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Copper Complexes with Polypyridyl Tridentate Ligands and their Biological Significance: A Review

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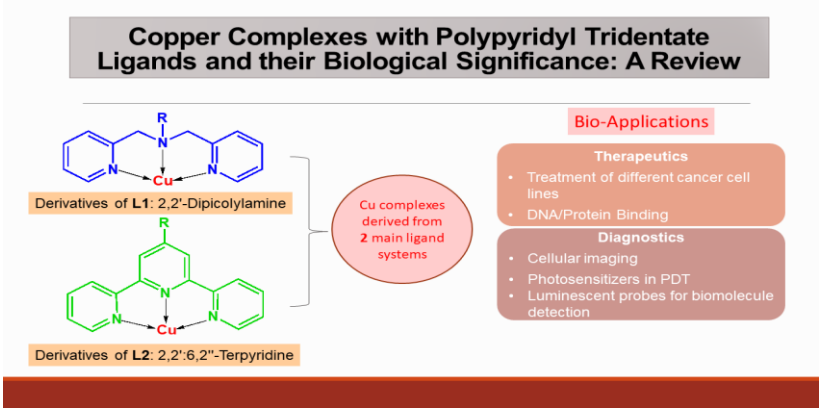
Copper based metal-organic complexes have been evaluated for their suitability as potential therapeutic and diagnostic agents as an attempt to overcome the limitations of the initial platinum-based drugs, including low selectivity, acquired resistance to the introduced drugs and the subsequent side effects. Copper containing complexes, particularly with tridentate NNN coordinating ligands having polypyridyl groups, such as 2,2'-Dipicolylamine and 2,2':6,2"-Terpyridine, are promising alternatives as they entail versatility in their structures and possess chemical and electronic properties which facilitate their targeted cytotoxic and diagnostic activities. Delocalization of excited electrons within the planar, conjugated structures, along with the display of metal to ligand charge transfer transitions (MLCT) leading to intense fluorescent signals, have elevated the suitability of these ligands for the synthesis of biologically beneficial complexes. This itinerary contributes to the popular global trend in the development of more effective chemotherapeutic and theranostic agents.

Graphical abstract



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1. Introduction

Organo-transition metal complexes or organometallic complexes identify as metal complexes which possess at least one metal carbon bond in their molecular structures [1]. In addition, transition metal hydrides and metal-phosphine containing complexes are also discussed under the broad theme of organometallic chemistry, although they do not stringently adhere to the classification criteria for organometallics [2, 3]. Similarly, a related but separate term, "metal-organic compounds" is introduced to distinctly classify metal comprising coordination compounds in which the metal centre is linked to other coordinating atoms instead of carbon [4]. Their significant evolution over the past two decades has established them as favourable candidates for detection of various pathologies and effective drug design. Metal-organic complexes entail a wide range of physico-chemical properties including structural variety, redox properties, ligand exchange ability [5] and also catalytic properties which have enabled their comprehensive use in numerous medicinal purposes,

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giving such type of complexes an upper hand over classical metal coordination complexes and purely organic compounds [6].

The ability to modify known ligand systems with bioactive pharmacophores and the ability to readily exchange such resulting ligands, would facilitate different binding modes [3] for the complexes and also increase their pharmacological applicability remarkably [7]. If the metal centre is inert, it would more likely entail a structural role, [8] whereas if the metal centre involves in the transfer of electrons, its redox activity can be fruitfully exploited in medicinal applications. One such example is the case of the redox activity of iron in the antimalarial drug, Ferroquine [9], which is a modification of chloroquine with a ferrocene moiety. The introduction of iron with its redox properties was found to drastically reduce the activity of the malarial agent, *Plasmodium falciparum*, which has exhibited resistance to chloroquine [10, 11].

Modern day research has focused greatly on the importance of metal-organic complexes in biological systems and their usage as therapeutic and diagnostic agents. A variety of metal-organic complexes have been explored for their possible anticancer activities, including many Pt(II), Au(I), Au(III), Ru(III) [12, 13] and Cu(II) [14] metal containing drugs. The therapeutic effects of such metal complexes can extend to antibacterial, antiviral [15, 16], and anti-inflammatory [17, 14] properties as well. In addition, metal-organic complexes can adopt a diagnostic role where they are used to detect possible anomalies within the body, as indications of various prevailing diseases [18]. Furthermore, metal complex based radiopharmaceuticals have been often used in various biomedical imaging procedures such as positron emission tomography (PET), magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT) where they function as contrast agents, also referred to as radiotracers enabling the visualization and determination of the interactions between the metal complex and a certain biological target [19, 20]. For example, the incorporation of ^{64}Cu nuclide in to the formation of Cu(II) complexes containing thiosemicarbazone ligands, has rendered to be successful in PET imaging, with applications as perfusion traces and in hypoxia imaging [21].

When designing biologically significant metal-organic drug molecules, certain criteria must be considered as there are numerous possible ways of combining various ligands and metals. The drug molecule should essentially be able to penetrate the cell membrane, bind with a sub cellular organelle or chemical species and bring about its respective activity [22]. For the above to occur successfully, the drug molecule should possess the ability to properly recognize and bind selectively with the binding site. Lipophilicity of the ligand system is another important aspect to be considered when choosing a suitable metal-ligand combination, as the cell membrane, consisting of a lipid bilayer, is the pathway through which the drug molecule will enter to the cell through passive transport. Once inside the cell, the drug molecule will be exposed to the cellular interior which is mostly aqueous. Hence, in order to facilitate the interactions between the metal complex and certain sub-cellular entities such as proteins and DNA, and also to stabilize the drug molecule within the cell, the metal complex should possess a certain degree of hydrophilicity as well [23].

The promising use of copper in drug development has garnered attention due to certain antimicrobial [24], antimalarial [25], anti-tuberculosis [26], antiviral [16], anti-inflammatory [27] and antitumor properties [24, 27] of copper. The ability of copper to exist in different oxidation states, enabling the transfer of electrons between species, and the flexibility of copper coordination enabling variable geometries have also contributed to the successful use of copper in drug development [28]. Therefore, the main objective of this article is to critically analyse and review copper based complexes of dipicolylamine and terpyridine (which are both polypyridyl tridentate ligand systems), and understand their structural and biological properties

2. Polypyridyl Ligands

Polypyridyl derivatives are multidentate ligands that provide certain characteristic properties to the metal complexes they form. Some such complexes are able to absorb light strongly by means of metal-to-ligand charge transfer (MLCT) [29]. The use of such ligands to form metal polypyridyl complexes in medicinal applications has been efficacious owing to various properties, including chemical, redox and configuration stability which helps them to develop specific toxicity over a range of biological targets. Hence, polypyridyl metal complexes encompass a considerable diversity of applications including the use as DNA binding agents, as antibacterial agents, as enzyme inhibitors and as cytotoxic agents [30].

The properties of the metal complexes based on this type of ligands can be altered by incorporating various substituents, which allows for the optimization of bioactivity. Symmetric ligands often lead to more stable complexes, which is crucial for maintaining the integrity of the complex in biological environments [31]. The shape and electronic properties of the metal complex, which are influenced by the symmetry of polypyridyl ligand systems, determine the specificity and potency of enzyme inhibition, elevating their biological potential [32].

2.1. 2,2'-Dipicolylamine (Dpa)

Dipicolylamine is a symmetric secondary amine with two picolyl substituents. (**Figure 1**). The cellular uptake of dipicolylamine is aided by its high degree of lipophilicity allowing it to easily cross through the cell membrane [33]. Conjugated systems (R groups) tethered onto the dpa moiety will facilitate the delocalization of excited electrons through the ligand during metal to ligand charge transitions [34, 35]. In other words, higher intensities of absorption and emission can be expected, causing intense fluorescent signals to appear. Dipicolylamine can be used to generate various derivative compounds which can contribute to the diversity of this ligand system. One such example is the generation of tertiary sulphonamides, in an attempt to conjugate sulfonyl compounds to the metal complex. In other words, the amine proton on the central sp^3 N can be derivatized as sulphonamides bearing R groups of interest. Facial coordination of the central donor N of the tridentate ligand has necessarily proven to account for remarkable biochemical properties [35-37].

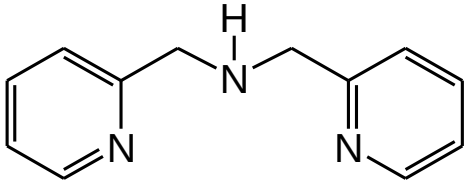


Fig.1. Line diagram of 2,2'-Dipicolylamine.

2.2. 2,2':6,2"-Terpyridine

Terpyridine is a strong chelating ligand consisting of 3 coordinating N atoms, which allow it to function as a tridentate ligand (**Figure 2**). Transition metal complexes based on terpyridine have found to possess unique applications in many fields including anti-tumour properties, catalytic properties [40], sensor properties, redox properties and properties of photo-luminescence [38- 42]. The structure of the ligand system can be modified by incorporating various substituents, giving rise to novel ligand systems. Previous studies have amended the free terpyridine structure with numerous electron-accepting and electron-donating substituents, particularly at the *p*-position of the terpyridine rings, so that the photo-physical and redox properties of the ligands and metal complexes could be manipulated [43]. In addition to that, the increased lipophilicity of the tridentate ligand has verified it to be a successful candidate for anti-microbial drug design. According to previous studies, higher lipophilicity observed in tridentate and bidentate ligands was correlated with high antimicrobial activity, having greater capability to cross the cell permeability barrier and hinder normal processes of the cell, when compared with their monodentate counterparts [44].

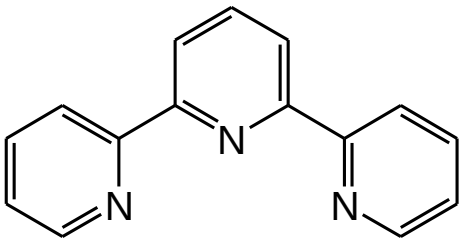


Fig. 2. Line diagram of 2,2':6,2″-Terpyridine.

3. Coordination with Copper: Structures and Geometry

3.1. Dipicolylamine based complexes

Copper complexes based on dipicolylamine (dpa) derivatized ligands have been widely employed over a large range of applications. One main reason for it is the synergistic ability of the dpa moiety to act concurrently as a σ-donor and π-acceptor, so that it can bind with the metal centres more strongly and also can function as a redox mediator [45]. The novelty of the complexes can be designated according to the substituent of the amine proton of the central N, which contributes to the resultant molecular geometry upon metal-ligand coordination [46]. Due to the many different binding modes of this type of ligands, the spectroscopic, structural and elemental data have been compared to determine the coordination geometries of the resultant complexes with a copper metal centre.

Accordingly, coordination of dpa with copper was first reported in 2003 (**Figure 3**) with the synthesis of a mono dpa-copper (II) complex [Cu(dpa)Cl_2]. The structural data of this complex suggested that the ligand acts as a tridentate donor and would adopt a distorted square pyramidal geometry [47]. This provided the basis for the ensuing syntheses of copper complexes with derivatized dpa ligands.

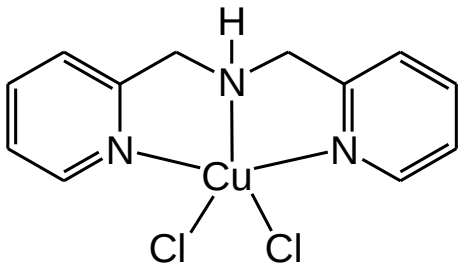


Fig. 3. Line diagram of [Cu(dpa)Cl_2] as synthesized by Choi et al., 2003 [47].

Subsequently, many other copper-dpa complexes were synthesized with significant bio-activity. The amine proton of central N of dpa was substituted with methyl-substituted benzene R groups forming novel ligands, and their corresponding copper complexes were synthesized [48]. The ligand was functionally tridentate, resulting in pentacoordinate complexes, where the apical chlorine was found to be slightly longer, so that the metal complex was distorted square pyramidal in shape, which was agreeable with previous literature (**Figure 4**). The apical chlorine had an increased bond length, hence its bond energy was low so that it was found to be more vulnerable for dissociation and formation of adducts.

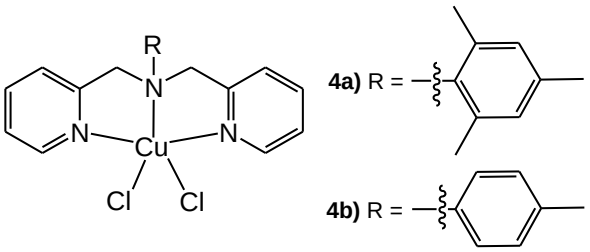


Fig. 4. Line diagrams of **a)** [Cu(2,4,6-trimethyl-*N,N*-bis(pyridin-2-ylmethyl)aniline)Cl_2] and **b)** [Cu(4-methyl-*N,N*-bis(pyridin-2-ylmethyl)aniline)Cl_2] synthesized by Muley et al., 2024 [48].

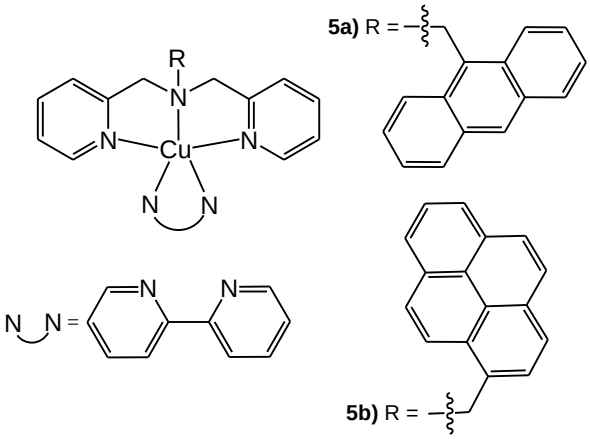


Fig. 5. Line diagrams of **a)** [Cu(1-(anthracen-9-yl)-*N,N*-bis(pyridin-2-ylmethyl) methanamine)(bpy)]$(ClO_4)_2$ and **b)** [Cu(1-(pyren-1-yl)-N,N-bis(pyridin-2-ylmethyl) methanamine)(bpy)]$(ClO_4)_2$ synthesized by Mathur et al., 2023 [49].

Similarly, two unique complexes were synthesized using the mixed ligand approach where anthracene and pyrene were used as the chromophores and 2,2'-bipyridine was used as the

subsidiary ligand in both cases [49]. The single crystal XRD data have confirmed that the complexes possessed a distorted square pyramidal geometry. In the anthracene based complex (**Figure 5a**), one of the N atoms of the ancillary ligand (bpy) can be found in the axial position as a result of intramolecular π–π interactions of that ligand. In contrast to that, the pyrene based complex (**Figure 5b**) consists of intramolecular π–π interactions between the pyrene moiety and bipyridine rings, leading to the central sp^3 N of the dpa-based system to lie in an axial position. Therefore, the axial coordination of the synthesized complexes is different albeit the similarity in geometry, which is possible due to the bulkiness of the ligands used.

The bis coordination of dpa-based ligands with a copper centre was investigated in 2000. Bis (dipicolylamine)copper(II) perchlorate, $[Cu(dpa)_2](ClO_4)$, was synthesized along with two of its geometric isomers which resulted in different coordination geometries [50]. Copper (II) complexes bis-coordinating with tridentate NNN coordinating ligands were prevalent of the Jahn Teller effect, which lead to distorted octahedral geometries with a lengthened or compacted z axis [51]. The *cis-fac-* coordination of the ligands with the copper centre, formed a hexacoordinate complex, where both dpa ligands coordinated facially on a *cis* plane with the metal, by means of the central N and one of the pyridyl N atoms, with the remaining pyridyl groups coordinating axially, creating a distorted octahedral geometry (**Figure 6a**). Interestingly, the *trans-fac-* coordination of the dpa ligands resulted in two complexes with different geometries. In the first, the central N atoms and the N atoms of one of the pyridyl groups of both ligands coordinate with the metal centre in one equatorial plane with slightly elongated pyridyl groups in the two axial positions, creating a distorted octahedral geometry (**Figure 6b**). The other structure adopts a square pyramidal geometry, where tridentate coordination is observed for one of the dpa ligands while the other ligand coordinates by means of only the central N and one of the pyridyl N atoms. Hence, the equatorial plane consists of the NNN atoms of the tridentate ligand and one of the pyridyl groups of the bidentate ligand (**Figure 6c**).

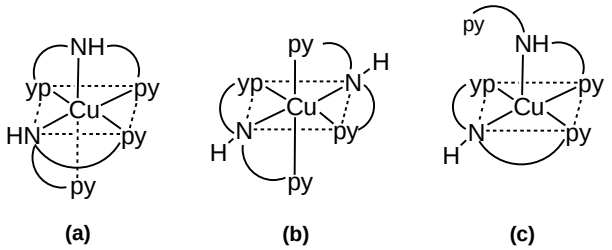


Fig. 6. Geometric isomers of $[Cu(dpa)_2](ClO_4)_2$ as described by Huang et al., 2000 [50].

3.2. Terpyridine based complexes

Terpyridines have been a remarkable class of compounds which possess the ability to bind with various transition metal centres through the N atoms of each of the 3 pyridyl groups and form complexes which bring about important biochemical properties. Binding properties with copper was investigated by the synthesis of the complexes [Cu(2,2':6,2"terpyridine)$(Cl)_2$] and $[Cu(2,2':6,2"\text{-terpyridine})_2][NO_3]_2$, while also adding terminal functionalities to the ligand to generate novel complexes [40]. The R groups in both pentacoordinate and hexacoordinate structures (**Figure 7**) were different in each of the synthesized complexes as follows, 1) R = H, 2) R = Cl, 3) R = Br, 4) R = COOH, 5) R = OMe and 6) R = NMe_2. All the structures synthesized with a 1:1 metal : ligand ratio exhibited a distorted square pyramidal geometry, with the basal Cu-Cl bond being shorter than the apical Cu-Cl bond, which was occurring as a result of the Jahn Teller Effect. Crystal structures of two metal complexes synthesized using a 1:2 metal : ligand ratio, were obtained (R = H and R = OMe) and they demonstrated a distorted octahedral geometry. It was also evident that the nature of the counter-ion also assists the used experimental conditions to govern the structure of the synthesized complexes [52]. In other words, a weaker chelating counter-ion would more readily enable the binding of another terpyridine ligand with the metal center, facilitating the formation of complexes with octahedral geometry. In these complexes, when the functionality on the ligand (R) was hydrogen, it was observed that the two chelating terpyridine ligands were almost planar and perpendicular to each other, while in the other structure where R = OMe, the two ligands were approximately perpendicular to each other.

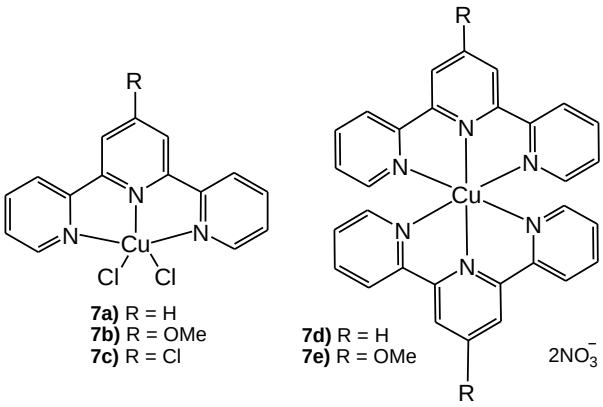


Fig. 7. Line diagrams of some of the complexes synthesized by Karges et al., 2020 [52]. **a)** $[Cu(terpy\text{-}H)(Cl)_2]$, **b)** $[Cu(terpy\text{-}OMe)(Cl)_2]$, **c)** $[Cu(terpy\text{-}Cl)(Cl)_2]$, **d)** $[Cu(terpy\text{-}H)_2][NO_3]_2$ and **e)** $[Cu(terpy\text{-}OMe)_2][NO_3]_2$.

More frequently, the coordination of a single terpyridine ligand with copper by means of its 3 N atoms on the pyridyl groups, was observed to render many diverse complexes which are distorted square pyramidal in geometry with many different substituents at the central pyridine ring [53-55].

4. Biological Applications of Copper Based Polypyridyl Complexes

A variety of copper based complexes containing modified dipicolylamine and terpyridine ligands, both of which contain multiple pyridyl rings have been synthesized previously and their significance in a biological context have been evaluated. It was determined that these type of complexes possessed noteworthy anticancer properties [55, 56]. Furthermore, due to the planar structures and different coordination geometries facilitated by the copper centre, these complexes were decent candidates to bind with intracellular molecules such as albumins and DNA [57]. In addition, the fluorescent activity and luminescence properties of such type of complexes have also been explored in order to test their use as potential diagnostic agents [31].

4.1. Copper-Polypyridyl Complexes as Potential Anticancer Agents

Copper based complexes have been administered to tumour cells throughout the years to bring about autophagy (a process by which cellular breakdown takes place, disrupting impaired cells and anomalous proteins and other sub cellular species found in the cytoplasm) and apoptosis which is the course of automated cell death [24]. It was found that copper based complexes achieve the above by means of various mechanisms [58]. One approach is the production of reactive oxygen species (ROS), which leads to oxidative stress within the cells as an increase in ROS disrupts the balance between the oxidants and antioxidants in the body [59]. An increase of ROS thereby causes damage to the cytoplasm, mitochondria, lipids, DNA and proteins within tumour cells while peroxides bring about apoptosis [60].

Another mechanism used by metal complexes which display anticancer activity is the inhibition of the cell cycle, which is a tightly controlled process with the use of many signals [58, 42]. The proliferation of tumour cells could occur as a result of abnormalities in the rates of cell division. Various critical phases of the cell cycle, including the G1-S, S and G2-M points, are attacked by metal complexes displaying this mode of action in order to block the replication of DNA and control the growth of tumour cells [61]. Angiogenesis is the initial process by which tumour cells obtain the necessary nutrients from blood vessels to grow and rapidly increase in number, reaching their optimal metastatic capacity. Some drugs are capable of confronting this phenomenon by blocking the access of oxygen and necessary nutrients required for the tumour cells to grow and/or inhibit the expression of growth factors required by the vascular endothelial tissue, preventing the formation of tumour cell blood vessels, causing these cancerous cells to eventually die [58, 62]. Many drugs have become efficacious in bringing about one or more of these approaches simultaneously so as to strengthen their anticancer potential [63, 64].

A novel pyrrole-appended copper-dpa complex, labelled as PPMdpa-Cu was synthesized (**Figure 8a**) and its antitumor activity was tested against 3 separate cancer cell lines, U87, AsPC-1 and HepG2, which are the human glioblastoma cell line (derived from malignant human brain tumours), human pancreatic adenocarcinoma cell line and a human liver cancer cell line respectively [65]. MTT assays conducted for the copper-dpa complex disclosed that the metal complex exhibited exceptional anticancer activity, surpassing the anticancer activity of the ligand used and that of a newly synthesized platinum based dpa complex of the same type. Accordingly, PPMdpa-Cu was found to possess a low IC50 value (27.3 μM), making it a potent drug, and it was also found to be able to induce apoptosis via the generation of ROS in HepG2 cells and bring about the loss of matrix metalloproteinases (MMPs) which have a pivotal role in tumour cell metastasis and angiogenesis.

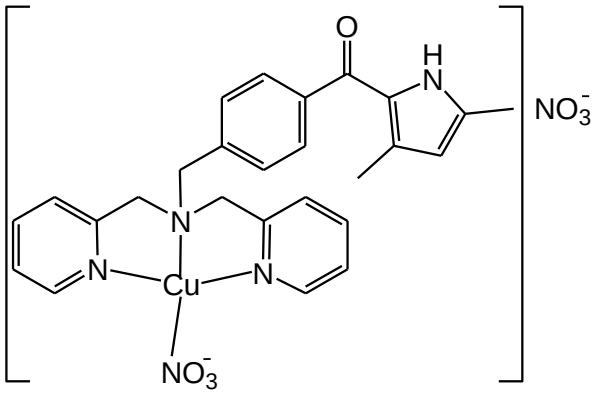
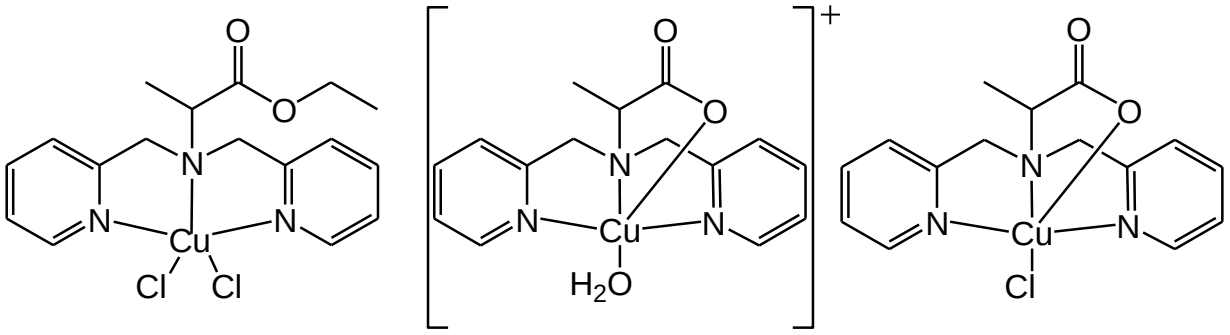


Fig. 8a). Line diagrams of PPMdpa-Cu complex synthesized by Huang et al., 2024 [65].

Three original complexes, [(Etdpa)$CuCl_2$], [(Adpa)Cu(H_2O)](ClO_4), and [(Adpa)CuCl] were synthesized (**Figures 8b-I, 8b-II and 8b-III** respectively) by modifying the substituents on the sp^3 N of dpa [66]. Their antitumor activity *in vitro* was evaluated and compared with that of the conventional Cu-dpa complex, [Cu(dpa)Cl_2]. This was achieved by means of MTT assays against MCF-7 (breast cancer), A549 (non-small cell lung cancer), Hela (cervical cancer), and Eca109 (human esophageal cancer) cell lines. The percentage of inhibition of proliferation of cancer cells by these complexes were concluded by using their IC_{50} values. It was found that the synthesized complexes were able to hinder the proliferation of MCF-7 cells more successfully than [Cu(dpa)Cl_2], indicating lower IC_{50} values than the latter. Also, a higher activity against Eca109 cells could be observed for complexes [(Adpa)Cu(H_2O)](ClO_4), and [(Adpa)CuCl], which possessed substituent groups on the sp^3 N of dpa, indicating that the substituents on the central N played a significant role in monitoring the anticancer properties of these copper(II) complexes.



8b-I) **8b-II)** **8b-III)**

Fig. 8b). Line diagrams of **8b-I)** [(Etdpa)$CuCl_2$] **8b-II)** [(Adpa)Cu(H_2O)](ClO_4) **8b-III)** [(Adpa)CuCl] synthesized by Wang et al., 2009 [66].

Similarly, many terpyridine based complexes have been reported for their cytotoxic significance [58, 62]. Four novel copper containing complexes synthesized in 2022 (**Figure 8c**) have been assessed against several cancer cell lines, and were successful especially against BEL-7402 cells, which were derived from human hepatocellular carcinoma [54]. Gu].

The remarkable feature of such complexes is that they demonstrated low toxicity to the healthy, functional liver cells, which is a critical aspect considered in drug design and administration. It was also concluded that the synthesized complexes were capable of the arrest of G0/G1 phase, varying how certain proteins associated with the cell cycle are expressed.

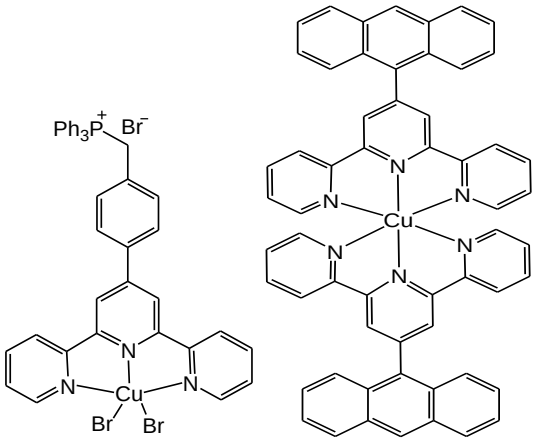


Fig. 8c and 8d. Line diagrams of **8c)** Cu-terpyridine based complex synthesized by Gu et al., 2022 [54]. **8d)** Cu(II) complex of anthracenyl terpyridine synthesized by Kumar et al., 2011 [68].

A turning point in the use of copper containing pharmaceutical drugs in cancer therapy is their success when compared with the more frequently employed platinum containing drugs such as cisplatin and carboplatin, which accompany many side effects and also tend to develop intrinsic or acquired resistant properties over time. Therefore, it is optimal to synthesize copper based compounds with greater toxicity to cancer cells and minimal resistance and side effects [67]. A metal complex based on the 4'-(9-anthryl)-2,2':6',2"terpyridine ligand was synthesized (**Figure 8d**) and evaluated for cytotoxic properties compared to the well-known carboplatin [68] [48-new 63 Kumar]. The novel complex displayed positive anticancer activity against a broad range of cancer cell lines, including breast cancer (MCF-7), cervical cancer (SiHa, HeLa, CaSki), lung cancer (H1299) and liver cancer (HepG2), and the degree of inhibition was found to be greater than that of carboplatin tested under the same conditions. Furthermore, the copper-based complex was found to be more toxic to cancer cell lines HeLa, SiHa and CaSki cell lines which were priorly introduced to the Human papillomavirus (HPV), than to the cancer cell lines without the above virus, such as the MCF-7, HepG2 and H1299 cell lines. Flow cytometric studies concluded that the novel copper complex was able to induce apoptotic cell death followed by the occurrence of nuclear fragmentation in HeLa, CaSki, SiHa and H1299 cell lines. However, it was determined that in the MCF-7 cell line, the cell cycle is arrested at the G2/M phase so that a significant nuclear fragmentation does not follow apoptosis.

Despite the success of many copper polypyridyl anticancer drugs, many tumours have demonstrated a tendency to develop resistance to multiple drugs, owing to the ineffective delivery method of such metal complexes to their targeted site of action [69]. One such solution to this issue would be to associate the metal complex with a nanocarrier [69, 70]. In order to allow the successful uptake of Cu(II) terpyridine complexes by tumour cells, a novel synthetic approach was followed, where the metal complex was encapsulated into polymeric nanoparticles, overcoming the poor solubility of the molecular metal complex (**Figure 8e**) in water [70]. The synthesized nanoparticles were evaluated for their cytotoxic potential against the human breast adenocarcinoma cells. It was clear that the metal complex encapsulated nanoparticles were able to enter into the target cells more effectively and accumulate primarily within lysosomes leading to cell death via apoptosis. The therapeutic effect of the synthesized nanoparticles was further analyzed by incorporation into three dimensional multicellular tumour spheroids of human breast adenocarcinoma, which mimic clinical solid tumors. ATP concentrations of the tumour spheroids were measured by means of a luciferase based assay of luminescence. The IC_{50} value for the nanoparticles were found to be in the nanomloar range, indicating significant cytotoxic potential when compared to the free molecular complex, as well as the popular cytotoxic drug, cisplatin.

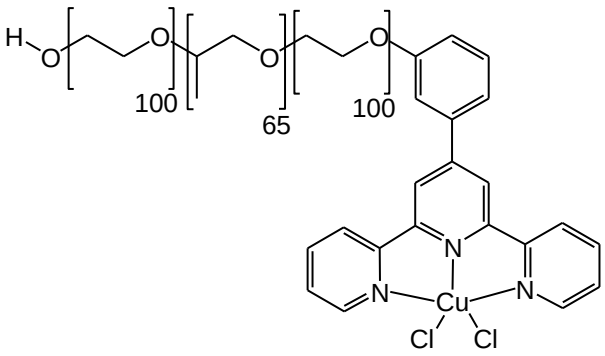


Fig. 8e. Line diagram of Polymer encapsulated Cu(II)-terpyridine complex synthesized by Montesdeoca et al., 2024 [70].

Some drug molecules have the ability to bind with various important intracellular species such as DNA and proteins, making them promising candidates in biological action. The planar structures of many of the Cu(II)-polypyridyl complexes have been advantageous in DNA intercalation [71, 72], bringing along with it, other inhibitory mechanisms, such as the production of ROS [73], in order to selectively induce apoptosis in tumour cells. Eight new complexes based on 2,2':6',2"-terpyridines, were synthesized (**Figure 8f**) with aromatic substitutions at the 4'-position, and their biological significance was evaluated for their anti-proliferative abilities and binding properties with DNA and Bovine Serum Albumin (BSA) [74]. In this study, it was found that the synthesized complexes would accumulate within the cell's nucleus and produce ROS, which influences the binding and the subsequent cleaving of pDNA upon binding with the metal complexes. This could be confirmed with the loss of the supercoiled and circular isoforms and with the emergence of the linear isoform. This process was found to be made possible through either an oxidative or hydrolytic pathway, where the synthesized metal complex would bind non-covalently with DNA and cleave it directly through a Fenton mechanism [75] or indirectly by means of the action of topoisomerases [76]. Furthermore, the binding with BSA has been considered due to the structural resemblance of BSA to human serum albumin, as it is a highly abundant blood plasma protein with a role in systemic transport of these synthesized complexes to the specific tumour site. Likewise, the binding modes of the synthesized complexes with the DNA helix were

investigated via calf thymus DNA studies, which concluded that the complexes with 4-quinolinyl, 4-methoxy-1-naphthyl, 2-furanyl and 2-pyridynyl substituents at the 4'-position displayed a strong intercalative interaction mode. It was concluded that the complexes with the aforementioned pendant groups have been successful against the HCT116DoxR cell line which is a colorectal carcinoma resistant to doxorubicin. The complexes have exhibited lower IC_{50} values compared to doxorubicin and have also displayed selective activity for the tumour cells. In addition to that, the complexes were capable of causing apoptosis and autophagy in tumour cells with the increased production of ROS, arrest of the cell cycle at G0/G1 and G2/M phases. They were also able to display anti-angiogenic and anti-metastatic properties with no *in vivo* toxicity.

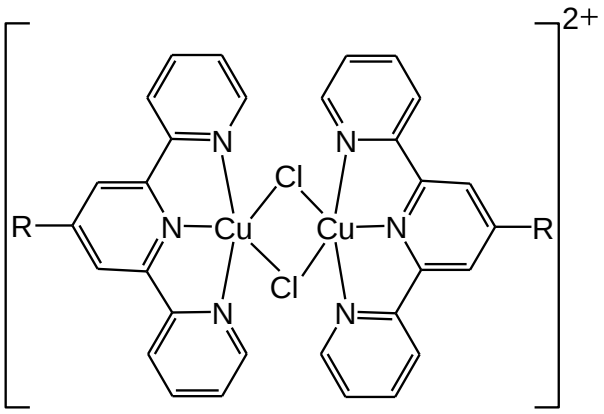


Fig. 8f. Line diagram of $[Cu_2Cl_2(R\text{-terpy})2](PF_6)_2$ synthesized by Choroba et al., 2024 [63].

4.2. Copper-polypyridyl Complexes as Potential Diagnostic Agents

Fluorescent cell imaging is based on the excitation ability of a certain sample, leading to the absorption of electromagnetic radiation by that sample and emission of light as fluorescence, which is detected, enabling the *in vitro* imaging of cells. Fluorophores of metal-organic complexes possess certain photo-physical properties which permit their usage as effective imaging agents and intracellular sensors [77]. Some such properties include localization ability, excitation ability at non-damaging wavelengths, display of a particular demarcated Stokes shift and stability in biological systems. Usually, low energy near IR radiation is used in cell penetration in order to minimize any phototoxic damage and obtain a deeper tissue penetration [78]. Therefore, a certain fluorophore binding with a cell or a sub-cellular species will allow imaging of the behaviour of that cellular species subsequently. Tridentate ligand systems have been frequently explored as efficient fluorescent probes, as they have displayed a strong affinity to metal ions and exhibited a versatile array of structural modifications in the metal complexes that they form.

Fluorescent probes can often be utilized as theranostic agents, where a biological role in certain metal-organic complexes have been syndicated to the imaging and diagnostic ability [79]. Previous studies indicate that metal complexes bearing ligands with polypyridyl groups forming cyclo-metalated compounds have been competent candidates in this regard as they have demonstrated their versatile abilities to be used as anticancer agents, nuclear probes and DNA binding agents [79, 80]. Another important mechanism by which fluorescent active metal-organic complexes operate is their role as photosensitizers in photodynamic therapy (PDT). In this method, a fluorophore containing metal complex is introduced where it selectively binds with a specific tumour site. With the selected wavelength of radiation, the tumour area is then irradiated so that it stimulates and induces the *in-vivo* toxicity of the bound metal complex, so that it is able to generate ROS, causing apoptosis [81]. The success of copper based complexes with polypyridyl ligands, which have displayed decent fluorescent activity, has been assessed over the years in this regard.

Three novel complexes containing tridentate dipicolylamine coordinated Cu(II) complexes of the type $[Cu(L)Cl_2]$ were synthesized and evaluated for their theranostic applications including cell imaging and anticancer properties [82]. Out of the complexes, two consisted of BODIPY (borondipyrromethene) moiety as the third substituent at the sp^3 central N atom, while one complex merely consisted of a $-CH_2Ph$ group as the third substituent (**Figures 9a-I to 9a-III**). Out of these complexes, complex 2 (**Figure 9a-II**) consisted of a green light emitting BODIPY unit and it was determined to be a useful cellular imaging agent which could selectively localize in the cytoplasm of the HeLa and MCF-7 cancer cell lines. This can be considered as an advantage over chemotherapy drugs such as cisplatin which target the nucleus where they are often subjected to the nucleotide excision repair (NER) mechanism, by repairing the DNA damage induced by such drugs which leads to resistance [83]. Complex 3 (**Figure 9a-III**) which possessed an iodine containing BODIPY system, was found to be exceptionally functional as a photosensitizer even though it was non-emissive, so that it was capable of significant PDT effect in HeLa and MCF-7 cells, which is often linked with the production of ROS leading to apoptotic cell death. This complex was determined to be around 30-fold greater in photo-cytotoxicity compared to the commonly used PDT drug Photofrin. However, its toxicity was also found to be less in the dark. Therefore, it was confirmed that with suitable modifications to the ligand structures, metal complexes can be designed for their fitting applications in cell imaging and photodynamic therapy inducing apoptosis.

Additionally, four terpyridine–based Cu(II) complexes have been designed to be used as luminescent probes for the detection of the biothiol homocysteine (Hcy), which is identified as an Alzheimer's risk factor and causative agent of hyperhomocysteinemia at extreme levels [84]. The synthesized complexes were labelled according to their substituents and the structural modifications on the terpyridine moiety, Tpy1Cu, Tpy2Cu, RuCu and IrCu (**Figure 10a-I to 10a-IV**). It was found that Tpy2Cu and IrCu were more successful in the detection of Hcy in water than Tpy1Cu and RuCu. The synthesized Cu(II) complexes were reduced to the Cu(I) form by Hcy, resulting in four–coordinated terpyridine–Cu^+ species. Such formed Cu(I) complexes of Tpy2Cu and IrCu were able to aggregate as nanoparticles, inhibiting the oxygen–induced luminescence quenching. Detection of Hcy by Tpy1Cu and RuCu was somewhat weak as a result of rapid fluorescence quenching induced by the dissolved O_2 in water. Additional cell imaging testing indicated that in the presence of Hcy, Tpy2Cu would illuminate the entire cell, while only the cytoplasm was lit up with IrCu. IrCu, which was a terpyridine–based Cu(II) complex modified using the $[Ir(ppy)_2(bpy)]^+$ substituent, displayed a 1500–fold increment of luminescence intensity at 603 nm in the detection of Hcy. Hence, it was concluded that Cu-terpyridine complexes were efficient agents in cell imaging with complexes bearing more hydrophobic substituents exhibiting more intense and long-

lasting fluorescent signals.

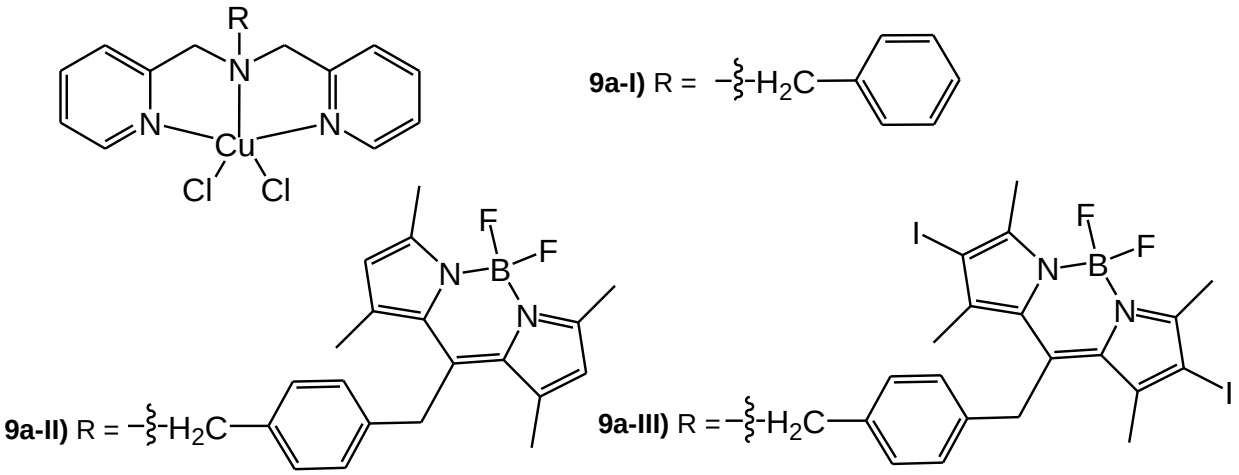


Fig. 9. Line diagrams of the copper-polypyridyl complexes **9a-I)** Complex 1, **9a-II)** Complex 2 and **9a-III)** Complex 3 synthesized by Bhattacharyya et al., 2016 [82].

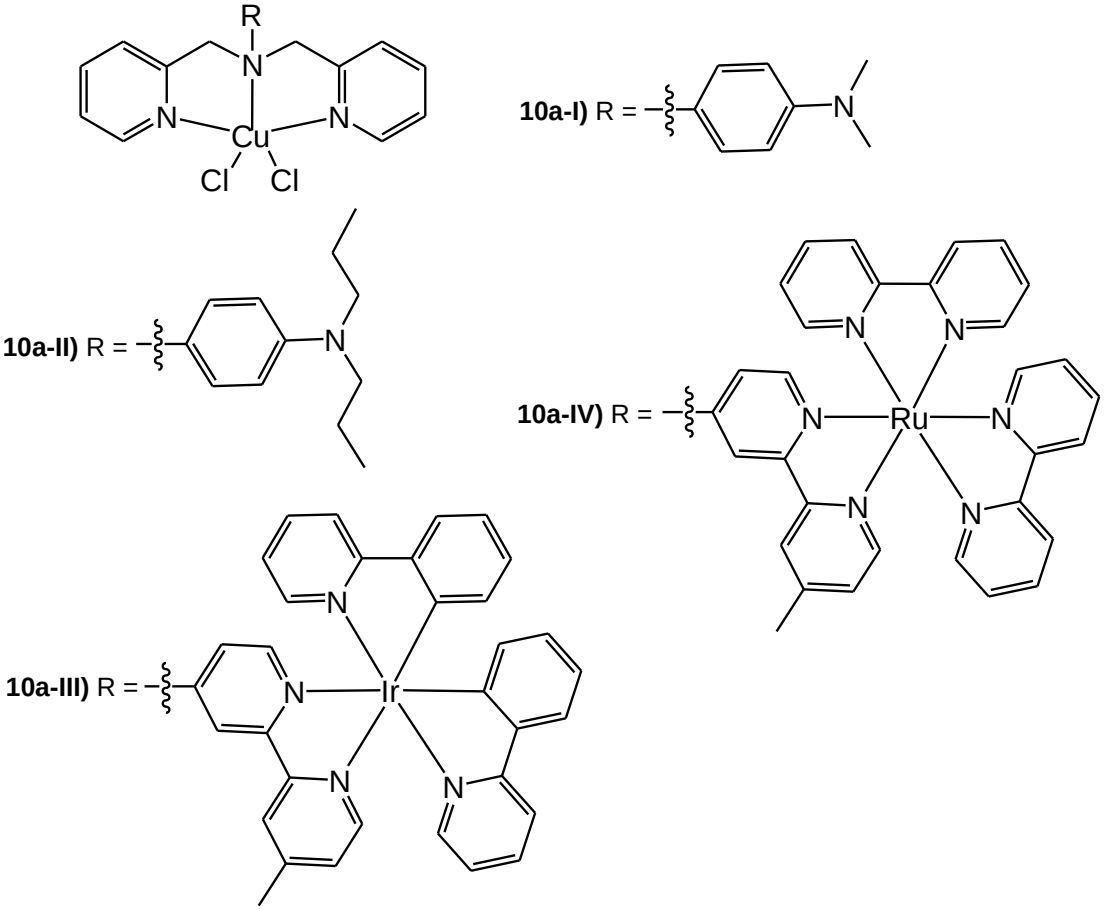


Fig. 10. Line diagrams of the copper-polypyridyl complexes **10a-I)** Tpy1Cu, **10a-II)** Tpy2Cu, **10a-III)** RuCu **10a-IV)** IrCu synthesized by Chao et al., 2017 [84].

5. Conclusions

Design of novel metal-organic complexes has been widely popular due to their various therapeutic and diagnostic applications, which highlight their biological role. Copper containing complexes based on polypyridyl ligands 2,2'-Dipicolylamine and 2,2':6,2"Terpyridine have been evaluated in the above regard as they possess the ability to give rise to numerous novel complexes with the addition of different substituent groups at the central sp^3 N of dipicolylamine and at the *p*-position of the middle pyridyl ring of terpyridine. With both types of ligands, structures were reported with one and two ligands coordinating with the metal centre, leading to pentacoordinate and hexacoordinate structures respectively.

Among such compounds, the structures with single ligand coordination were more frequently synthesized and isolated. Both the ligands were found to be tridentate NNN donors and were evaluated for their biological applications. Anticancer abilities were displayed by most of the copper complexes derived from these ligands, where they were capable of simultaneously bringing about different mechanisms of tumour cell death including arrest of cell cycle, production of reactive oxygen species (ROS), DNA binding resulting in plasmid cleavage and fragmentation and activation of anti-metastatic and anti-angiogenic mechanisms. Some of the reported complexes were found to be successful as cellular imaging agents, with enhanced luminescence properties and DNA binding abilities while some have displayed the ability to be localized at a specific site and act as photosensitizers to be utilized in photodynamic therapy. Structural diversity and the wide array of applications as diagnostic and therapeutic agents have empowered further evaluation and development of these types of complexes towards the future advancement of biomedical research.

Author Contributions

Aishwarya Wevitavidana was involved in conducting the literature review, organizing the information in an attempt to analyze the diagnostic and therapeutic effects of NNN coordinating polypyridyl ligands, 2,2'-Dipicolylamine and 2,2':6,2"-Terpyridine coordinating with copper. Theshini Perera was involved in providing detailed feedback, overseeing and supervising the overall structure and development of the manuscript. Both authors contributed towards discussing and concluding the findings so that they could be included into the writing of the manuscript.

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