

Meccals in Meclicine and Biology New organoruthenium complexes with dipyrido[3,2-a:2',3'clphenazine based ligands

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Ruthenium complexes with dipyrido[3,2-a:2',3'-c]phenazine (dppz) ligands have been extensively investigated as potential anticancer agents due to possibility of modulation of their intracellular accumulation and respective anticancer mechanism of action [1,2]. In recent years we have explored the anticancer activity of a variety of ruthenium(II)-arene complexes with dppz based ligands and some of them demonstrated remarkable cytotoxic activity [3]. Following these studies here we present a series of Ru(II)-arene complexes with the general formula $[(n^{6}-arene)Ru(dppz-R)Cl]PF_{6}$, where arene fragment was benzene, toluene or pcymene and R was -NO₂, -Me or -COOMe with aim to study influence of both of half-sandwich Ru(II)-arene fragments and the variation of dppz ligands on improvement of the therapeutic potential of those complexes. All compounds were fully characterized by physico-chemical methods. The anticancer activity of dppz ligands and respective Ru complexes was assessed against MDA-MB-231, HCT116 and CT26 cancer cell lines and healthy MRC5 lung fibroblasts. In vivo efficacy of lead Ru-dppz complex revealed significantly reduction of tumor burden in mice with colorectal cancers without inducing liver and kidney toxicity. Thus, all the results indicated that introducing appropriate dppz into ruthenium-arene scaffold was a promising strategy for developing potent antitumor agents.

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References

[1] V. Pierroz, T. Joshi, A. Leonidova, C. Mari, J. Schur, I. Ott, L. Spiccia, S. Ferrari, G. Gasser, Molecular and cellular characterization of the biological effects of ruthenium(II) complexes incorporating 2-pyridyl-2-pyrimidine-4-carboxylic acid, J. Am. Chem. Soc., 134 (2012) 20376-20387. [2] M.L. Di Pietro, G. La Ganga, F. Nastasi, F. Puntoriero, Ru(II)-Dppz Derivatives and Their Interactions with DNA: Thirty Years and Counting, Appl. Sci., 11 (2021) 3038.

[3] S. Nikolić, L. Rangasamy, N. Gligorijević, S. Aranđelović, S. Radulović, G. Gasser, S. Grgurić-Šipka, Synthesis, characterization and biological evaluation of novel Ru(II)-arene complexes containing intercalating ligands, J. Inorg. Biochem., 160 (2016) 156-165.

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