Synthesis, characterization and DNA intercalation studies of a novel plumbagin-based copper (II) metal complex

C Padumadasa[1*], K L N Perera[2], E M N Sankalpanie[1]

[1]*Department of Chemistry, Faculty of Applied Sciences, University of Sri Jayewardenepura, Nugegoda*

[2]*Genetech, Kitulwatte Road, Colombo 08*

[*]*Email: chayanikapadumadasa@yahoo.com*

Plumbago indica L., called "Rathnitul" in Sinhala is a plant belongs to the family Plumbaginaceae, which is widely used worldwide for its medicinal properties. In Sri Lanka it is extensively used in traditional medicine and Ayurveda. The major secondary metabolites in the roots of these plants are naphthoquinones of which plumbagin (2-methyl-5-hydroxy-1,4-naphthoquinone) is predominant.[1] Previous studies claim that plumbagin exhibits highly potent biological activities most importantly anticancer activities.[1] Although plumbagin has been shown to be more toxic to cancer cells, it has also been shown to be toxic to normal cells at high concentrations. Plumbagin, in addition to possessing the common problems associated with natural compounds such as inefficient systemic delivery, poor bioavailability and reduced oxidative stability, is also volatile.[1] Therefore, design of a "hybrid drug molecule" of plumbagin by combining it with appropriate metals and other ligands may provide an opportunity to overcome these problems in its use for cancer treatment.

Plumbagin was extracted from *P. indica* roots using hexane.[2] After recrystallization using hexane plumbagin was obtained as orange coloured needles (0.36 g, 0.72 %). In GC/MS studies, the gas chromatogram showed a single peak and corresponding mass spectrum with a molecular ion at m/z 188. IR and UV spectroscopic results and melting point (76-78 ^{0}C) were in accordance with published data and confirmed that plumbagin has been successfully isolated.[3] The synthesis of the Cu (II) metal complex was carried out using plumbagin (PLN) and phenanthroline (PHEN) as ligands in methanol.[4] The crude obtained after the slow evaporation of the reaction mixture was recrystallized using methanol to yield the pure metal complex as dark red crystals (0.254 g, 68.85%). In the IR spectrum of the metal complex, C=O stretchings of PLN were observed at 1660 and 1621 cm^{-1} (C=O stretching at 1621 cm^{-1} has shifted from 1641 cm^{-1} due to complexation) and C-H stretchings of PHEN were observed at 848 and 785 cm^{-1} (shifted from 719 and 623 cm^{-1} due to coordination of PHEN nitrogen atoms with the metal).[5] UV absorption studies also indicated the presence of both PLN and PHEN ligands in the metal complex. Most importantly, EI-MS (molecular ion at m/z 430) confirmed that [Cu(PLN)(PHEN)]NO_3 has been synthesized (Figure 1).

In DNA binding studies using E-gel imager UV transillumintor, the fluorescence produced by ethidium bromide bound DNA gradually decreased in the presence of increasing concentrations of the metal complex and was not observed at and beyond 400 μM of the metal complex (Fig. 2). Ethidium bromide is a well-known DNA intercalating ligand. Our studies indicate that the synthesized metal complex is able to successfully intercalate to DNA replacing ethidium bromide. These findings may lead to the possible use of plumbagin as a "hybrid drug molecule" for the treatment of human cancers.

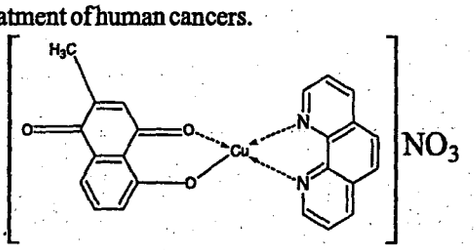

Figure 1. [Cu(PLN)(PHEN)]NO_3complex

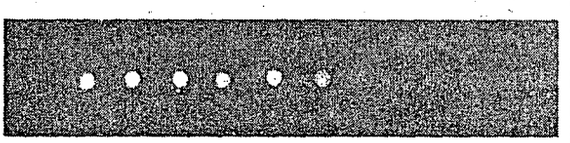

Figure 2. Effect on fluorescence intensity of ethidium bromide bound human DNA on varying concentrations of [Cu(PLN)(PHEN)]NO_3. (left to right: NG 2 – ethidium bromide only, NG 1 – DNA and ethidium bromide, ethidium bromide bound human DNA on varying concentrations of metal complex 25, 50, 100, 150, 200, 300, 400, 500, 600, 700 μM)

Acknowledgements: The mass spectral services provided by the Chemistry Research Laboratory of University of Oxford, United Kingdom is greatly appreciated.