

Latest developments in Metal Complexes for the treatment Cancer - A Review

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Abstract:

Historically, metal-based complexes were extensively utilized in the treatment of various diseases; however, the absence of a clear differentiation between therapeutic and toxic doses posed significant challenges. The discovery of cisplatin by Barnett Rosenberg in 1960 represented a significant milestone in the development of metal-based compounds for the treatment of cancer. This discovery laid the groundwork for the contemporary era of metal-based anticancer medications in cancer therapy. Nevertheless, the slow therapeutic progress of other metal-based compounds has hindered research advancements in this domain. Recently, there has been a resurgence of interest in utilizing structural information to enhance and develop alternative metal-based compounds, which operate through mechanisms distinct from established drugs like cisplatin. In this context, numerous metal-based compounds have been synthesized by modifying existing chemical structures through ligand substitution or by creating entirely new compounds with improved safety and cytotoxic profiles. However, due to the growing focus on the clinical significance of metal-based complexes, a limited number of these drugs are currently undergoing clinical trials, while many others await ethical approval to participate in such trials. This review aims to provide a comprehensive overview of previous analyses regarding the cytotoxic effects of metal-based complexes, with a particular emphasis on newly designed metal-based complexes and their cytotoxic impact on cancer cell lines, as well as innovative approaches to metal-based drug design and molecular targets in cancer therapy.

Keywords: metalcomplexes, cancer, metallodrugs

1. INTRODUCTION:

Numerous metallic composites play vital part in living system. Transition metals have important place in pharmaceutical assiduity. Recent exploration has shown significant progress in operation of transition essence complexes as medicines to treat several mortal conditions like melanoma, tubercles, sarcoma and leukemia, each with subtypes to different tissues and organs. Metal complexes have proved as good anticancer agents due to their distinctive properties and implicit to target cancer cells in numerous ways. These complexes can destroy cell processes like DNA replication, protein function, and cell signalling pathways, eventually leading to cancer cell death. In 1960, the inorganic complex cisplatin was discovered, and over 50 times latterly, it remains one of the most successful anticancer medicines. Recent advancements in cell biology have introduced new targets for anticancer agents that serve by forming DNA adducts with cancer cells, leading to the inhibition of DNA replication [1]. Still, this also impacts normal cells, similar as hair follicles and the

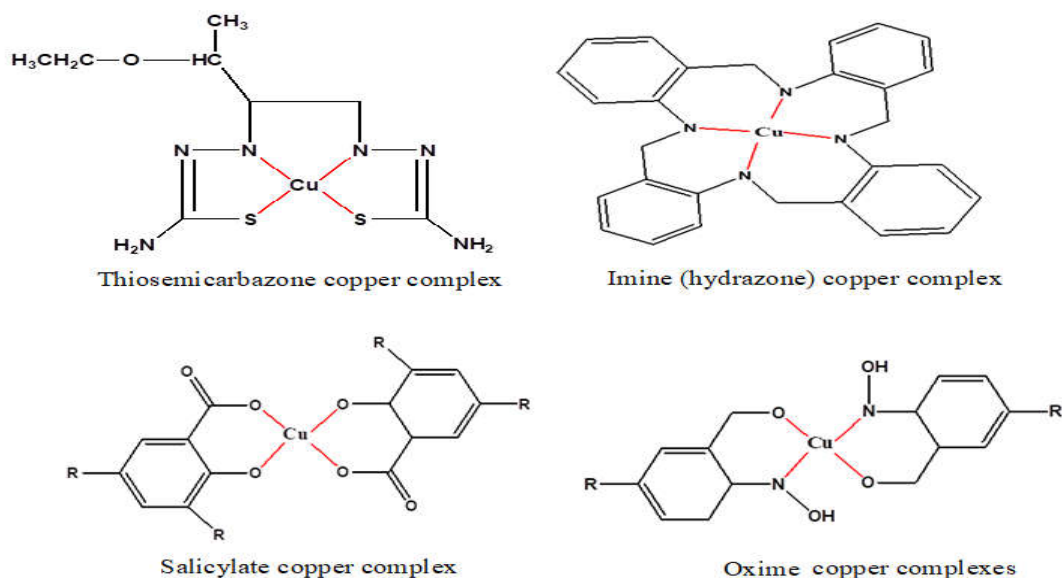
mucosal filling of the gastrointestinal tract. Various techniques have been employed to mitigate these effects by minimizing side effects, preventing drug resistance, and enhancing efficacy [2]. For instance, medicines have been conjugated with porphyrin rings to ameliorate the particularity of complexes for tumor tissues. In addition to platinum, other transition metals, including titanium and gold complexes, have demonstrated significant antitumor parcels. Currently, metal complexes in the form of nanoshells are being employed in the treatment of many types of cancer [3]. This review discusses the role of selected metals in biological processes for their complexes in the design and development of metallodrugs for the treatment of cancer.

2. Copper complexes as anticancer agents.

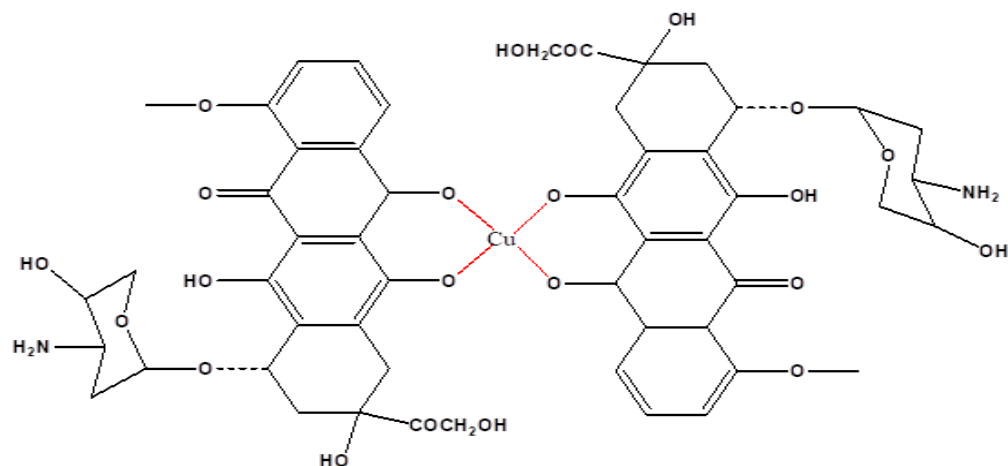
Copper (II) is a biologically essential element, and its coordination capabilities along with favorable redox potentials appear to regulate its involvement in biological reactions. This metal serves as an active centre in over a dozen metalloproteins [4].

The coordination complexes of copper have been extensively studied in relation to antitumor chemotherapy, with many demonstrating efficacy as anticancer agents in animal models. These compounds encompass complexes of thiosemicarbazones [5], oximes, imines, hydrazones [6], salicylates [7], aminocarboxylates [8], and various other nitrogen donor ligands [9] (Fig no-1).

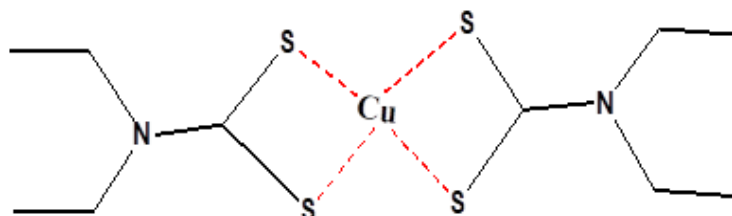
Fig no 1 represent some of the most active antitumor copper complexes.



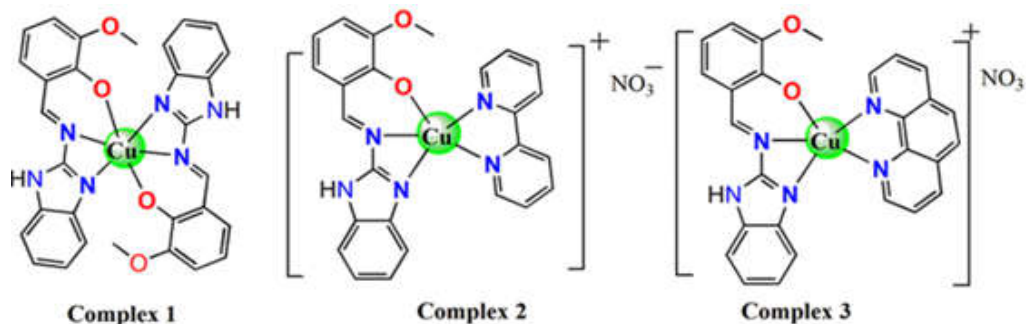
The metals in inorganic drugs can also coordinate to the endogenous ligands available at the active sites of the enzymes blocking interactions of the natural substrates. For example, Copper (II) complex of epidoxorubicin was found to be inhibit PKC by the direct interaction between Cu(II) and PKC blocking the contact of natural substrates [10].

Fig no 1.1 Copper (II) complex of epidoxorubicin

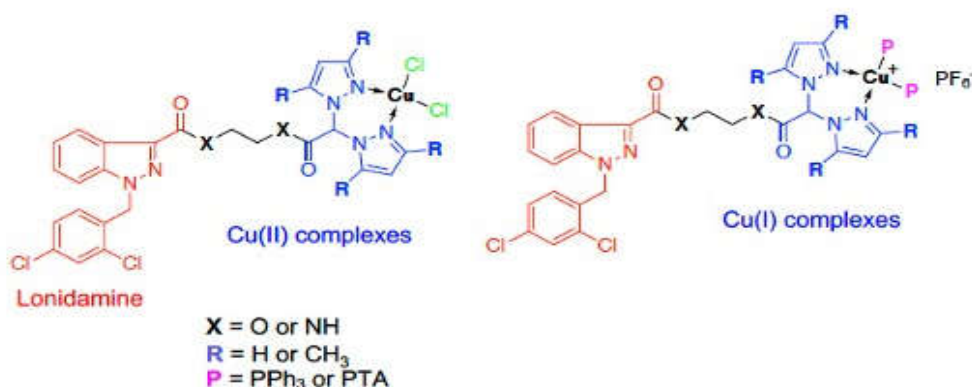
Drug repurposing uses approved drugs as candidate anticancer therapeutics, for example disulfiram (DSF), was studied for its antitumor efficacy in a copper-dependent manner. The combination of DSF and copper could achieve a tumor cell growth inhibition effect comparable to those of 5-fluorouracil and taxol on head and neck cancer cells[11].

**DSF and copper complex**

In another report three copper complexes (1–3) with benzimidazole-derived scaffolds have been designed, synthesized *In-vitro* and *in-silico* molecular modeling studies, was carried out on human serum albumin (HSA) which exhibited significant binding affinities of the complexes with HAS[12].

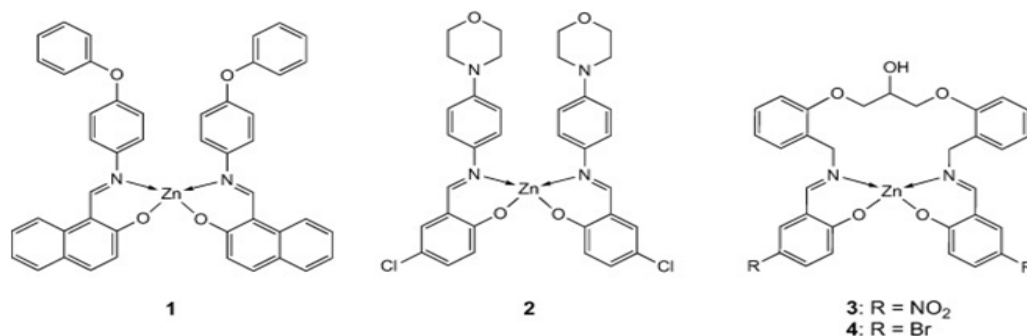


The antineoplastic drug lonidamine was conjugated with bis(pyrazolyl)acetates to obtain new Cu(I) and Cu(II) complexes, whose electronic and molecular structures were investigated by SR-XPS and XAS. All complexes showed significant anticancer activity in human tumour cell lines and were more effective than cisplatin against 3D spheroids of PSN-1 cancer cells. Moreover, although to a different extent, the most interesting complexes proved to accumulate into cancer cells [13].

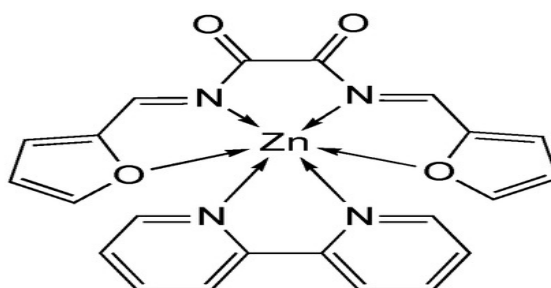


3. Zinc complexes as anticancer agents:

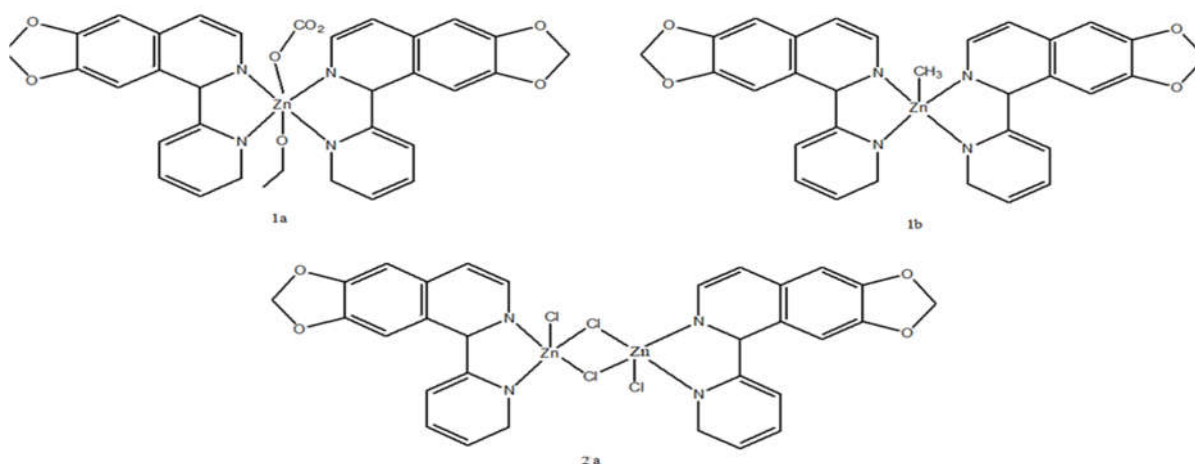
Zinc, present in all forms of life, it is an essential element for humans. It is one of the most abundant metals in our body. Because of its importance, any malfunctions of its homeostasis can lead to different disease states, also related to the development of cancer. On the other hand, several Zn complexes have been recognized for their biological activities principally for preventive effects on infectious diseases and for low toxicity. Among different applications in medicinal chemistry, zinc-based complexes have shown to be appealing as anticancer drugs with low toxicity [14].



Zinc can have beneficial therapeutic and preventive effects on infectious diseases and, compared to other metal-based drugs, Zn(II) complexes generally exert lower toxicity and offer few side effects. Zinc derivatives have been proposed as antitumor agents[15].

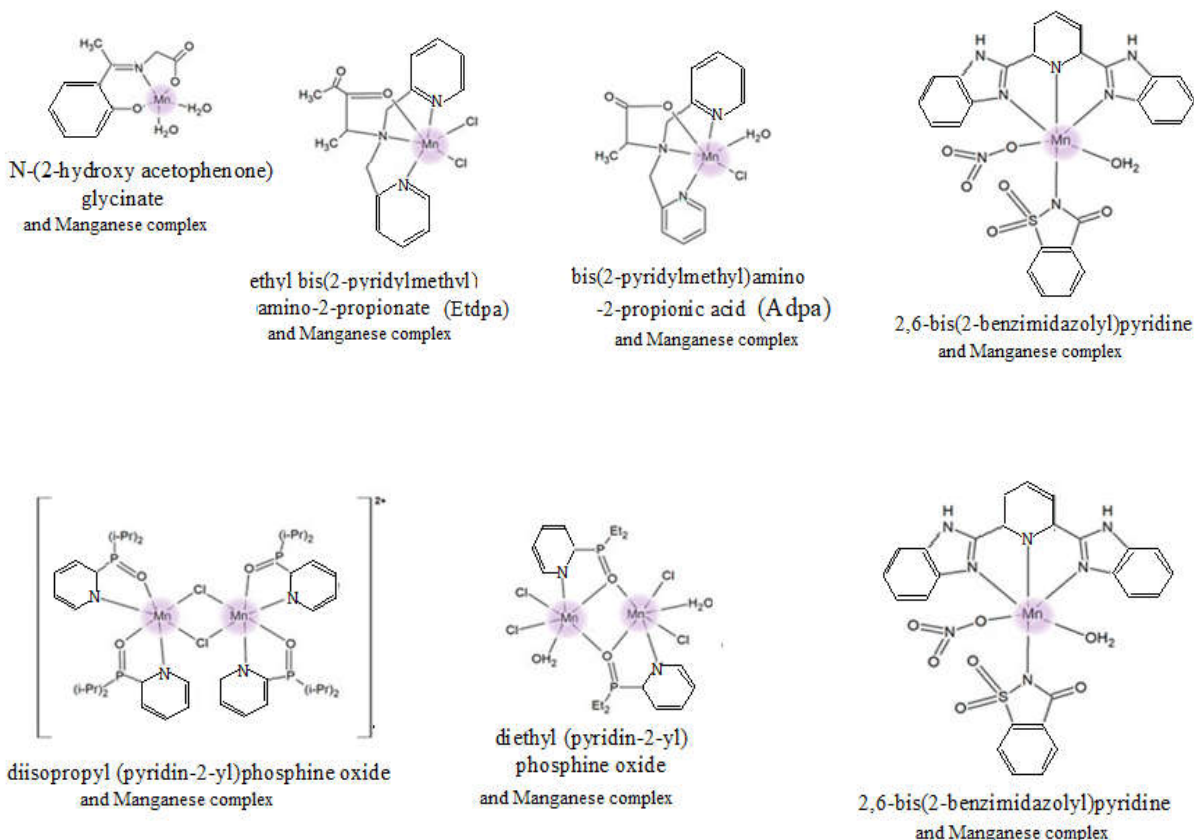


Studies on Zn derivatives showed a remarkable anticancer activity and selectivity to tumor cells, in particular binuclear zinc complexes which is more active than mononuclear complexes 1a and 1b, complex 2b showed a noticeable cellular uptake and DNA accumulation, and DNA interaction via an intercalating mode. In vitro test with MGC-803 cell line [16].



4. Manganese complexes as anticancer agents

Manganese (Mn), found in all tissues and fluids is one of the biocompatible core elements of metal enzymes playing many physiological roles *in vivo*. The anticancer properties of manganese inorganic compounds are underexplored. So far only several anticancer manganese (II/III) complexes containing Schiff base, porphyrin, flavonoids, and polypyridyl ligands have been characterized [17-19].



5. Gallium complexes as anticancer agents

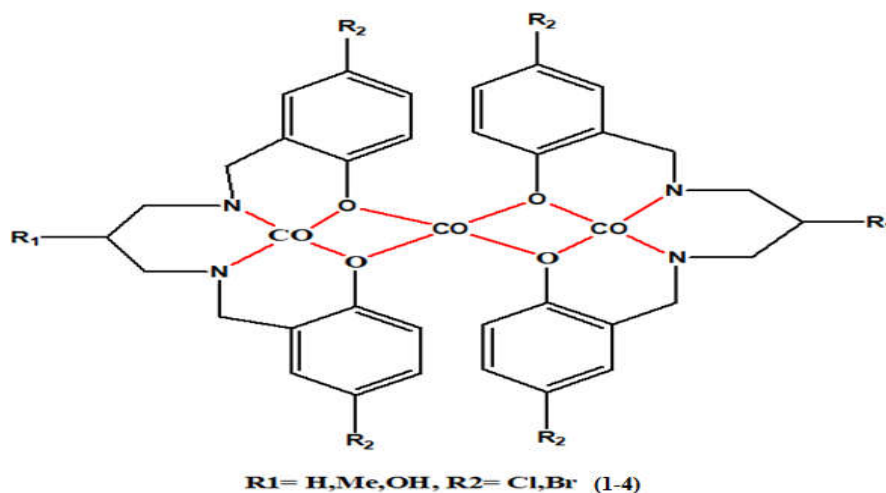
Gallium complexes are being investigated as potential anticancer agents due to their ability to disrupt iron-dependent processes in cancer cells, leading to cell death. Gallium, in its trivalent form (Ga(III)), can act as a mimic of iron (Fe(III)), and is taken up by cells through the same pathways as iron, including transferrin receptors. This can lead to a disruption of iron homeostasis within the cell, impacting essential cellular processes like DNA replication and mitochondrial function [20]

6. Cobalt (II) complexes as anticancer agents

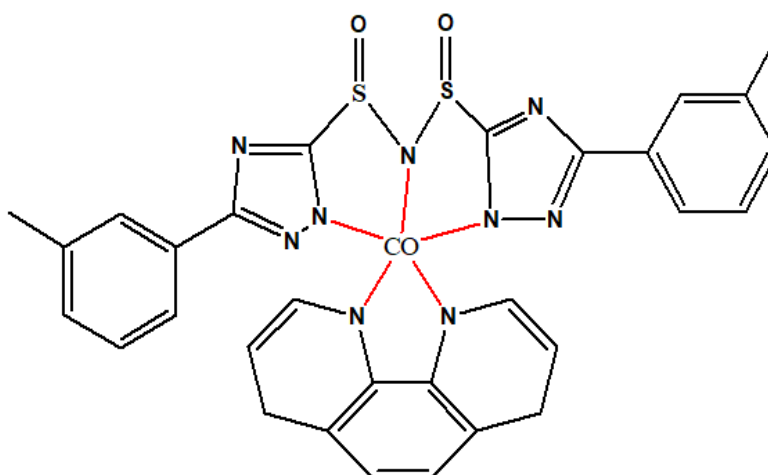
Cobalt-based compounds are emerging as a non-platinum-based anti-cancer effective therapeutic agent. However, there is a limited study regarding the therapeutic efficacy of Cobalt-based drugs against Non-Hodgkin's Lymphoma (NHLs) such as T cell lymphoma.

Panel Peishan Zhao and co-workers reported here four cobalt(II) complexes $[\text{Co}_3(\text{L}1)_2(\text{HCOO})_2]$ (1), $[\text{Co}_3(\text{L}2)_2(\text{HCOO})_2(\text{CH}_3\text{OH})_2] \cdot 2\text{CH}_3\text{OH}$ (2), $[\text{Co}_3(\text{HL}3)_2(\text{OAc})_2(\text{DMF})_2]$ (3) and $[\text{Co}_3(\text{HL}4)_2(\text{HCOO})_2(\text{DMF})_2] \cdot 2\text{H}_2\text{O}$ (4) bearing the bis-Schiff base ligand of bis(5-bromosalicylidene)-1,3-propanediamine (H2L1), bis(5-bromosalicylidene)-2-methyl-1,3-propanediamine (H2L2), bis(5-chlorosalicylidene)-2-hydroxyl-1,3-propanediamine (H3L3) and bis(5-bromosalicylidene)-2-hydroxyl-1,3-

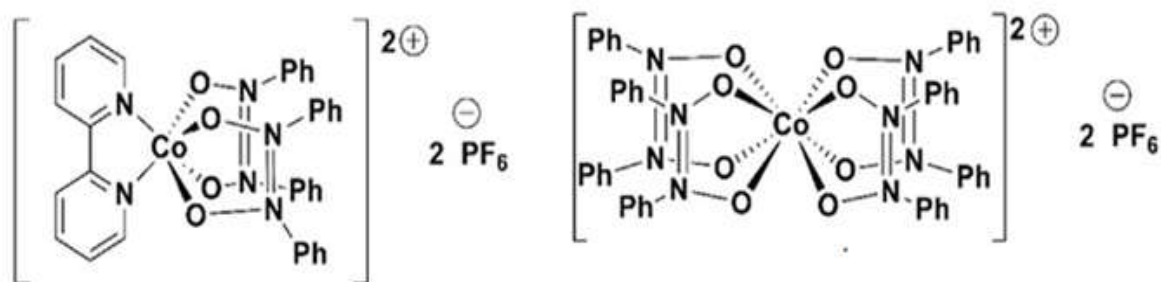
propanediamine (H3L4), respectively. The anti-tumor activities of the four titled complexes were screened on a series of tumor cell lines [21].



Praveen Kumar Verma et al., investigated the anti-tumor role of cobalt(III) complex $[Co(ptsm)NH_3(o-phen)] \cdot CH_3OH$ on Dalton's Lymphoma (DL) cells [22].

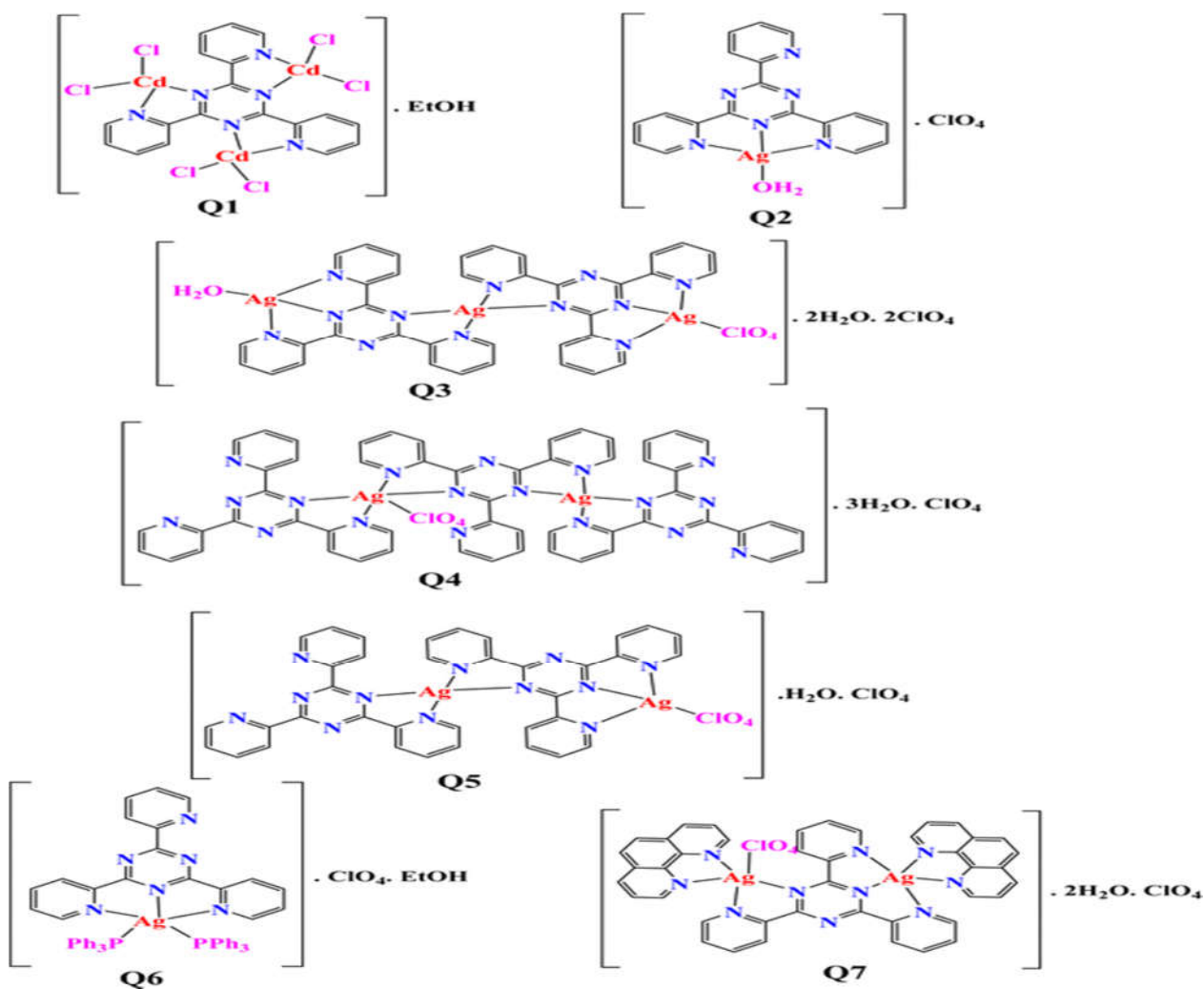


Norah J. Alghamdi reported The cobalt(II) complex salts $[Co(bpy)(az)_2](PF_6)_2$ and $[Co(az)_4](PF_6)_2$, each bearing the unusual *cis-N,N'*-diphenylazodioxide ligand, were both screened as possible anticancer agents against SK-HEP-1 liver cancer cells [23].



7. Silver and Cadmium complexes as anticancer agents

Stacey J and co-workers synthesized seven new metal coordination complexes (Q1–Q7) with potential biomedical applications. Novel mononuclear, polynuclear and mixed-ligand coordination compounds of the elements, cadmium (II) and silver(I) derived from a pyridine containing ligand (2,4,6-tris-(2-pyridyl)-1,3,5-triazine (*TPT*)) have been synthesized. The complexes were evaluated for *in vitro* efficacy against the MCF-7 human breast cancer cell line was assessed to determine the anticancer activities [24].



CONCLUSION:

Cancer treatment has benefited greatly from the use of metallodrugs, especially those based on metals. However, in order to overcome the shortcomings of existing treatments, there is an increasing need for new and enhanced metallodrugs. The goal of ongoing research is to create

metallo drugs that are more potent, less toxic, and more targeted. Additionally, combination therapies and methods to combat drug resistance are being investigated. The development of metallo drugs has enormous potential for the treatment of cancer in the future.

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