Metal complexes with diflunisal as potential anticancer drugs

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Although diflunisal is a well-known and commercially available non-steroidal anti-inflammatory drug (NSAID), recent studies have also focused on the repurposing of this therapeutic agent for the treatment of cancer. To attempt to contribute to the investigation of metal complexes with NSAIDs, three novel complexes containing diflunisal (Hdif) and neocuproine (neo) were designed, prepared, and spectroscopically and structurally characterized. Furthermore, their biological activity was investigated in terms of DNA interaction as well as antiproliferative activity against prostate (PC-3), colon (HCT116) and breast (MDA-MB-468) cancer cell lines. Although molecules have similar composition of [MCl(dif)(neo)], where M is Zn(II), Co(II), and Cu(II), respectively, the copper complex significantly differs in molecular and supramolecular structure with diflunisalato ligand (dif) coordinated in bidentate chelate mode, while zinc and cobalt complexes are isostructural with dif bound in monodentate manner. All three complexes showed exceptional cytotoxicity against the tested cancer cell lines with IC_{50} values in nanomolar concentration range, while the free diflunisal was found to be inactive (IC_{50} > 100 μM). Even though the complexes have similar composition, differences in their cytotoxic effects have been observed, with the Cu(II) being the most active. Cu(II) complex induces caspase-independent apoptosis in PC-3 cell line. Interestingly, the binding affinity of the complexes to the genomic DNA samples isolated from the respective cell lines shows the same trend as the cytotoxicity. Since the obtained results indicate that the interaction of the complexes with DNA might be directly involved in the mechanism of action of the studied compounds on the cellular level, further studies of their effects on the DNA replication and transcription can be performed.
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