Abstract

In response to current research efforts aimed at identifying coordination compounds as alternatives to the clinically used platinum(II) cytostatics, this doctoral dissertation focuses on the synthesis, structural characterization, and evaluation of the anticancer potential of novel platinum(II) and ruthenium(II) azole complexes. As part of the dissertation, coordination compounds of platinum(II) of the $[PtCl_2(N\text{-donor})_2]$, $[PtCl_2(DMSO)(N\text{-donor})]$, and $[Pt(N\text{-donor})_2(ox)]$ types, where (1S,4R,5R)-4-(4-phenyl-1H-1,2,3-triazol-1-yl)-2-((S)-1-phenylethyl)-2-azabicyclo[3.2.1]octane, (benzofuran-2-yl)-2-(1H-1,2,4-triazol-1-yl)ethenone or (benzofuran-2-yl)-2-(1H)-imidazol-1-yl)ethenone are the N-donors were synthesized, as well as biphenyl ruthenium(II) complexes of the $[(\eta^6\text{-bip})RuCl_2(N\text{-donor})]$ type, where 5,7-dimethyl-1,2,4-triazolo[1,5-*a*]pyrimidine, 7-isobutyl-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine or 5,7-diphenyl-1,2,4-triazolo[1,5-*a*]pyrimidine are the N-donor were prepared.

The compositions of the coordination spheres were confirmed using a combination of experimental techniques (^1H, ^{13}C, ^{15}N, and ^{195}Pt NMR, IR, single-crystal diffraction), and density functional theory (DFT) calculations. These studies confirmed square-planar geometry for the platinum(II) complexes and pseudooctahedral geometry for the ruthenium(II) complexes.

The biological activity of the synthesized compounds was comprehensively evaluated through the determination of lipophilicity, assessment of glutathione reactivity, cytotoxic and antiproliferative studies, and analysis of their effects on the cell cycle and DNA interactions. Four (three platinum(II) and one ruthenium(II)) coordination compounds were identified as promising anticancer candidates. Compared to cisplatin, these compounds exhibited higher lipophilicity (logP = 0.87 - 1.43), reduced reactivity toward glutathione, lower toxicity toward normal cells (IC_{50} = 5.01 - 23.87 μM), and a mechanism of action independent of direct DNA binding.

Furthermore, it was shown that the encapsulation of the selected platinum(II) and ruthenium(II) complexes in Pluronic®P123 micelles significantly improves their anticancer properties, enabling the achievement of submicromolar IC_{50} values (IC_{50} = 0.07 - 0.94 μM). The collected results indicate that the combination of platinum(II) or ruthenium(II) azole complexes with polymeric nanocarrier systems (Pluronic®P123) is a promising approach to designing next-generation chemotherapeutic agents.