**Supporting Information**

**Novel ceramide mimetics induce necroptotic cell death in multiple cancer cell lines.**

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**Chemistry.**

Commercially available materials were used as received without further purification. 1H NMR (400 MHz) spectra were recorded on a JEOL ECZ 400S spectrometer (JEOL, Tokyo, Japan). Chemical shifts (δ) of the signals are reported in parts per million (ppm) relative to tetramethylsilane (TMS, 0.00 ppm) as an internal reference standard. All data are reported as follows: chemical shift, relative integration value, multiplicity (s = singlet, d = doublet, t = triplet, and m = multiplet), and coupling constant (*J* in Hz). High-resolution mass spectra (HRMS) were measured on a JEOL JMS-700T (JEOL, Tokyo, Japan) double-focusing magnetic sector mass spectrometer with an ionization mode of EI or positive FAB. SiliaFlash® P60 (Silicycle, Quebec, Canada) was used for flash column chromatography unless otherwise noted.

**2-(4-(1-Hydroxydodecyl)phenethyl)isoindoline-1,3-dione (RT-25).**

**RT-25** was synthesized by the scheme shown in Supplementary Figure 1A. Compound **2** was synthesized by Friedel-Crafts acylation of (2-bromoethyl)benzene (**1**), and the resulting ketone was reduced to give **3**. Finally, a substitution reaction was carried out with potassium phthalimide to give **RT-25** as a white solid. 1H NMR (400 MHz, CDCl3) δ 7.83 (d, *J*=5.6 Hz, 1H), 7.82 (d, *J*=5.6 Hz, 1H), 7.71 (d, *J*=5.2 Hz, 1H), 7.70 (d, *J*=5.2 Hz, 1H), 7.24-7.27 (m, 4H), 4.63 (m, 1H), 3.91 (m, 2H), 2.98 (m, 2H), 1.76 (m, 2H), 1.22-1.30 (m, 18H), 0.87 (t, *J*=7.2 Hz, 3H).; HRMS (EI) m/z calcd for C28H37NO3 [M]+ 435.2773 found 435.2778.



**Supplementary Figure 1A** Synthesis of RT-25.

**(*S*)-1-Butoxy-3-(4-(butyloxy)phenyl)propan-2-amine (RT-71).**

RT-71 was synthesized by the scheme shown in Supplementary Figure 1B, starting from Tyrosine derivative **4**, which was alkylated to give **5**. The ester was then reduced to give the alcohol **6**. The alcohol was alkylated to **7**, and finally a deprotection of Boc group was performed to give **RT-71** as a white solid. 1H NMR (400 MHz, D2O) δ 7.16 (d, *J*=8.8 Hz, 2H), 6.90 (d, *J*=8.8 Hz, 2H), 3.97 (t, *J*=6.4 Hz, 2H), 3.53-2.59 (m, 2H), 3.38-3.46(m, 3H), 2.84-2.87 (m, 2H), 1.61-1.69 (m, 2H), 1.41-1.49 (m, 2H), 1.31-1.39 (m, 2H), 1.20-1.27 (m, 2H), 0.85 (t, *J*=7.6 Hz, 3H), 0.80 (t, *J*=7.6 Hz, 3H).; HRMS (FAB+) m/z calcd for C17H30NO2 [M+H]+ 280.2277 found 280.2278.

**(*S*)-1-(Benzyloxy)-3-(4-(butyloxy)phenyl)propan-2-amine (YM-07).**

A white solid of **YM-07** was obtained in the same procedure as RT-71. 1H NMR (400 MHz, CDCl3) δ: 7.22-7.35 (5H, m), 7.04 (d, *J*=8.0 Hz, 2H), 6.76 (d, *J*=8.4 Hz, 2H), 4.55 (d, *J*=12 Hz, 1H), 4.45 (d, *J*=12 Hz, 1H), 3.89 (t, *J*=6.4 Hz, 2H), 3.50-3.61 (m, 3H), 3.23 (m, 1H), 2.95 (m, 1H), 1.73 (m, 2H), 1.47 (m, 2H), 0.96 (t, *J*=7.2 Hz, 3H).; HRMS (EI+) m/z calcd for C20H27NO2 [M]+ 313.2042 found 313.2047.



**Supplementary Figure 1B** Synthesis of RT-71 and YM-07.