Studies on the Complexation of Platinum(II) by Some 4-Nitroisothiazoles and the Cytotoxic Activity of the Resulting Complexes

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Streszczenie

Five novel platinum(II) complexes **C1**–**C5** were synthesized in the reaction of the appropriate substituted 4-nitroisothiazoles with K_2PtCl_4 and characterized with elemental analysis, ESI MS spectrometry, NMR spectroscopy, and IR spectroscopy. Also, a new methyl 3-methyl-4-nitroisothiazole-5-carboxylate (**L2**) was obtained. The structures of trans complex **C4** and the new isothiazole derivative **L2** were additionally confirmed by X-ray diffraction (XRD) method. The cytotoxicity of the investigated complexes was examined in vitro on three human cancer cell lines (MCF-7 breast, ES-2 ovarian, and A549 lung adenocarcinomas) in both normoxic and hypoxic conditions. The tested complexes, except for the most polar cis **C5**, which appeared to be the least active, showed cytotoxic activity comparable to that of the reference cisplatin. cis-complex **C1**, trans **C2**, and trans **C3** showed slightly better cytotoxic activity than cisplatin against the MCF-7 cell line. The complexes had the weakest effect on the A549 cell line. No differences in the cytotoxic activity of the complexes were observed between normoxic and hypoxic conditions, except for the A549 cell line, where all the complexes, except for **C2**, were inactive in hypoxia. However, most complexes, including the reference cisplatin, were equally toxic to healthy BALB/3T3 cells and cancer cells. The trans complex **C2** (isomeric to cis **C1**) showed even greater toxicity to healthy cells than to MCF-7 and A549 cancer cells. Some complexes were tested for stability against glutathione (GSH) solution to gain additional information that may facilitate the explanation of the pharmacological activity of the tested compounds. Additionally, some theoretical calculations on the thermochemistry of the complexation process were performed using quantum density functional theory (DFT), which indicate that complexation should occur through the coordination of the platinum cation by the nitrogen rather than the sulfur atom of the isothiazole ring.

Słowa kluczowe

4-nitorisothiazoles-Pt(II) complexes, synthesis, spectral analysis, structural analysis, X-ray crystallography, thermochemistry, cytotoxic activity, normoxia, hypoxia, L-glutathione (GSH)

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