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Mixed Ligand Based Samarium Complex as DNA Binding and Anticancer Agent

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Abstract: Metallodrugs have strong imprint on the pharmaceutical field, since historical era. Such a landmark in the history of "Elemental Medicine" was established due to the discovery of Cisplatin, a platinum containing metal drug. Samarium compounds have been used for radiation therapy. Therefore, the present study designed non-radioactive lanthanide based metal complexes which can interact with DNA and can be developed as chemotherapeutic agent. The mixed ligand approach for the synthesis of the lanthanide complex will provide the planarity to the structure enabling the binding to the biomolecules and cytotoxicity. In this study, samarium complex of 8-hydroxyquinoline was synthesized and substituted phenanthroline ligands (4,7-phenyl-1,10-phenathroline) using reflux condensation. The characterized complex was subjected to assess the DNA binding study using UV Visible Spectroscopic techniques. Molecular docking of the complex on the DNA helix was performed by AutodockVina.

Keywords: Cisplantin, Radioactive lanthanide, Metallodrugs, Ligand, Samarium, Molecular docking

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Introduction

Metallotherapeutics have strong imprint on the pharmaceutical field, since historical era (Orvig and Abrams, 1999; Rosenberg, 1999). Such a landmark in the history of "Elemental Medicine" was established due to the discovery of Cisplatin, a platinum containing metal drug (Jung and Lippard, 2007). The clinical use of cisplatin against malignancies is, however, severely limited by dose-limiting side-effects causing neurological, hepatic disorders and nephrotoxicity (Sardari and Hakimi, 2012). In addition to the high systemic toxicity, inherent or acquired resistance is the second problem often associated with platinum-based drugs, which further limits their clinical use (Naseri *et al*., 2011). This limited the use of chemotherapy treatment in the cancer patients. Thus, complexes containing different metal cores have been explored by the scientists in order to achieve the aim of less toxic and highly potent cytotoxic metallodrugs. Various cancers can be

treated using radiation therapy as well. Radiation causes the fragmentation of cellular DNA inhibiting the growth of the cancer cells and eventually leading to the cell death.

Samarium compounds have been used for radiation therapy. 153Sm-TPTTC (Naseri *et al*., 2012), 153Sm-TTHMP (Mao *et al*., 2009) and 153Sm-PL3 (Moghadam *et al*., 2019) with isotope Samarium-153 have been synthesized and their health benefit has been investigated in radiotherapy. It has three radioactive isotopes 147, 148 and 153. Samarium 150 isotope is non-radioactive and stable in the nature. Therefore, this study designed non-radioactive lanthanide based metal complexes which can interact with biomolecules to emerge as effective chemotherapeutic agent. Samarium (153Sm) lexidronam, Samarium-153-ethylene diamine tetramethylene phosphonate, abbreviated as Samarium- 153 EDTMP marketed under the trade name "Quadramet" is a samarium based drug. It is mainly used for the treatment of pain when cancer has spread to the bone. Samarium 153 isotope is a radioactive lanthanide. It has a half-life of 46.3 h and it decays by emitting beta particles (electrons), which kill the nearby cells. It is commonly used in lung cancer, prostate cancer, breast cancer, and osteosarcoma. Bioinorganic chemists in the early 2000s, initiated the design of lanthanide metal complexes based on heterocyclic ligands. The synthesized and designed complexes were also assessed for various biological activities. In 2007, $Sm(CCA)_2NO_3.H_2O$, (Kostova *et al*., 2007) a samarium based coumarin carboxylic acid complex was synthesized and its anticancer potential was assessed against the Chronic myeloid leukemia-derived K-562 cell lines. It exhibited significantly weak activity with IC_{50} of 108.39 uM. The reports of borderline anticancer potential of samarium complex attracted the attention of the medicinal chemists and thus chemists started the synthesis of samarium metal complex using an anticancer drug as a ligand instead of heterocyclic compounds. It was reported that plumbagin based samarium (III) complexes exhibited 52% inhibitory rate against Human papillomavirus-related endocervical adenocarcinoma (Chen *et al*., 2011). In 2019, polycyclic samarium complex based on phenathroline backbone was reported for (Moghadam *et al*., 2019) chemotherapeutic potential against Human T-cell acute Lymphoblastic leukemia.

In this study, samarium complex of 8-hydroxyquinoline was synthesized and substituted phenanthroline ligands (4,7-phenyl-1,10-phenathroline) using reflux condensation. The characterized complex was subjected to assess the DNA binding study using UV Visible Spectroscopic techniques. Molecular docking of the complex on the DNA helix was performed by AutodockVina.

Materials and Methods

8-Hydroxyquinoline, Bathophenanthroline (4,7-phenyl-1,10-phenathroline) and Samarium chloride hydrate, Calf thymuses DNA (CT-DNA) and TrisHCl Buffer were purchased locally. UV absorption titration with calf thymus (CT) DNA was carried out to ascertain the binding mode of compound. *In silico* studies such as molecular docking has been used to simulate the behaviour of the interaction of the different molecules.

Results and Discussion

(A) *Synthesis and Characterization of the complex*

Hot ethanolic solutions (20 ml) of 8-Hydroxyquinoline (1 mol) and Bathophenanthroline (1 mol) and were added to the ethanolic solution of Samarium chloride hydrate (1 mol) and refluxed for 4h at 60-70°C. The obtained yellow reaction mixture was evaporated and the pale yellow colored crystalline product obtained was washed and dried.

Synthesized complex was subjected to the UV visible spectroscopy. The complex exhibited the λ_{max} of 255 nm with ligand metal charge transfer peak at 350 nm (Fig. 1). FTIR spectrum of the complex revealed the weak OH band at 3305 cm^{-1} (Fig. 2). It supported the presence of coordinated

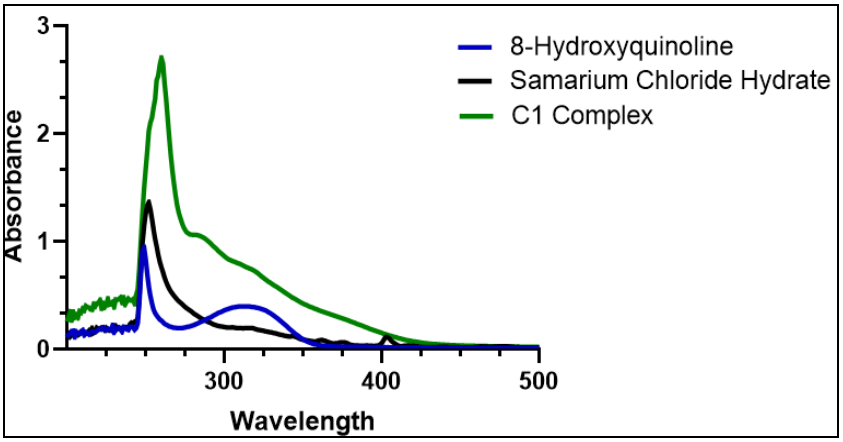

Fig. 1: UV visible spectrum of Complex in the presence of 8-hydroxyquinoline and samarium chloride hydrate.

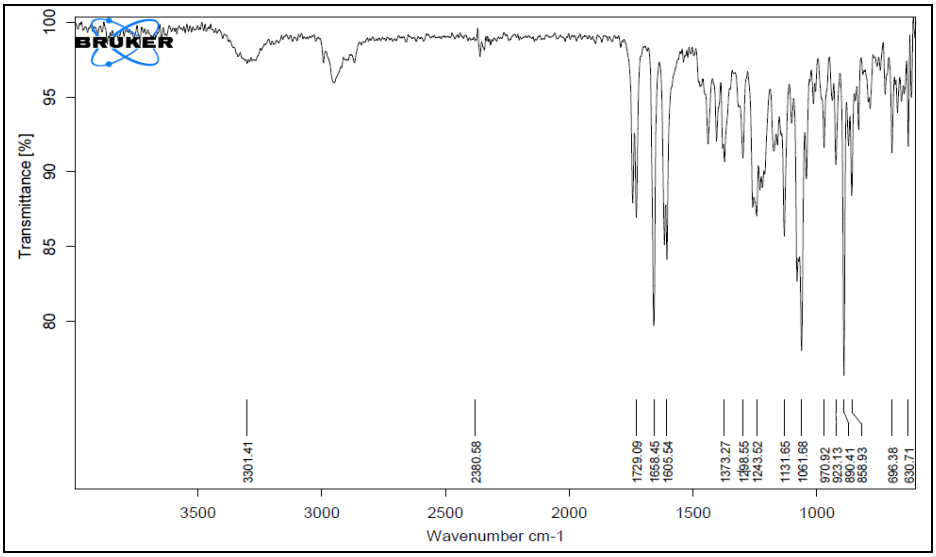

Fig. 2: FTIR spectrum of the Complex.

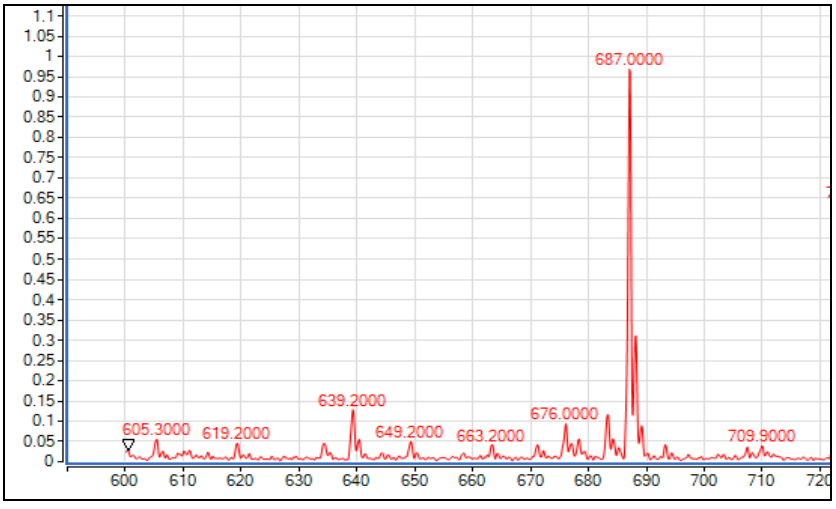

Fig. 3: ESI MS spectrum of the Complex.

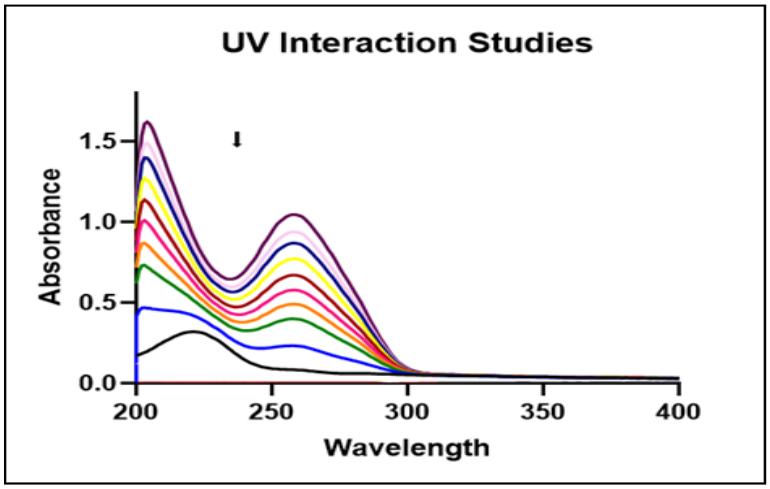

Fig. 4: UV DNA interaction studies of the complex.

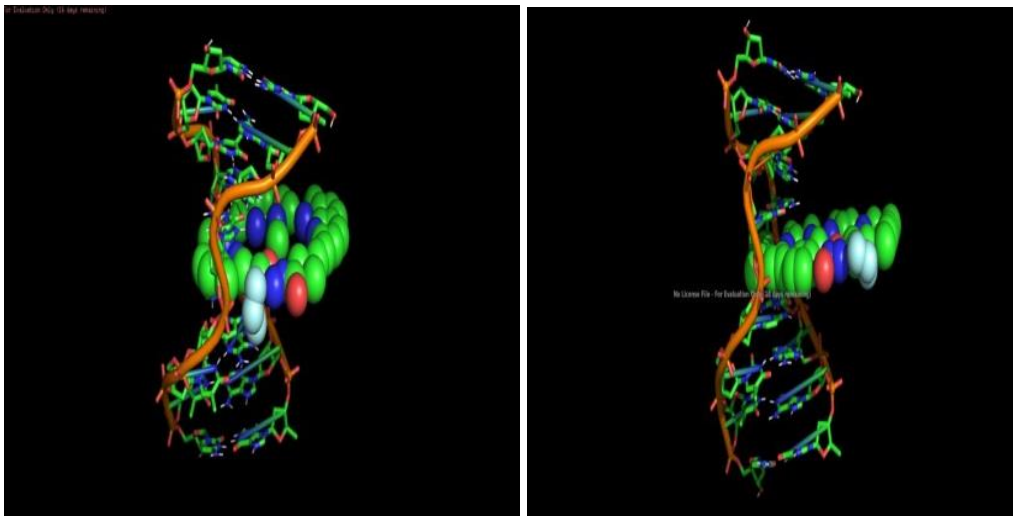

Fig. 5: Molecular Docking studies of the complex.

OH moiety to samarium. ESI Mass spectral studies showed the molecular ion peak at 687, molecular weight (Fig. 3).

(B) *DNA Interaction Studies of complex*

Interaction of the complex with calf thymus DNA (CT-DNA) was investigated by monitoring the ligand to metal charge transfer transition of the complex at 280 nm in the presence of increasing amount of CT-DNA. Hypochromism observed for the complex in the presence of DNA (Fig. 4), is characteristic of intercalative mode of DNA binding. The isosbestic point observed in UV titration curves is indicative of equilibrium between the free and bound forms. The planar hydrazone moiety of the complex may have inserted between the DNA base pairs forming a π-π stacking interaction and thus leads to the changes in the absorbance spectra after the addition of DNA.

(C) *Molecular Docking Studies*

Molecular docking was carried out using AutodockVina and MGL Tools 1.5.2. The results were viewed in software Pymol Viewer. The grid points in the dimension of 56 × 54 × 58 with 1.0Å spacing were calculated around the docking area for all the ligand atom types using default optimization parameters.The generated best conformer of the complex from the software was docked using DNA (PDB ID: 2D55) and was found to get intercalated in the base pairs (Fig. 5).

Conclusion

A novel samarium complex synthesized on the backbone of nitrogen heterocycle and substituted phenanthroline. It was characterized using spectral techniques such as UV, FTIR and Mass spectral studies. UV DNA interaction studies showed a partial DNA intercalative mode of the complex with Calf thymus DNA. Molecular docking studies with DNA suggested and correlated the intercalative ability of the complex, as the planarity of the bathophenthroline may have imparted the ability to get inserted as an intercalator in the base pairs of DNA to the synthesized complex.

Ethical Statement

No animal or microbes have been used or sacrificed for this study, hence Ethical Approval not required.

Author Contributions

Author has read and agreed to the published version of the manuscript.

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Conflict of Interest

The author declares no conflicts of interest.

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