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The effect of the degree of oxidation and the molecular structure of cobalt complexes with imidazole on the metabolic profiles of CCD 841 CoN and HT-29 cells

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INTRODUCTION

Colorectal cancer is among the most prevalent causes of cancer-related morbidity and mortality on a global scale, underscoring the necessity of novel chemotherapeutic strategies that exhibit enhanced selectivity and diminished systemic toxicity. Transition metal complexes have emerged as promising candidates for anticancer drug development due to their diverse coordination chemistry and ability to interact with biomolecular targets through mechanisms distinct from traditional organic drugs. Among these, cobalt-based complexes have gained increased interest due to their redox activity, tunable oxidation states, and capacity to modulate cellular pathways, including apoptosis and reactive oxygen species (ROS) generation [1].

RESULTS & DISCUSSION

The present study evaluates the cytotoxic activity and selectivity of three structurally distinct cobalt-imidazole complexes (Fig. 1) against human colon adenocarcinoma cells (HT-29) and normal colon epithelial cells (CCD 841 CoN), with the aim of identifying promising candidates for further biological development (Fig 2).

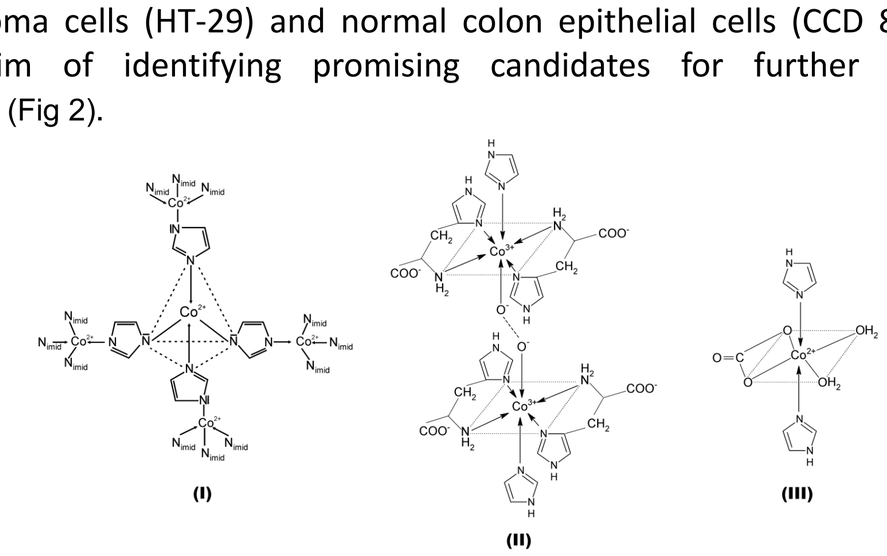
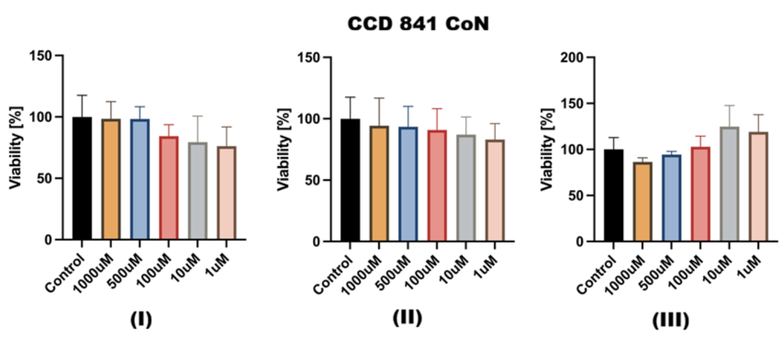


Fig. 1. The structures of cobalt complexes:
(I) $[Co(II)(imid)_2]_n$; (II) $[Co(III)(Himid)(L\text{-}(\alpha)\text{-histidine})_2]_2O_2^{2-}$; (III) $Co(II)(Himid)_2(H_2O)_2CO_3$.



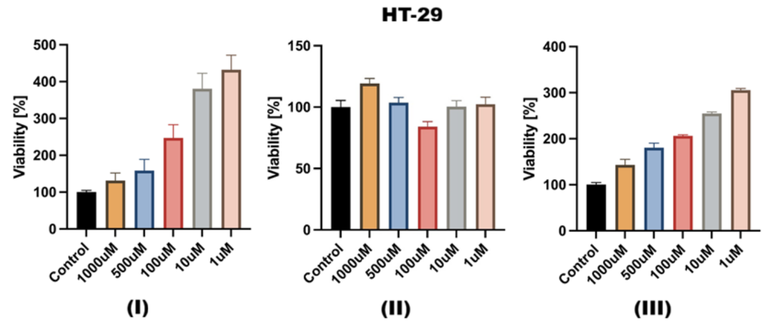


Fig 2. The effect of complexes: (I) $[Co(II)(imid)_2]_n$; (II) $[Co(III)(Himid)(L\text{-}(\alpha)\text{-histidine})_2]_2O_2^{2-}$; and (III) $Co(II)(Himid)_2(H_2O)_2CO_3$ (C = 1-1000 µM, 48-hour incubation) on normal human colon epithelial cells (CCD 841 CoN) and colon cancer cells (HT-29) viability measured in the MTT assay. The data shown as the mean ± SD.

In the CCD 841 CoN cell line, complex (I) exhibited a moderate, concentration-dependent reduction in cell viability, maintaining approximately 75-80 % survival even at the maximum concentration of 1000 µM. Conversely, in the HT-29 line a significant, inverse relationship between compound concentration and cell viability was observed, with cell viability reaching over 400 % at 1 µM.

This pronounced increase in cell viability suggests that the polymeric Co(II) species may trigger compensatory proliferative pathways or interfere with mitochondrial dehydrogenase activity in malignant cells [2].

Of the complexes investigated, (II) was found to demonstrate the most favorable profile. In both CCD 841 CoN and HT-29 lines, cell viability remained near control levels (approx. 100 %) throughout the tested concentration range. The relative inertness of this species can be attributed to the Co(III) oxidation state and the presence of L-histidine ligands, which likely stabilize the coordination sphere and minimize non-specific cellular interactions compared to its Co(II) counterparts. The presence of a µ-peroxo bridge (O_2^{2-}) is an additional structural feature which influences the biological activity of a compound [3,4].

Similar to complex (I), compound (III) induced a biphasic response. While exhibiting mild cytotoxicity in CCD 841 CoN cells at high concentrations, it stimulated a drastic increase in cell viability in the HT-29 line, reaching 300 % at 1 µM. The presence of labile ligands H_2O, CO_3^{2-}) in this mononuclear complex may facilitate the release of Co(II) ions, which are known to mimic hypoxic conditions. The anomalous increase in viability observed in HT-29 cells (complexes I and III) is a phenomenon frequently associated with cobalt-induced "pseudohypoxia" [5].

METHOD

The assessment of cell viability was conducted by means of the MTT assay. Following a 48-hour incubation with tested compounds, 20 µL of MTT solution was added to each well. The plates were then left to incubate for a further hour. Subsequently, the formazan crystals were dissolved in solubilization buffer, and the absorbances were measured at 570 nm using a microplate reader. The cel viability in the samples was calculated as a percentage of the untreated control.

CONCLUSION

The biological activity of the studied cobalt complexes is primarily determined by the metal oxidation state and ligand environment. The Co(III) complex showed excellent biocompatibility, maintaining normal viability in both CCD 841 CoN and HT-29 cells. In contrast, the Co(II) complexes induced a strong, dose-dependent increase in metabolic activity in HT-29 cells, reaching up to 400 % of control values. This phenomenon is indicative of Co(II) induced pseudohypoxia - characterized by the stabilization of hypoxia-inducible factors - which may affect cellular proliferation.

Conflicts of Interest: The authors declare no conflict of interest.

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