Molecular mechanisms of apoptosis and cell selectivity of zinc dithiocarbamates functionalized with hydroxyethyl substituents

ABSTRACT

In the solid state each of three binuclear zinc dithiocarbamates bearing hydroxyethyl groups, {Zn[S2CN(R)CH2CH2OH]2}2 for R = iPr (1), CH2CH2OH (2), and Me (3), and an all alkyl species, [Zn(S2CNEt2)2]2 (4), features a centrosymmetric {ZnSCS}2 core with a step topology; both 1 and 3 were isolated as monohydrates. All compounds were broadly cytotoxic, specifically against human cancer cell lines compared with normal cells, with greater potency than cisplatin. Notably, some selectivity were indicated with 2 being the most potent against human ovarian carcinoma cells (cisA2780), and 4 being more cytotoxic toward multidrug resistant human breast carcinoma cells (MCF-7R), human colon adenocarcinoma cells (HT-29), and human lung adenocarcinoma epithelial cells (A549). Based on human apoptosis PCR-array analysis, caspase activities, DNA fragmentation, cell apoptotic assays, intracellular reactive oxygen species (ROS) measurements and human topoisomerase I inhibition, induction of apoptosis in HT-29 cells is demonstrated via both extrinsic and intrinsic pathways. Compounds 2–4 activate the p53 gene while 1 activates both p53 and p73. Cell cycle arrest at the S and G2/M phases correlates with inhibition of HT-29 cell growth. Cell invasion is also inhibited by 1–4 which is correlated with down-regulation of NF-κB.

Keyword: Zinc; Dithiocarbamate; Cell selectivity; Apoptosis; Cell cycle; Topoisomerase I