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Study of the incorporation of a Ga(III) complex with doxycycline in cancer cells.

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Cancer is the second leading cause of disease-related deaths in several countries. In Brazil, the National Cancer Institute (INCA) estimates the occurrence of 704 thousand new cases of cancer each year from 2023 to 2025, with the Southern and Southeastern regions accounting for approximately 70% of the incidence. The most important use of metal complexes in medicine is in the treatment of cancer. Unfortunately, the appearance of cellular resistance and the toxic side effects of the known drugs makes it necessary to find alternatives for cancer treatment. This study investigated the anticancer potential of a new gallium(III) complex with doxycycline. On the one hand, doxycycline is an inhibitor of matrix metalo-proteinases [1] and, on the other hand, gallium is the second metal to be used in cancer treatment, after platinum [2]. The interactions of Ga(III) with doxycycline were studied in aqueous solution by UV-Vis spectrophotometry, circular dichroism and spectrofluorimetry. Gallium(III) ions form a stable complex with doxycycline in aqueous solution at pH 7.0. The complex exhibits cytotoxic activity in chronic myeloid leukemia cells, K562 cell line, with an IC_{50} of 5.7×10^{-6} mol L^{-1}. Cytotoxicity studies in a normal human epithelial cell line, HaCat, showed that the complex does not affect cell viability at concentrations in which it is cytotoxic in K562 cells. Uptake of the complex by K562 cells was studied by graphite furnace atomic absorption spectrometry (GFAAS) [3] and by fluorescence microscopy [4]. The intracellular concentration of gallium determined by GFAAS, after incubating cells with the IC50 value, was 4.0×10^{-16} mol L^{-1} $cell^{-1}$. Although free doxycycline is only poorly fluorescent, the complex emits fluorescence, and this property allowed the assessment of its localization inside cells. Calcein was used as a cytoplasm marker. The complex is distributed throughout the cytoplasm without accumulation within a specific organelle or the nucleus. Therefore, its mechanism of action does not seem to involve DNA binding, but interactions with cytoplasmatic proteins, such as ribonucleotide reductase. These results reveal the potential of the Ga(III) complex with doxycycline as an anticancer agent.

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