Triggered Release of a potent LPAAT-β inhibitor from inactive prodrugs to kill cancer cells

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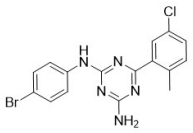
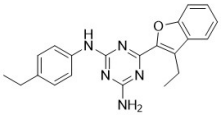
Lysophosphatidic acid acyltransferase β (LPAAT-β) is an enzyme controlling signaling pathway in mammalian cells and a potential cancer target.[1] In our hands however, the enzyme appeared to be similarly expressed in several cancer and non-cancer cells, and the nanomolar LPAAT-β inhibitors CT32228 and aminotriazine (**1**) appeared to be equally cytotoxic to both cell types.[2] Herein we report our investigation of a prodrug strategy to target **1** to cancer cells. By a structure-activity relationship study, we identified two potential vectors for connecting **1** to a cleavable linker. We then elaborated substituent and linker chemistry and obtained a redox-triggered release of active analogs of **1** from peptide-conjugated prodrugs.



CT32228



LPAAT-β inhibitor **(1)**
IC_{50} = 51 nM

[1] Michael Coon, Alexey Ball, Jeannine Pound, Sophe Ap, David Hollenback, Thayer White, John Tulinsky, Lynn Bonham, Deborah K. Morrison, Robert Finney, Jack W. Singer, *Mol. Cancer Ther.*, **2003**, 2, 1067–1078.
[2] Marion Poirier, Mahendra Awale, Matthias A. Roelli, Guy T. Giuffredi, Lars Ruddigkeit, Lasse Evensen, Amandine Stooss, Serafina Calarco, James B. Lorens, Roch-Philippe Charles, Jean-Louis Reymond, *ChemMedChem*, **2019**, 14, 224–236.