Chapter – 2

Scope of the present work

Structure and activity of the drugs are closely related to each other and any changes in the structure of the drug will reflect in its activity as well as in its physical and chemical properties. The interesting difference observed between the anticancer drug cisplatin (CDDP) and its ineffective isomer trans-DDP in the clinical trial is attributed to the different ability of these compounds to form different DNA cross link adducts. Both of these isomers form bifunctional DNA adducts by binding to the N7 positions of guanine as well as to adenine. The trans-DDP is unable to form 1,2-intrastand d(GpG) or d(ApG) adducts. Upon the uptake of cisplatin only 1- 4 % of CDDP reaches the nucleus and makes the DNA adducts with purines of DNA. It has several disadvantages like solubility, dose limits and its toxicity such as gastrointestinal, hematological toxicity, decreased blood cell and platelet production in bone-marrow suppression, immunosuppression, nephrotoxicity, neurotoxicity, hearing loss, cardio toxicity. But in the case of carboplatin where the two chloride ligands have been replaced with 1,1-cyclobutanedicarboxylate, leads to the slow aquation of this compound and possess less toxic, administered in higher doses of 300-450 mg m\textsuperscript{-2} than CDDP (20-120 mg m\textsuperscript{-2}). Now it is used as a preferred drug for the treatment of ovarian cancer than CDDP. Oxaliplatin is another platinum based drug with replacement of two ammine groups by a (1R,2R)-cyclohexane-1,2-diamine and two chlorides with oxalate. The toxicity side effects were greatly reduced due to the presence of oxalate ligand in oxaliplatin. In case of nedaplatin, the two...
chlorides are replaced with hydroxyacetato ligands, which gave ten times more solubility than CDDP and less nephrotoxicity than CDDP and carboplatin, the anticancer activity was much higher than carboplatin and equal to CDDP. Lobaplatin, another platinum based drug with replacement of both amines and chlorides by 1,2-cyclobutanedimethanamine and 2-hydroxypropanoato ligands which does not induce alopecia, renal and neurotoxicity. Another interesting platinated drug heptaplatin which is similar to lobaplatin but having the propanedioate, 2-(1-methylethyl)-1,13-dioxolane-4,5-dimethanamine ligands attached to platinum showing better stability in solution, high anticancer activity in certain CDDP-resistant cancer cell lines, as well as no notable toxicity. Satraplatin, picoplatin, ProLindacTM, and LipoplatinTM are the modified platinated drugs currently in the final phase of the clinical trials. Recently ruthenium complexes NAMI-A, KP101961-62 and radio-labeled copper complex 64Cu(ATSM)63 have entered into the clinical trials for the treatment of metastatic and colon cancer tumors respectively.

The above facts show that any changes in the structure of ligands attached to the metal play a vital role in drug development of platinum complexes. These facts were applied in designing various transition metal complexes either changing the ancillary ligand38-39, 44, 64-65 in particularly phenanthroline and bipyridines attached to the metal or changing the oxidation state65-67 of the metal or changing the substitution around the coordination sphere30, 37, 68-69 or introducing two different metal centers in a system70-72 / bimetallic system73-75 or changing the metal center with fixed ligands.31-32, 43, 76-79
Cobalt is a rare metal but has a lot of biological importance in vitamin B$_{12}$-dependent enzymes and humans require 1 to 2 µg per day. Naturally cobalt has present in two oxidation states, cobalt(II) and cobalt(III). Cobalt(III) complexes are kinetically inert and act as prodrug whereas cobalt(II) complexes are quite labile, which can undergo rapid ligand exchange. Also cobalt(III) can be reduced to cobalt(II) in biological environments. In recent years cobalt complexes attracted much attention in cancer therapy because of their ability to redox-dependent targeting the malignant tissues. Battaglia et. al. have reported that cobalt(II) is an inducer of apoptosis triggered by mitochondrial oxidative stress and can produce ROS in vivo and in vitro by catalyzing the generation of hydroxyl radicals from H$_2$O$_2$ in a Fenton-like reaction. The cobalt-alkyne derivative (Co-ASS) of the drug aspirin shows high cytotoxicity in breast cancer cells. Recently, Tomco et. al. and Gurley et. al. have shown that the cobalt complexes exhibit higher inhibition of chymotrypsin-like activity in purified proteasomes as well as improved apoptotic induction in PC-3 cancer cells. Other than cytotoxicity effects cobalt complexes are used as artificial proteases, HIV protease inhibitor. Up-to-date only one cobalt(III) Schiff base complex, Doxovir has reached clinical trials.

In the case of cobalt chemistry, anticancer studies of cobalt complexes are available either by modifying any one of these following parameters namely redox potential / oxidation state (charge of the complex), chelating ligand (hydrophobicity) and nuclearity.
So, in order to achieve better cobalt based anticancer drugs, it is necessary to carry out studies by comparing the effect of ligands (hydrophobicity), charge of the complex (ionicity) against the anticancer activity in similar systems that will give a new direction to achieve this goal. For this purpose, a study on “Cobalt complexes containing substituted diimine ligands: Effect of hydrophobicity, ionicity (charge) and presence of labile ligand on anticancer activity” is undertaken.