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Title: Syntheses, Characterization and Anti-Cancer Profiles of Glutamic Acid Derivatives and their Metal Ion Complexes.
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Abstract

Generally, the name "cancer" brings about a huge sense of terror. It is a big threat to human beings all over the world. The number of cancer related deaths in the world is expected to rise to 9.0 and 11.0 million in 2015 and 2030, respectively. Presently, different strategies are being employed for ensuring safe and effective treatment of cancer. The ultimate goal of every cancer treatment procedure is the complete elimination of cancer cells and tissues without any damages to the normal cells and tissues of body. Chemotherapy stands out as one of the commonly used modalities for the treatment of cancer. The history of chemotherapy can be traced back to the discovery of the anti-leukemic properties of mustard gas used as a chemical warfare agent in World War I. This discovery served as stimulus to extensive experimentation leading to the development of a pool of organic and metallodrugs with good anticancer properties. Besides, a large number of natural products were screened for their anticancer properties among which some are being used worldwide for the treatment of different cancers. However, till today we do not have an anticancer drug that can control cancers at late stages without any side effects.

Glutamic acid derivatives (azaserine, acivicin, thalidomide, etc.) have displayed exciting anticancer properties. Metallodrugs have occupied a pioneer position in medicinal chemistry for the development of anticancer agents with several advantages over the organic based drugs. Copper, nickel and ruthenium complexes have been extensively explored for their anticancer properties with interesting results. The main objectives of this research work are to synthesize different multidentate ligands using glutamic acid and its derivatives (thalidomide and pyroglutamic acid) and their complexes with Cu(II), Ni(II) and Ru(III) ions as DNA binding and anticancer agents. The synthesized compounds were characterized, and investigated for their DNA binding propensities, hemolysis assays and anticancer profiles. The present thesis is divided into six chapters as summarized below.

First chapter describes the origin of cancer, current cancer scenario in India and the world. The main causes and the contemporary treatments of cancer with emphasis on chemotherapy have been discussed.

Second chapter presents the detailed information of the materials and instruments used in the research work. Besides, details of the experimental methodologies along with their theoretical background have been given in this chapter.

Third chapter describes the syntheses, characterization, DNA binding, hemolysis assays and anticancer profiles of glutamic acid based ligands and their Cu(II), Ni(II) and Ru(III) complexes. The ligands (L1g to L4g) and the complexes

(CuL1g to RuL4g) were characterized by various physico-chemical, analytical and spectroscopic techniques. All the ligands and their complexes were freely soluble in water. Besides, all the complexes were resistant to degradation in PBS at pH 7.4. The DNA binding constants of the synthesized compounds were in the range of 0.7×10^{3}-5.24×10^{4} M^{-1}, indicating good binding abilities of the compounds. All the compounds were significantly less toxic to RBCs as compared to standard drug doxorubicin. Finally, good anticancer activities of the compounds revealed their bright candidature for further investigation as anticancer agents.

Fourth chapter depicts the syntheses, characterization, DNA binding and anticancer profiles of Cu(II), Ni(II) and Ru(III) complexes of a thalidomide based dithiocarbamate ligand. The ligand (Lt) and the complexes (CuLt, NiLt and RuLt) were characterized by CHNS analysis, FTIR, UV-Vis., ^{1}H NMR and mass spectroscopic techniques, conductance measurements and molecular modelling. The values of DNA binding constants ranged from 3.6×10^{4}-1.4×10^{5} M^{-1}, indicating appreciable binding abilities of the compounds. All the compounds were significantly less toxic to RBCs as compared to standard drug doxorubicin. Besides, all the compounds had good anticancer activities against MCF-7 cell lines. Briefly, good anticancer activities and low toxicities of the reported compounds on human cancer cell lines revealed their potential as anticancer agents.

Fifth chapter deals with the syntheses, characterization, DNA binding, hemolysis assays and anticancer profiles of Cu(II), Ni(II) and Ru(III) complexes of two oxopyrrolidine based ligands (L1p and L2p). All the complexes (CuL1p to RuL2p) had good stabilities in PBS solutions at physiological pH. The DNA binding constants of the compounds indicated their good binding abilities. Hemolysis assays confirmed that the ligands and their complexes (except RuL1p) were less toxic to RBCs than doxorubicin. Finally, good anticancer activities of the compounds on MCF-7 cell lines revealed their potential for further examination as anticancer agents.

Sixth chapter describes the docking studies of the ligands reported in the chapters 3, 4 and 5. Interestingly, all the ligands preferred to enter and interact through the minor groove of DNA. L1g formed one hydrogen bond with DNA and showed considerable Van der Waal's interactions. The docking energies of L2g, L3g and L4g were in the order, L3g > L2g > L4g. Interestingly, their Van der Waal's energies were also in the same order. Lt formed one hydrogen bond between oxygen atom of carbonyl group of the pyrolidinedione moiety and hydrogen atom of adenine. L1p formed one hydrogen bond between its $-NH_2$ group and oxygen atom of guanine residue. L2p interacted significantly with DNA mainly through Van der Waal's forces of attraction. Overall, the docking results were quite interesting and were in good agreement with the spectroscopic observations of DNA binding. Briefly, docking results indicated good affinities of the developed compounds towards DNA.

Overall, the results presented in this thesis indicated appreciable binding of the reported compounds with DNA, wherein the complexes exhibited better DNA binding propensities as compared to their ligands. Interestingly, all the compounds (except RuL1p) were less toxic to RBCs as compared to the standard anticancer drug doxorubicin. Thus, the therapy with the present lot of compounds would be with less side effects. Besides, good anticancer activities of the reported compounds against cancer cell lines encourages their further examination as anticancer agents.