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Hydroxycoumarin OT-55 kills CML cells alone or in synergy with Imatinib or Synribo: involvement of ER stress and DAMP release

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Abstract

We synthetized and investigated here the anti-leukemic potential of the novel cytostatic bis(4-hydroxycoumarin) derivative OT-55 which complied with the Lipinski's rule of 5 and induced differential toxicity in various chronic myeloid leukemia (CML) cell models. OT-55 triggered ER stress leading to canonical, caspase-dependent apoptosis and release of danger associated molecular patterns. Consequently, OT-55 promoted phagocytosis of OT-55-treated CML cells by both murine and human monocyte-derived macrophages. Moreover, OT-55 inhibited tumor necrosis factor α-induced activation of nuclear factor-κB and produced synergistic effects when used in combination with imatinib to inhibit colony formation *in vitro* and Bcr-Abl$^+$ patient blast xenograft growth in zebrafish. Furthermore, OT-55 synergized with omacetaxine in imatinib-resistant KBM-5 R cells to inhibit the expression of Mcl-1, triggering apoptosis. In imatinib-resistant K562 R cells, OT-55 triggered necrosis and blocked tumor formation in zebrafish in combination with omacetaxine.