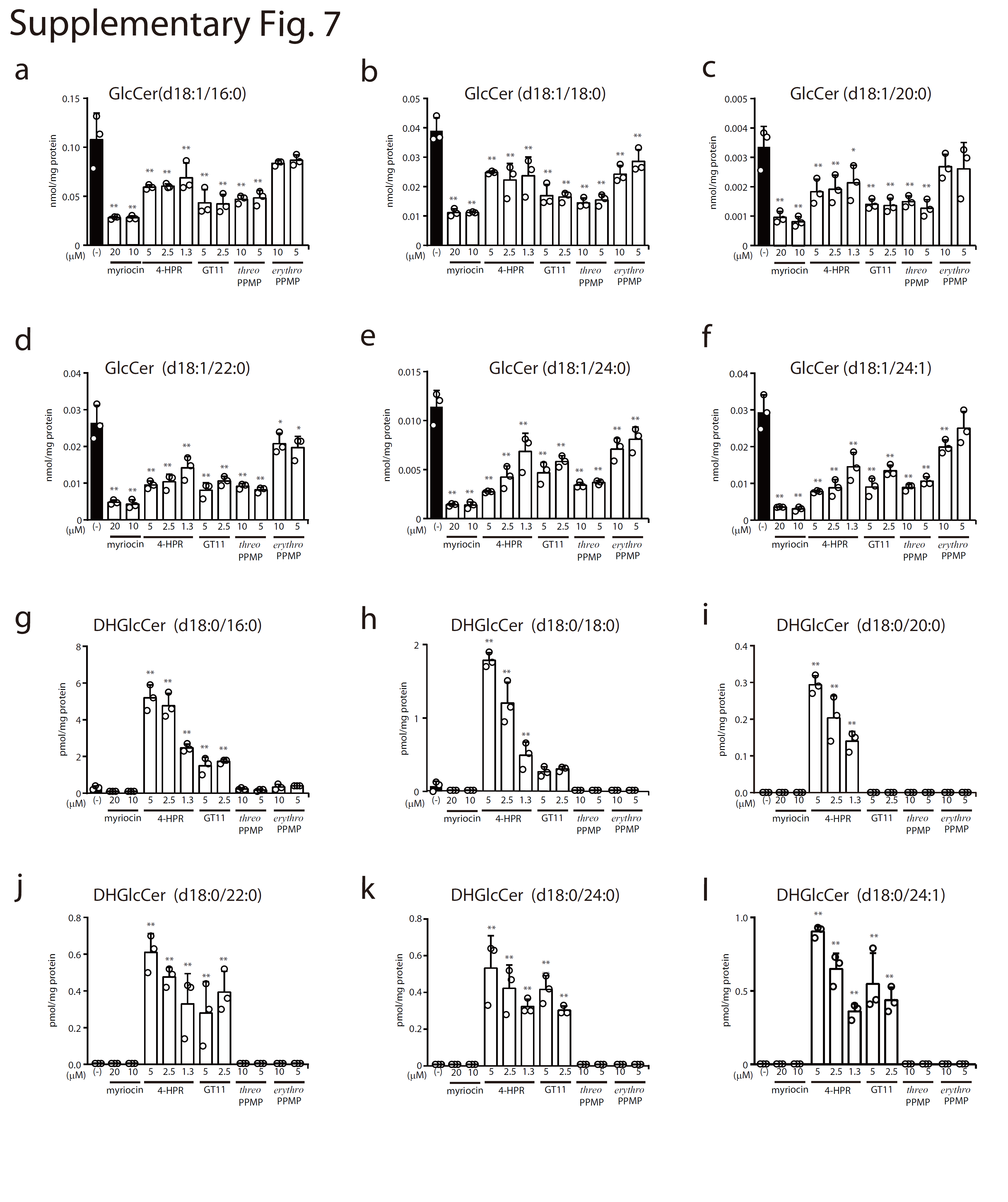


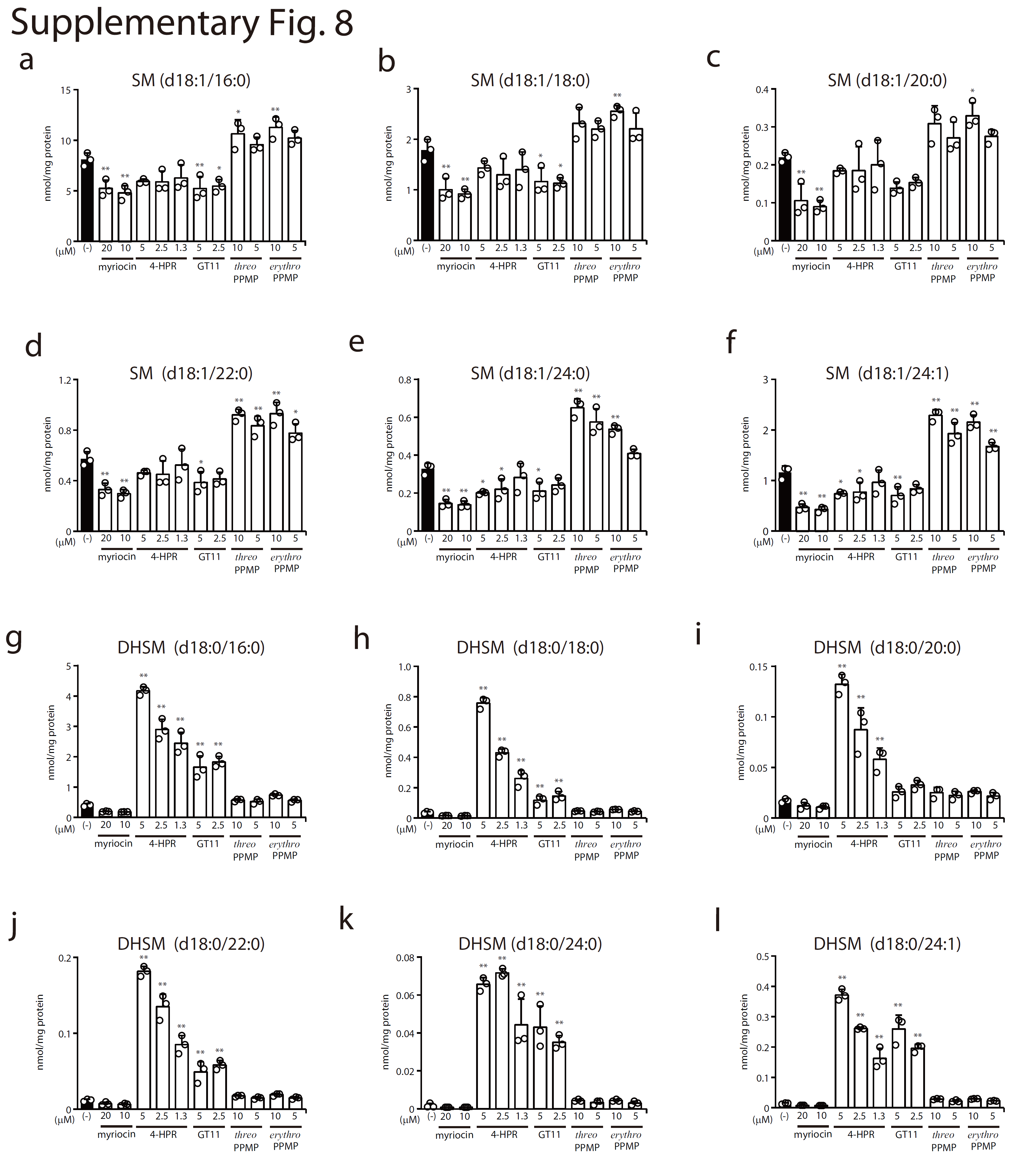


**Supplementary Figs. 2-4 | Effect of inhibitors of sphingolipid-metabolizing enzymes on cellular sphingolipid species in 293FT/ACE2/TMPRSS2/DSP1-7 cells.** 293FT/ACE2/TMPRSS2/DSP1-7 cells were treated for 2 days with each of the compounds as follows: 40 M myriocin, 40 M fumonicin B1, 5 M 4-HPR, 10 M GT11, 10 M *threo*-PPMP, 10 M *erythro*-PPMP, 40 M CBE, 40 M HPA12, 10 M GW4869, 40 M amitriptyline, 1.3 M ceranib-2, 10 M SKI-II, and 5 M FTY720. The cellular levels of sphingolipid species with a distinct acyl chain were quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis. The bar graphs show levels of Cer (panels **a-f**) and DHCer (panels **g-l**) in Supplementary Fig. 2, those of GlcCer (panels **a-f**) and DHGlcCer (panels **g-l**) in Supplementary Fig. 3, and those of SM (panels **a-f**) and DHSM (panels **g-l**) in Supplementary Fig. 4. Statistical significance was determined by one-way ANOVA followed by Dunnett test for multiple comparisons; \* *p* < 0.05, \*\* *p* < 0.01 when compared with vehicle/dimethyl sulfoxide (DMSO)-treated cells. Abbreviations: CBE, conduritol B epoxide; 4-HPR, *N*-(4-hydroxyphenyl)retinamide; Cer, ceramide; DHCer, dihydroceramide; GlcCer, glucosylceramide; DHGlcCer, dihydroglycosylceramide; SM, sphingomyelin; DHSM, dihydrosphingomyelin

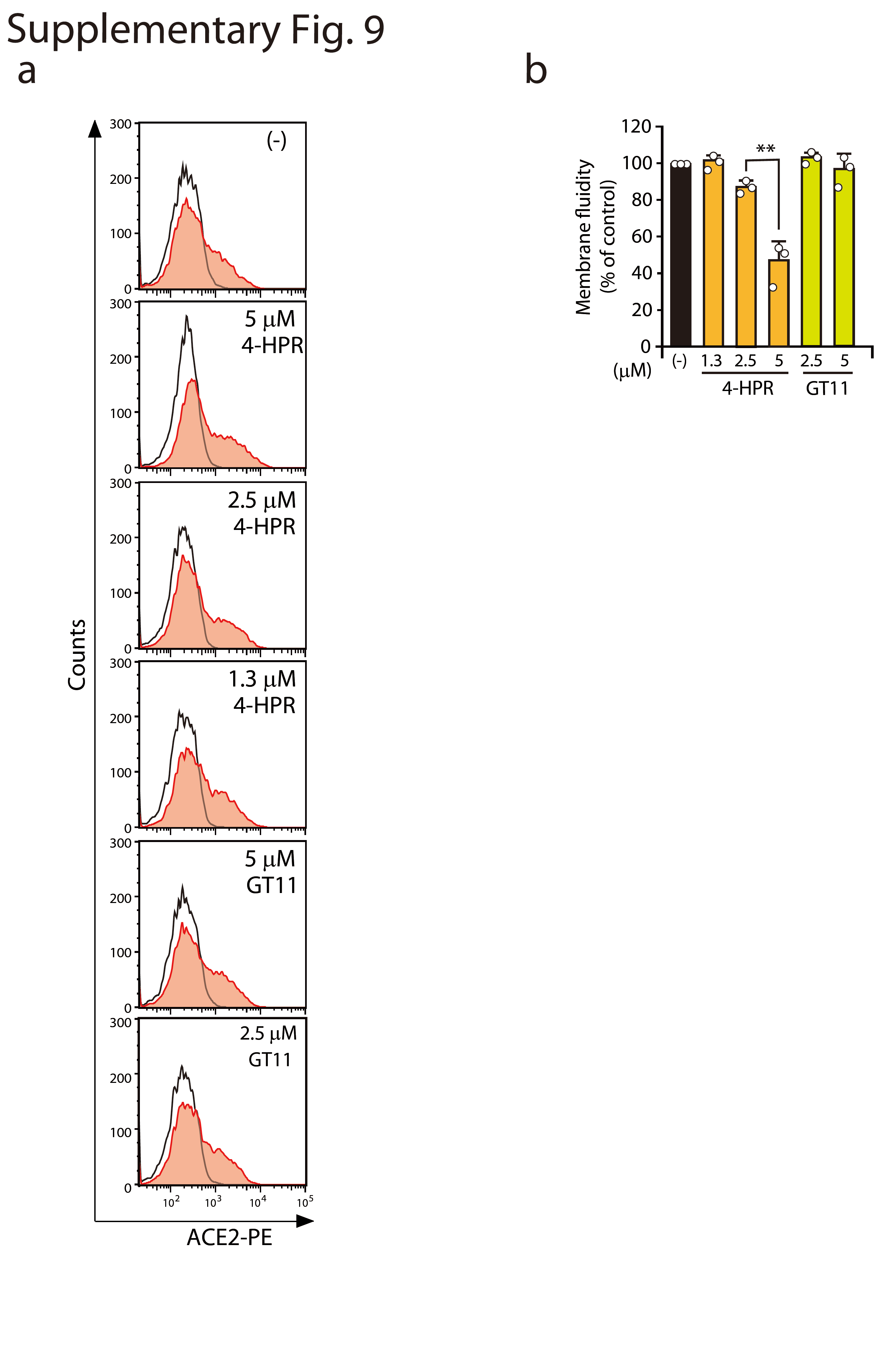








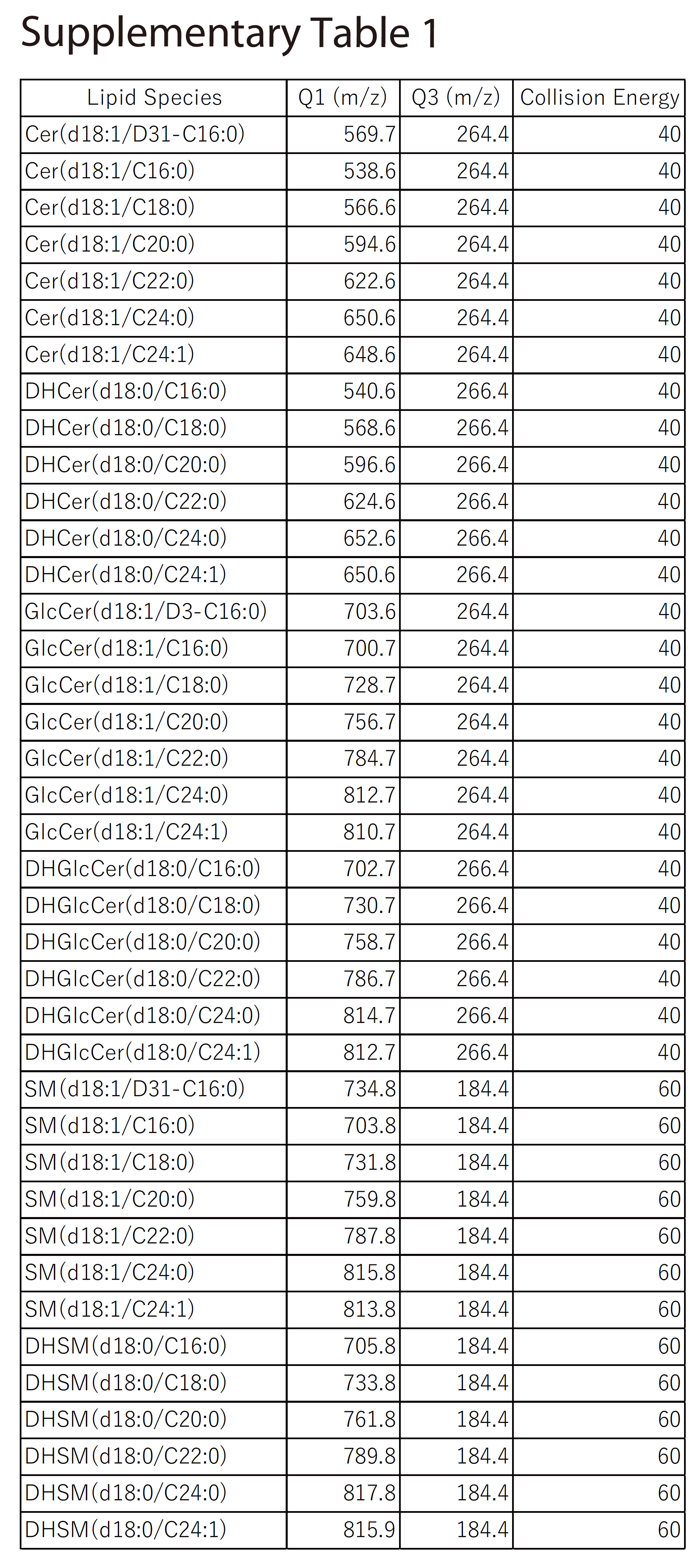
**Supplementary Figs. 5-8 | Effect of inhibitors of sphingolipid-metabolizing enzymes on cellular sphingolipid species in VeroE6TMPRSS2 cells.** VeroE6TMPRSS2 cells were treated for 3 days with the indicated concentrations of the compounds. The cellular levels of sphingolipid species were quantified by liquid chromatography with tandem mass spectrometry (LC-MS/MS) analysis. The bar graphs show levels of Cer (upper panel) and DHCer (lower panel) (**a**), those of GlcCer (upper panel) and DHGlcCer (lower panel) (**b**), and those of SM (upper panel) and DHSM (lower panel) (**c**) in Supplementary Fig. 5. Furthermore, the cellular levels of sphingolipid species with a distinct acyl chain were quantified by LC-MS/MS analysis. The bar graphs show levels of Cer (panels **a-f**) and DHCer (panels **g-l**) in Supplementary Fig. 6, those of GlcCer (panels **a-f**) and DHGlcCer (panels **g-l**) in Supplementary Fig. 7, and those of SM (panels **a-f**) and DHSM (panels **g-l**) in Supplementary Fig. 8. Statistical significance was determined by one-way ANOVA followed by Dunnett test for multiple comparisons; \* *p* < 0.05, \*\* *p* < 0.01 when compared with vehicle/dimethyl sulfoxide (DMSO)-treated cells. Abbreviations: 4-HPR, *N*-(4-hydroxyphenyl)retinamide; Cer, ceramide; DHCer, dihydroceramide; GlcCer, glucosylceramide; DHGlcCer, dihydroglycosylceramide; SM, sphingomyelin; DHSM, dihydrosphingomyelin



**Supplementary Fig. 9 | Effect of 4-HPR on cell-surface levels of ACE2 and membrane fluidity in VeroE6TMPRSS2 cells.** VeroE6TMPRSS2 cells were treated for 3 days with the indicated concentrations of the compounds. (**a**) Cell-surface expression levels of ACE2 in compound-treated cells were analysed by flowcytometry using an anti-ACE2 antibody (filled histogram). Open histograms indicate the isotype control. One representative experiment is shown, and similar results were obtained in three independent experiments. (**b**) Membrane fluidity in compound-treated cells was examined with a fluorescent lipophilic pyrene probe. Results are normalised to the rate of membrane fluidity in vehicle/dimethyl sulfoxide (DMSO)-treated cells. Values represent the mean ± S.D. from three independent experiments. Statistical significance was determined by one-way ANOVA followed by the Tukey-Kramer test; \*\* *p* < 0.01. Abbreviations: 4-HPR, *N*-(4-hydroxyphenyl)retinamide

**Supplementary tables**

**Supplementary Table 1 | Multiple reaction monitoring transition for Cer, DHCer, GlcCer, DHGlcCer, SM, and DHSM.**



Abbreviations: Cer, ceramide; DHCer, dihydroceramide; GlcCer, glucosylceramide; DHGlcCer, dihydroglycosylceramide; SM, sphingomyelin; DHSM, dihydrosphingomyelin