Endocrine- and chemo-resistance are major causes for failure of treatment in recurrent breast cancer. Normal apoptotic pathways targeted by chemotherapeutic agents become altered, diminishing their efficacy and increasing resistance mechanisms. The proapoptotic sphingolipid compound \( \text{N-Octanoyl-D-erythro-sphingosine} \) (C8-ceramide) mimics endogenous long chain ceramide and is a potent drug in endocrine-/chemo-resistant breast cancer cells. In this study, we examined basal expression levels of modifier enzymes for endogenous ceramide regulation across drug sensitive, chemoresistant and hormone therapy- resistant breast cancer cells lines. Differences were found among UDP-galactose ceramide galactosyltransferase, sphingosine kinase-1, and acid sphingomyelinate gene expression in: MCF-10A, MCF-7, MDA-MB-231 and MCF-7TN-R cell lines. Using C8-ceramide as the lead compound, 8 novel ceramide analogs were synthesized with either enol or amide backbone substitutions and tested for biological activity. The enol substitution was found to be the most potent, with \((2S,3R,E)-2-((E)benzylideneamino)octadec-4-ene1,3-diol\) (Analog C) displaying the greatest reduction in proliferation. Analog B appeared to be the most potent cytotoxic drug in MCF-7 and MDA-MB-231 cell lines with IC\(_{50}\) values of 6.2\(\mu\)M and 3.0 \(\mu\)M respectively. In the cytotoxicity assay MCF-7TN-R cell line, Analog A appeared to be the most potent with an IC\(_{50}\) of 2.4\(\mu\)M. The clonogenic proliferation assay provided very different, yet promising results. Analog D had the lowest IC\(_{50}\) of 460nM in MDA-MB-231, Analog C had an IC\(_{50}\) of 100nM in MCF-7TN-R, and Analog A had an IC\(_{50}\) of 1.48uM in the MCF-7 breast cancer cell line. All of the IC\(_{50}\)s for proliferation assays were at least an order of magnitude more potent than the control drug C8 (IC\(_{50}\) of 5uM). Due to the potency of these drugs, these results exemplify the potential of novel ceramide-targeted therapies in chemo-resistant and endocrine-resistant breast cancer cell lines.