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New carbohydrate-bearing 8-hydroxyquinoline compounds as multifunctional chelators of copper(II) and zinc(II) ions

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Mounting evidence suggests a pivotal role of metal imbalances in protein misfolding and amyloid diseases. As such, metal ions represent a promising therapeutic target and therefore, the synthesis of chelators that also contain complementary functionalities to combat the multifactorial nature of neurodegenerative diseases is a highly topical issue Recent investigations have rekindled interest in 8-hydroxyquinolines (OHQs) as therapeutic agents for cancer, Alzheimer's disease and other neurodegenerative disorders. We have recently demonstrated that glycosylation is a versatile and powerful strategy for improving drug features including solubility, pharmacokinetics, drug targeting, and biological activities [1–4]. Here, we report several OHQ glycoconjugates whose multifunctional properties are highlighted, including their Cu(II) and Zn(II) binding abilities, and antioxidant and metal-induced antiaggregant capacity. Glucose, trehalose and cyclodextrin were the carbohydrates of choice because of their interesting properties such as antioxidant, antiaggregant and inclusion abilities.

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Antimicrobial properties of Cu-based nanoparticles: interaction with DNA, ROS production and lipid peroxidation

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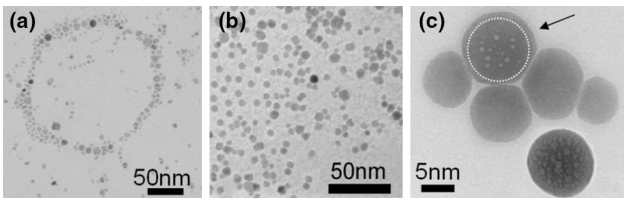
The abuse of antimicrobial drugs has led to increasing number of infections associated with antibiotic-resistance microbes. By using water as a solvent or typical solvothermal synthesis and in the presence of surfactants, copper based nanoparticles (Cu-based NPs) were formed, while synthesis control is achieved to tune their composition, size and shape. The higher biological activity of the NPs combined with lower applicable doses could give rise to the next generation of antimicrobials, namely nano-antimicrobials.

Herein, we solvothermally prepared Cu-based NPs of different composition and sizes capped with the non ionic surfactants tetraethylene glycol, polyethylene glycol 1000, polysorbate 20 and oleylamine. The antimicrobial activity of the synthesized Cu, Cu/Cu_2O, Cu_2O and CuO NPs has been screened against Gram-positive (*Staphylococcus aureus*, *Bacillus cereus*), Gram-negative bacteria (*Escherichia coli*, *Xanthomonas campestris*, *Bacillus subtilis*) and fungus (*Saccharomyces cerevisiae*). The results clearly indicated that the composition of the NPs was the main factor affecting their performance, since Cu_2O NPs found with enhanced antimicrobial effect and specificity against the Gram-positive strains. In an attempt to further explore their mechanism of action, we studied their interaction with DNA and Cu-based NPs found to induce pDNA, ds CT-DNA and fungal DNA degradation in a dose-dependent manner. The ROS production and lipid peroxidation have also been verified, while ionic contribution to the bactericidal activity of NPs cannot be supported as the released ions found below the value of inhibiting bacterial growth.



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Cystic fibrosis: new molecular imaging tools

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Cystic Fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encodes the CFTR protein, a chloride channel expressed in the apical membrane of epithelial cells in the airways, pancreas, intestine and exocrine glands. Therapies based in drugs that correct the trafficking or gating defects of CFTR (termed correctors or potentiators, respectively) are emerging. Although the ultimate endpoints to assess the efficacy of pharmacological correction would be the benefits upon the clinical phenotype, there is no available methodology to detect the presence of normal (or corrected) CFTR at the membrane in living organisms.

Molecular Imaging can be the solution, since it allows the in vivo non-invasive visualization of a target molecule by virtue of its interaction with an imaging probe. Single-photon emission computed tomography (SPECT) and positron emission tomography are the most sensitive imaging modalities available, and allow early disease diagnosis and follow up of therapy. So, the aim of this work is the development of non-invasive radiolabelled imaging probes for the detection of CFTR at the plasma membrane of human cells. The probe reported in this communication was based on a CFTR inhibitor known to interact specifically with CFTR at the region of the channel pore.

The ^{99m}Tc radioisotope, used in SPECT, was the chosen radionuclide due to its physical properties, low cost and easy availability. The CFTR inhibitor was radiolabelled with the *fac*-$[^{99m}Tc(CO)_3]^+$ core, using the bifunctional chelator (BFC) approach. This strategy involved a three-component system constituted by a high affinity biomolecule ($CFTR_{inh}$), a radiometal (99mTc) and a BFC, designed to bind both to the radiometal and the biomolecule. Cellular studies in human bronchial epithelial cells expressing wt-CFTR were performed and the amount of radiolabelled probe that can interact with CFTR assessed. To evaluate if the metal complex of $CFTR_{inh}$ still maintained its ability to interact with CFTR, a non-radioactive surrogate rhenium complex was synthesized and its inhibitory efficacy was assessed through a functional assay in cells expressing CFTR. In the future, these types of probes may have the potential to be used on SPECT imaging to assess early therapy response in drug evaluation.

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DNA binding and cytotoxic activity of Zn(II) and Cu(II) complexes with new bis(thiosemicarbazone) derivatives

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Bis(thiosemicarbazone) complexes of Zn(II) and Cu(II) have received considerable attention in the design of metallodrugs, either as anticancer therapeutics or diagnostic radiopharmaceuticals. Moreover, the availability of several medically relevant copper radioisotopes (e.g. ^{62}Cu, ^{64}Cu and ^{67}Cu) makes them potentially useful tools for cancer theranostics, profiting from a versatile chemical modification of the bis(thiosemicarbazone) framework and a stable coordination of radiocopper ions. The mechanism involved in the anticancer activity of Zn(II) and Cu(II) bis(thiosemicarbazonates) is not fully understood. However, it has been shown in a few studies that there is an accumulation of the complexes in the nucleus of tumor cells, indicating that DNA could be a potential target of their action. In this context, we have embarked in the synthesis of Zn(II) and Cu(II) complexes with new bis(thiosemicarbazone) chelators, symmetrically functionalized with protonable cyclic amines of the piperidine and morpholine type (Fig. 1). We have hypothesized that the presence of the cyclic amine groups could enhance the DNA affinity of the compounds and, together with the planarity of the metallic center, could promote some selectivity towards different types of DNA (e.g. G-quadruplex *vs.* duplex DNA). In this communication, we report the DNA binding and cytotoxic activity studies of these new M(II)-bis(thiosemicarbazone) complexes, performed with the aim of assessing their usefulness in the design of metal-based drugs for cancer theranostics.

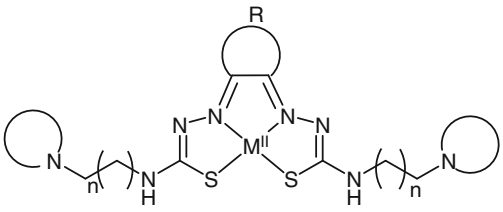

Fig. 1

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Biological evaluation of zinc(II) chlorido complexes with O^6-substituted 9-deazahypoxanthine derivatives

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In this work, a series of new zinc(II) complexes with the general formula $[Zn(L_n)_2Cl_2]$ involving O^6-substitued 9-deazahypoxanthine derivatives (L_n) were biologically evaluated for their in vitro cytotoxic and immunomodulating activity. The present study showed that the compounds exhibited no cytotoxic effect on the human prostate (PC3, LNCaP), ovarian carcinoma (A2780) and monocytic leukemia (THP-1) cancer cell lines up to the concentration of IC_{50}>50 μM, and IC_{50}>10 μM, respectively. The effect of these complexes to influence the activity of inflammatory-related zinc-dependent matrix metalloproteinase (MMP-2) and to affect the secretion of pro-inflammatory cytokine IL-1β was determined using the lipopolysaccharide-activated macrophage-like THP-1 cell model. The ability of the complexes to attenuate IL-1β production was not observed. On the other hand, these complexes were able to increase the total amount of MMP-2 protein and significantly elevate the level of the active form of this protease. Increased activity of MMP-2 could be beneficial during wound healing, rheumatoid arthritis or repairing of injured nervous system due to the ability of this protease to remove some pro-inflammatory cytokines, promote neovascularisation and organise tissue remodelling [1–3].