A bismuth diethyldithiocarbamate compound promotes apoptosis in HepG2 carcinoma, cell cycle arrest and inhibits cell invasion through modulation of the NF-κB activation pathway

ABSTRACT

The compound with R = CH2CH3 in Bi(S2CNR2)3 (1) is highly cytotoxic against a range of human carcinoma, whereas that with R = CH2CH2OH (2) is considerably less so. Both 1 and 2 induce apoptosis in HepG2 cells with some evidence for necrosis induced by 2. Based on DNA fragmentation, caspase activities and human apoptosis PCR-array analysis, both the extrinsic and intrinsic pathways of apoptosis have been shown to occur. While both compounds activate mitochondrial and FAS apoptotic pathways, compound 1 was also found to induce another death receptor-dependent pathway by induction of CD40, CD40L and TNF-R1 (p55). Further, 1 highly expressed DAPK1, a tumour suppressor, with concomitant down-regulation of XIAP and NF-κB. Cell cycle arrest at the S and G2/M phases correlates with the inhibition of the growth of HepG2 cells. The cell invasion rate of 2 is 10-fold higher than that of 1, a finding correlated with the down-regulation of survivin and XIAP expression by 1. Compounds 1 and 2 interact with DNA through different binding motifs with 1 interacting with AT- or TA-specific sites followed by inhibition of restriction enzyme digestion; 2 did not interfere with any of the studied restriction enzymes.

Keyword: Bismuth; Apoptosis; Metallopharmaceuticals; Cell cycle; NF-κB