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REVIEW ARTICLE

Therapeutic Values of Terpyridine Cu (II) Complexes

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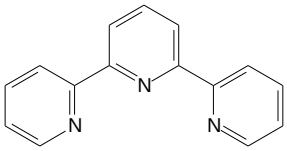
ABSTRACT:
The terpyridine complexes by transition metals have potential applications in the field of therapeutics, imaging and theranostics. Ni(II), Co(II), Fe(II), Cu(II), V(IV) etc., terpyridine complexes have been used as antibacterial, antifungal, antidiabetic, antiarthritic and anticancerous agents. Extensive studies of Pt(II) terpyridine complexes reported in medicinal field lack practical usage due to various side effects. However, it showed a gateway to prepare and study other transition metals which possess virtuous biological properties. Here, we report various works involving Cu(II) terpyridine complexes which are found to be potential therapeutic agents.

KEYWORDS: Terpyridine**,** therapeutic agents, Copper (II) complex, anticancer activity.

INTRODUCTION:
Terpyridine is a popular ligand in the fast growing area of coordination chemistry which has remarkable tenders in supramolecular photochemistry. The synthesis of 2,2':6',2''-terpyridine ligand fascinated different research groups because of its unique coordinating capability which has a three donor nitrogen atoms bonded to the metal ion.[1] The ligand can coordinate with metal ions as tridentate, bidentate and monodentate **1**.[2] Additionally, terpyridine and its structural correspondents as functional prototypes become popular in the supramolecular, coordination as well as materials science fields.[3] It showed diverse photophysical, catalytic, electrochemical, and magnetic properties of terpyridine complexes. These complexes partakes future claims like light-to-electricity transformation,[3] light-emitting electrochemical cells (LECs),[4] luminescent sensors[3] or non-linear optical gadgets.[6] The application of such complexes specially in the field of pharmacy and biomedical are rapidly growing as therapeutic agents.[7] The review focuses on the development of therapeutic agents (anticancer, antitubercular, antiproliferative, etc.) involving Cu(II) complexes of terpyridine and functionalized terpyridine ligands.



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Transition Metal Complexes of Terpyridine:
The transistion metal complexes speed up the proficiency of therapeutic and pharmacological properties.[8] The nature of the ligands and its metal ions affect the medicinal productivity of transition metal complexes.[9] Many transition metal ions forms complexes with terpyridine ligands. The exceptional photochemical, electrochemical, and photophysical, properties of such complexes consent assembly of supramolecular architectures.[10] The first-row transition metals such as Cr(II), Mn(II), Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) produces diverse bis complexes with terpyridine.[11-14] The stability of the metal complexes also is improved well by the chelating terpyridines. Furthermore, 4′-functionalized 2,2′:6′,2″-terpyridines complexes of transition metals fascinated researchers because of motivating electronic and magnetic properties,[15] photophysical, and structural characteristics whish are advantageous in molecular electronics,[16] catalysis,[17] molecular magnetism,[18] and anti-tumor therapy.[19] To modify the electronic properties of the ligand and its metal complexes 4′-substituted terpyridines are developed. The ability of the ligand to

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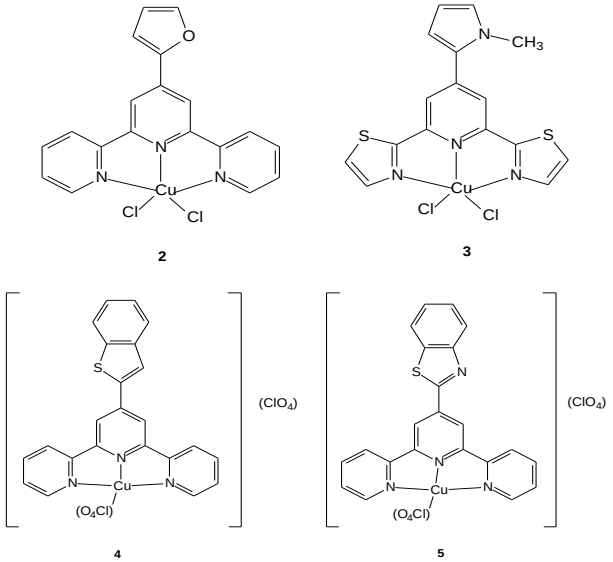
bind biomolecules such as proteins or DNA presents enormous possibility to coordinate with drugs. Also, the strong intercalative interaction of DNA grouped complexes are significantly performed by the planar nature of ligand.[20]

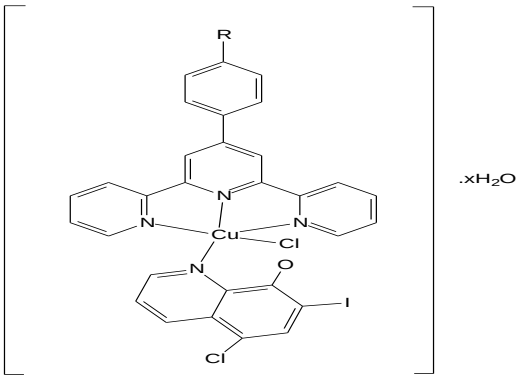
Applications as a Therapeutic Agent:

Among enormous number of metal drugs, platinum is widely studied as therapeutic agent because of their kinetic, structural and thermodynamic properties.[21,22-25] Cisplatin, a platinum based drug was found to be an appealing drug for the treatment of various types such as head and neck, lung, testicular, colorectal and ovarian cancers.[26,27] The encounter of cisplatin led to the incredible progress of research for cancer therapy using metal complexes.[28] Though cisplatin has many disanvantages, other platinum drugs (carboplatin, oxaliplatin, nedaplatin, lobaplatin) were approvcd for different types of cancer therapy. However, due to their severe side effects and drug resistance capacity, these platinum-based drugs cannot be much explored.[29] Consequently, this opened a gateway for the exploration of many non-platinum metal drugs and their pharmacological studies. With less side effect, more binding affinity, and target selectivity drug-protein interactions, many proposals are made in the synthesis of promising drugs. The evolution of platinum based cancer drugs have proven that modification of ligand environment is crucial in determining the drug efficacy, cytotoxicity, pharmacokinetics of metal complex based therapeutic drugs.[28] Terpyridine ligands offer a plethora of possibility of functionalization in the ligand environment.

Copper Complexes of Terpyridine:



Copper is minimally available in living organisms[30] and its complexes are active in antibacterial, antifungal, antidiabetic, antiarthritic and enzymatic activity. As copper complexes have less toxic effect to the normal cells than cancer cells, it draws much attention in the anticancer formulation. The bioessential nature of Cu(II) complexes of terpyridine initiates reactive oxygen species which are used for the oxidative breaking of DNA strands through photolytic,[31] hydrolytic,[32] as well as oxidative pathway[33] and thus, inhibiting the multiplication of cancer cells.[34] Being active under hypoxic condition, Cu(II) has selective penetration to tumor cell sheath.[35] Cu(II) complex of functionalized 2,2′:6′,2″-terpyridines **2** and 2,6-di(thiazol-2-yl) pyridines copper (II) complex **3** shows antiproliferative effect in A2780 ovarian carcinoma cells.[36] Since fused ring system (e.g. Raloxifene and benzothiazole derivatives) are much impend in using as anticancer angents, terpyridine with such functional group develop antiproliferative activity.[37,38] Copper (II) complexes of terpyridine fused ring benzothiophene **4** and benzothiazole **5** head groups show potential toxicity towards HepG2 (liver hepatocellular cells) and triple negative CAL-51 cell lines (breast carcinoma). These complexes exhibited toxicity to the cancer cell lines by enhancing the intercellular reactive oxygen species (ROS) level and cell cycle detention. Thus, induce cell death via apoptosis can serve as latent anticancer agents for advanced stage of cancer treatments.[32] Moreover, antimycobacterial screening of clioquinol against mycobacterium tuberculosis showed clear enhancement in the antitubercular activity on complexation with copper. Complexes of copper with clioquinol and substituted terpyridine **6** have been synthesized which revealed enhanced biological activity.[39] In vitro cytotoxicity of the bis(4′-(4-tolyl)-2,2′:6′,2″-terpyridine) copper (II) complex $[Cu(ttpy)_2]Cl_2$ **7** displays possible action against animal tumor Ehrlich ascites carcinoma (EAC) cell line with respect to the commercially used cisplatin. The induced apoptotic activity of the complex against EAC cells is confirmed by Hoechst 33258 (a dye utilized to identify the transitions of the cell's nuclear morphology), acridine orange/ ethidium bromide (AO/EB) and PI (Propidium iodide flow cytometry) staining methods and cell cycle analyses.[40] Hence, Cu(II) complexes with terpyridine showed amazing biological activities, these complexes boomed into therapeutic field for the treatment of threatening diseases.



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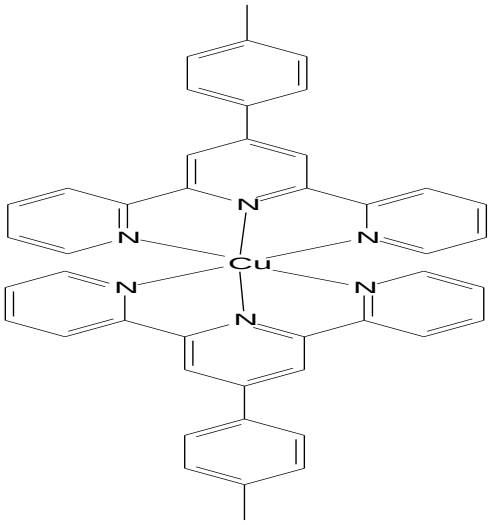

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CONCLUSION:

Terpyridine complexes of Ru(II), Os(II) and Ir(III) complexes outnumber any other metal terpyridine complexes because of their wide ranging applications in imaging, DNA intercalation and chemotherapy. Rare reports of Cu(II) complexes of terpyridine as therapeutic agents are assembled in this review. Cu(II) terpyridine complexes are reported to have excellent biological (antitubercular, anticancer, etc.) activities.

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