Liposomal formulation of a new Zn(II) complex exhibiting high therapeutic potential in a murine colon cancer model

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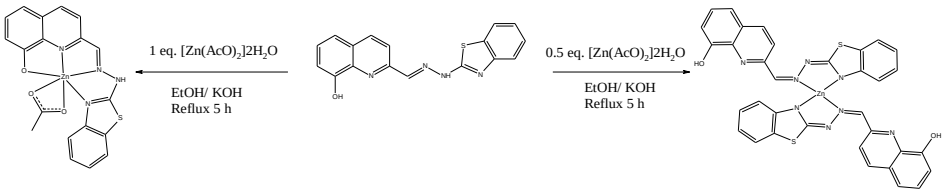
Colorectal cancer is the second cause of cancer-related deaths in the EU.[1] Current therapies rely on chemotherapeutic agents with poor specificity for tumour cells. The success of cisplatin in anticancer therapy inspired the search for novel metal-based compounds with improved therapeutic outcomes. In the present study, two zinc complexes, **[ZnL$_2$]** and **[ZnL(AcO)]**, where AcO is acetate and L is a Schiff base derived from the condensation 2-carbaldehyde-8-hydroxyquinoline with 2-hydrazinobenzothiazole, were synthesized, characterized and assessed concerning their antiproliferative properties. Despite showing high *in vitro* cytotoxicity towards colon cancer cell lines, the metal-complexes display low water solubility and specificity. While in 2D cell models, the IC_{50} values were < 22 μM in 3D settings, better models of *in vivo* tumors, much higher concentrations were needed to impact cell viability. Compound **[ZnL(AcO)]** displayed more suitable characteristics than **[ZnL$_2$]** and was chosen for further studies. Liposomal nanoformulations of **[ZnL(AcO)]** were characterized and screened *in vitro* (2D cell models), with the antiproliferative properties being maintained after incorporation (IC_{50} < 14 μM). Internalization studies of rhodamine-labelled liposomes into 3D spheroids of colon cancer cells were done by confocal microscopy and revealed that liposome penetration was time and concentration dependent. Preliminary safety of the formulations was evaluated by hemolytic activity and never surpassed 2% for both free and liposomal forms of **[ZnL(AcO)]**. Additionally, a syngeneic murine colon cancer mouse model was developed to assess the efficacy of the developed formulation and it revealed that while the free **[ZnL(AcO)]** did not impair tumour progression, its liposomal form was able to reduce the relative tumour volume in the same manner as the positive control, 5-fluoracil, using a metal complex dosage 3-fold lower (in mass).



[1] https://ec.europa.eu/eurostat/en/web/products-eurostat-news/-/edn-20200204-1, in Eurostat, 04-Feb-2020.