G_2/M cell cycle arrest on HT-29 cancer cells and toxicity assessment of triphenylphosphanegold(I) carbonimidothioates, $Ph_3PAu[SC(OR) = NPh]$, R = Me, Et, and iPr, during zebrafish development

ABSTRACT

Phosphanegold(I) thiolates, Ph3PAu[SC(OR) = NPh], R = Me (1), Et (2) and iPr (3), were previously shown to be significantly cytotoxic toward HT-29 cancer cells and to induce cell death by both intrinsic and extrinsic apoptotic pathways whereby 1 activated the p73 gene, and each of 2 and 3 activated p53; 2 also caused apoptotic cell death via the c-Jun N-terminal kinase/mitogen-activated protein kinase pathway. Apoptosis pathways have been further evaluated by mitochondrial cytochrome c measurements and annexin V screening, confirming apoptotic pathways of cell death. Cell cycle analysis showed the majority of treated HT-29 cells were arrested at the G2/M checkpoint after 24 h; results of both assays were confirmed by changes in populations of relevant genes (PCR array analysis). Cell invasion studies showed inhibition of metastasis through Matrigel™ matrix to 17–22% cf. untreated cells. LC50 values were determined in zebrafish (8.36, 8.17, and 7.64 μM for 1–3). Finally, the zebrafish tolerated doses of 1 and 2 up to 0.625 μM, and 3 was tolerated at even higher doses of up to 1.25 μM.

Keyword: Gold(I) compounds; Carbonimidothioates; Phosphanegold(I) thiolates; Apoptosis; HT-29 cancer cell; Zebrafish