Metal Dipicolylamines and their Biomedical Applications: A Mini Review

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Abstract

Research in synthetic inorganic chemistry demonstrates that metal complexes are widely utilized as therapeutic as well as diagnostic agents. Due to the coordinative saturation, substitutional inertness, and unique redox characteristics, metal polypyridyl complexes have ignited attention and have been exploited in a number of biological and biomedical fields. The polypyridyl ligand, dipicolylamine (DPA) is a symmetrical secondary amine with two pyridyl rings. Delocalization of excited electrons occurs throughout the ligand system due to its conjugated character and the metal-to-ligand charge transfer transitions, resulting in a strong fluorescence signal. The high lipophilic nature of this ligand has proven to improve metal-DPA complex absorption by cell membranes. The N–H amine group in DPA and its analogues have the additional function of allowing hydrogen bonds to form, and deprotonation of this amine has allowed the creation of mononuclear and polynuclear species, with deprotonation of the bridging amine nitrogen also playing a significant role in the coordination sequence. DPA-appended metal complexes have garnered attention in the quest for linkages between magnetic, spectroscopic, structural, and coordination geometries. A number of mononuclear metal-DPA complex crystal structures with four, five, or six coordinated metal centers have been synthesized and explored for their biological properties. This study reviews DPA-derivatized ligand-linked metal complexes as promising cancer, microbial, and fungal inflammatory therapeutics, as well as potential diagnostic agents for fluorescence imaging and radiopharmaceuticals.

Keywords: Dipicolylamine, metal complexes, coordination geometries, fluorescent agents

1. Introduction

The field of bioorganometallic chemistry was introduced in 1985 by the French chemist Ge'rard Jaouen who described the paradigm as the study of physiologically active compounds with at least a single direct metal-carbon bonding. This interdisciplinary field is a coalescence of bioinorganic chemistry, organometallic chemistry, and coordination chemistry.

For generations, metal complexes have been utilized to cure a variety of diseases and disorders. Although most metal complexes are reported to be poisonous and unstable in water and air, some of the metal complexes are known to be stable and less toxic (Hartinger and Dyson, 2009). Modern research has moved into a new era with the recognition of the significance of metal complexes in biological systems. Much research has discovered metal complexes that have the potential to be employed as therapeutic and diagnostic agents in cancer treatments (Muhammad and Guo, 2014, Allardyce and Dyson, 2006). Biomedical imaging techniques like Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Single-Photon Emission Computed Tomography (SPCET) rely heavily on metal complexes

(Storr et al., 2006). The use of organometallic complexes along with sulfonamides as antimicrobial agents is a modern approach to chemotherapy (Rizzotto, 2012, Chohan, 2008). Antiviral agents also could likewise be made from organometallic complexes (Allardyce and Dyson, 2006, Chuong et al., 2021). Hence Organometallic pharmaceuticals are a rapidly increasing class of anticancer drugs with a wide range of uses in imaging, microbial, and viral treatments.

Organometallic complexes are developed according to a desired architecture. Metal and ligand systems are available in a variety of configurations. The pharmacological effects of these complexes are heavily influenced by the metal ion and donor sequence features, as well as various biological qualities of the ligand system.Biologically relevant metal complexes must meet a number of conditions in respect of their artificial design. The metal-ligand link should be hydrolytically stable. The metal complex must be thermodynamically favorable to move metal towards the active site. Also, other essential conditions are the molecular weight of the metal complex and the kinetics of metal ion delegation and ligation processes (Rizzotto, 2012). Within living organisms, the interaction between ligands and metal is crucial.

Selecting a ligand system for a metal complex is done by considering the factors which include the ability to penetrate through the cell membrane, the potential to bind with the specific organelle, and altogether the efficiency of the ligand metal system as a drug. Lipophilicity is a key feature of organometallic compounds used in biological applications because the metal complex should have some kind of lipophilicity to cross the cell membrane through passive transportation. Therefore, the lipophilicity of the ligand plays a vital role. The complex must also be hydrophilic, as the drug must enter the inner cell membrane as well as the cytoplasm, which is an aqueous medium.

The optical properties of polypyridyl metal complexes have been used in a number of biological and industrial innovations. These ligands are great prospects for development as new medicinal and diagnostic chemicals due to their molecular structure diversity, chemistry, and redox characteristics.

The objective of this review is to explore some latest work on metal polypyridyl complexes of biological potential, with a focus on the Dipicolylamine ligand system and its metal-ligand complexes, and to address the structural characteristics of these complexes, along with their biological properties.

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1.1 Polypyridyl ligands

Ligands can significantly influence biological features of metal complexes such as reactivity and substitution inertness, as well as assist metal ion redistribution (Storr et al., 2006). Polypyridyl ligands have been effectively used to build stable compounds that could also create noncovalent adducts with significant functions in cells owing to polydentate complexation. Metal polypyridyl complexes are well known for their coordinative saturation, substitutional inertness, and unique redox characteristics. Despite this, their superior photochemical and photophysical properties have enabled them to be used in a broad array of applications.

For a range of metal derivatives, the *in vivo* toxicity, anticancer properties, antibacterial, and enzyme-inhibition activities of phenanthroline, bipyridine, and terpyridine complexes have all been examined (Knoll and Turro, 2015). As DNA intercalators and groove binders, metal polypyridyl complexes have been frequently employed (Salassa, 2011). The inertness and structural diversity of polypyridyl ligands can be used to make stable molecules that can form noncovalent complexes with key cellular proteins. Using biphenyl-like ligands, chemical characteristics like hydrophobicity and redox potential can be fine-tuned to achieve cytotoxicity in cancer cells.

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The availability of various coordination methods for transition metals and the vast variety of economically and artificially available diimine ligands, have led to a wide structural range of metal polypyridyl complexes. This versatility may theoretically be exploited to construct a variety of forms, physicochemical properties, and reactivities, all of which could be customized to improve the efficacy of this group of medications in chemotherapy (Perera et al., 2013).

*1.2 2,*2'-Dipicolylamine

Dipicolylamine is a symmetrical secondary amine, with two pyridine rings (Figure 1). This is a tridentate ligand that does not induce asymmetry at the metal center which is important in avoiding diastereomeric mixtures (Darshani et al., 2020a). Due to the conjugated nature of the dipicolylamine moiety, delocalization of excited electrons can be seen throughout the ligand during metal-to-ligand charge transfer transitions (Storr et al., 2005). This character has led to its use as fluorescent probes in a variety of applications. The highly lipophilic character of the ligand DPA has been shown to enhance the absorption of metal complexes by cell membranes. DPA can serve as a link of the sulfonyl compound to the metal complex by forming sulfonamides. The use of various substituents for the amine proton in $N(SO_2R)$ DPA has resulted in the formation of such a metal-to-nitrogen bond with a regular bond length range, resulting in excellent biochemical properties (Storr et al. 2005a)(Storr et al., 2005b).

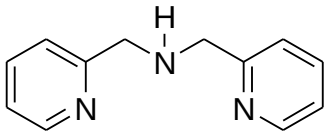

Figure 1 – 2,2'-Dipicolylamine (DPA)

2. The geometry of metal-dpa complexes

In transition metal chemistry, DPA and other aromatic nitrogen heterocycles are conventional yet evergreen ligands. They also have aromatic rings in their metal complexes, which are important when considering π-π stacking attractions as well as the bidentate or tridentate coordinating mode (Darshani et al., 2020a). The flexible ligand DPA typically exhibits good redox catalytic capabilities in its metal complexes (Du et al., 2003). Furthermore, the N–H amine group in DPA and its analogs has the additional function of allowing hydrogen bonds to form, and more intriguingly, the creation of mononuclear and polynuclear species has been permitted by the deprotonation of such an amine in DPA as well as its synthetic derivatives, with the deprotonation of the bridging amine nitrogen also playing a role in the coordination arrangement (Perera et al., 2013).

The search for links between magnetic, spectroscopic, structural, and coordination geometries has sparked interest in dpa-containing metal complexes. As an outcome of this interest, a variety of mononuclear metal-dpa complex crystal structures with four, five, or six coordinated metal atoms have been produced and characterized.

Three novel Pt complexes have been reported: [$PtCl_2$(N(SO_2(1-nap))DPA], [$PtCl_2$(N(SO_2(2-nap))DPA], and [$PtCl_2$(N(SO_2pip))DPA] (Thushara et al., 2021)where the ligands are bound in a bidentate manner through Pt–N(pyridyl) bonds in all three complexes, generating an eight-membered ring along with a sulfonamide N at the core of the complex not connected to Pt, resulting in a four coordinated metal complex (Figure 2).

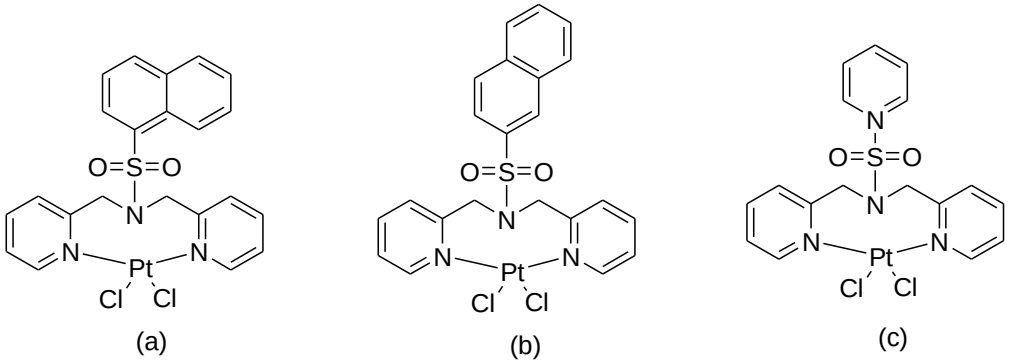

Figure 2 – (a) [$PtCl_2$(N(SO_2(1-nap))DPA)] (b) [$PtCl_2$(N(SO_2(2-nap))DPA)] and (c) [$PtCl_2$(N(SO_2pip))DPA)]

Three new DPA-coordinated ligands and their respective *fac*-Re(I) tricarbonyl complexes, *fac*-[$Re(CO)_3$(N(SO_2)(1-nap)DPA)]PF_6, *fac*-[$Re(CO)_3$(N(SO_2)(2-nap)DPA)]PF_6 and *fac*-[$Re(CO)_3$(N (SO_2Me_2Nnap)DPA)]PF_6 have been synthesized and characterized (Darshani et al., 2020a) where the ligand has shown a binding tendency to the central metal atom in a tridentate mode (Figure 3), binding the sulfonamide N to the center Re metal atom, generating a six-coordinated metal complex, according to structural studies.

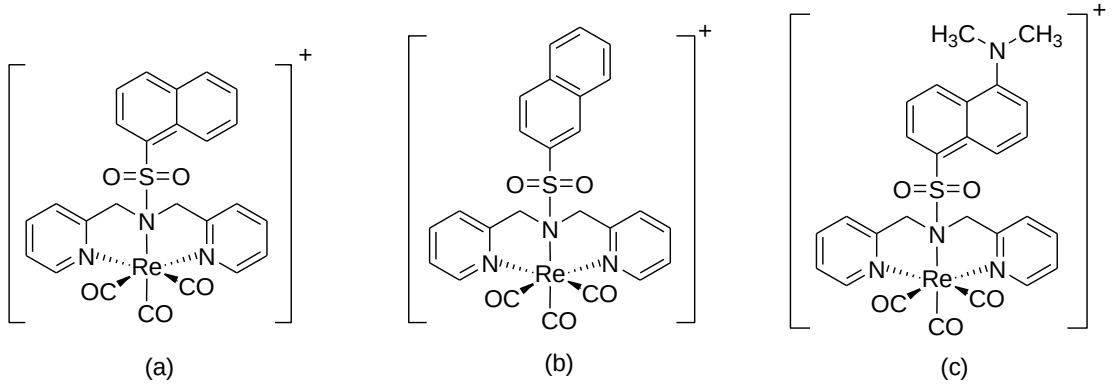

Figure 3 – (a) *fac*-[$Re(CO)_3$(N(SO_2)(1-nap)DPA)], (b) *fac*-[$Re(CO)_3$(N(SO_2)(2-nap)DPA)], and (c) *fac*-[$Re(CO)_3$(N (SO_2Me_2Nnap)DPA)]

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The sulfonamide derivatized DPA component of zinc complexes results in an unusual eight-membered chelate ring $Zn(N(SO_2)(1\text{-nap})DPA)Cl_2$, $Zn(N(SO_2)(2\text{-nap})DPA)Cl_2$ and $Zn(N(SO_2Me_2Nnap)DPA)Cl_2$. $CHCl_3$ has been synthesized and investigated (Figure 4) (Darshani et al., 2020a). The bidentate coordination mechanism reported within this research study might be explained by the electron stability of these chelating complexes. Zn and the pyridyl nitrogen bond lengths are reported to be slightly smaller in $Zn(N(SO_2R)DPA)Cl_2$ complexes than in five- or six-coordinate zinc complexes with the central nitrogen atom which has been bound to Zn. Zinc complexes of $Zn(N(SO_2R)DPA)Cl_2$ complexes arranged in an eight-membered chelate ring, on the other hand, have metal-ligand bond lengths that have been recorded.

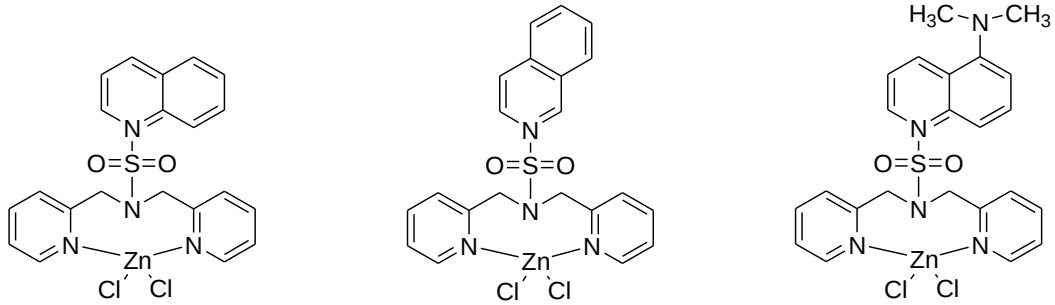

Figure 4 – (a) $Zn(N(SO_2)(1\text{-nap})DPA)Cl_2$, (b) $Zn(N(SO_2)(2\text{-nap})DPA)Cl_2$ and (c) $Zn(N(SO_2Me_2Nnap)DPA)Cl_2$

The best explanations for the coordination number of zinc(II) complexes are bonding interactions ,repulsive interactions between the zinc(II) ion and the relevant ligands complexed with the zinc core. The interactions between ligands that repel each other can be steric, electronic, or perhaps a combination of both (Beitat et al., 2011). Since the bond distance between the zinc(II) metal ion core and its coordinated ligands are shorter, the ligands repel each other more strongly, resulting in much more stability in forming a four-coordinated complex arranged in a tetrahedral form. The basic $Zn(N(H)DPA)Cl_2$ complex has been reported to be a five-coordinate complex because N(H)DPA is a strong electron donor, as well as bonding attractions, are much larger than repulsion forces in comparison to the large aromatic tertiary amine ligands. This consent has resulted in two small five-membered rings (Bose et al., 2004).

For years, the advancement of supramolecular structures for inorganic-organic hybrid compounds has been a fascinating field of study. Various network architectures have been generated by the usage of ligands by leveraging the validity of coordination geometry around metal centers. The goal would be to rearrange the composition, form, and functionality of the relevant materials, perhaps leading to unique characteristics in commonly used materials. A 2D sheet and a 3D supramolecular complex, which is a four-coordinated mononuclear complex $[Zn(dpa)(N_3)_2]$ and a hexacoordinated mononuclear compound $[Zn(dpa)(N_3)(NO_3)]_2$ have been synthesized respectively, using 2,2' -Dipyridylamine a specialized diimine attributing to its capability to construct a hydrogen-bonded pattern and luminescence via π-π* transitions (Bose et al., 2004). These molecules have established a potentially extendable way for constructing an inert inorganic-organic hybrid coordinating network, which is a fascinating subject of research for rational material design. A single crystal $Cu(dpa)X_2$ (X=Cl, Br) unit has been linked together by hydrogen bonds to form a pentacoordinate square pyramidal structure, having three bonded nitrogen atoms within the DPA ligand and a single chloride atom occupying the equatorial position and the other chloride atom occupying the axial coordinated position (Choi et al., 2003). A planar rearrangement is formed by the meridional coordination complexing arrangement of the three bonded nitrogen atoms in the DPA ligand. It is a one-

of-a-kind 'folded' rearrangement in which one of the pyridyl nitrogen in DPA has an axial position while the remainder of amine nitrogen, as well as the other pyridyl nitrogen, has equatorial positions. As a result, DPA forms a folded rearrangement with the Cu(II) ion on the surface. The meridional design of the complexes results in a square pyramidal geometry having five-coordinated metal centers. [$Cu(DPA)Cl_2$] has been synthesized and structurally described as a mono(DPA)copper(II) complex and it crystallizes in the monoclinic systems (Choi et al., 2003). The complex undergoes reversible one-electron oxidation to Cu(III) and reversible one-electron reduction to Cu(I) state, according to cyclic voltametric measurements.

3. Applications of metal-dpa complexes

DPA derivatized ligand-associated metal complexes have been synthesized and utilized as prospective therapeutic agents for malignancies, microbial and fungal inflammations, and as potential diagnostic agents for fluorescence imaging and radiopharmaceuticals.

3.1 Metal-dpa complexes as potential anti-cancer agents

Cancer is a disease that is characterized by the uncontrolled reproduction of altered cells that interferes with the body's regular functioning. Cancers of various forms have been discovered, with skin, breast, lung, liver, kidney, prostate, and cervical cancers being the most common. Along with the unexpected discovery of cisplatin in the 1960s, metal complexes are reported to be recognized as important in cancer treatment. Due to the capacity to arrange ligands in a three-dimensional form, metal-containing complexes have benefits over traditional carbon-based molecules. This allows for group functionalization that is customized to a certain molecular target. Transition metals with partially filled d orbitals exhibit intriguing electrical features that can be exploited to study anticancer drug creation.

Researchers have synthesized and analyzed three metal complexes based on naphthyl DPA sulfonamide derivatives just recently(Darshani et al., 2020). The $N(SO_2pip)$DPA ligand coordinated Pt complex is shown to have a high level of cytotoxicity towards the MCF-7 breast cancer cell line and exceeded that of cisplatin (Darshani et al., 2020b). Anticancer action was also observed in novel platinum complexes bound by ligands including naphthyl DPA sulfonamide derivatives. Low IC_{50} values for both ligands and complexes suggest that this component should be studied further in the quest for innovative anticancer drugs. A novel piperidinyl appended dipicolylamine ligand and its Re-tricarbonyl complex, $[Re(CO)_3(N(SO_2pip)dpa)]^+$, have also been produced and evaluated, with a comparatively low IC_{50} value determined by human breast cancer cell lines, MCF-7, indicating that this complex can be explored further as potential future anticancer agents (Subasinghe et al., 2016)

A DPA-based ligand was synthesized and characterized, as were the two mononuclear Zn(II), $[ZnLX_2]_2 \cdot CH_3OH$ complexes where X could be either Br or Cl and L is 4-methyl-N, N-bis(pyridine-2-ylmethyl) aniline) (Fantoni et al., 2021). Physio-chemical experiments have shown that the complexes and ctDNA are partly intercalated. Both of them demonstrate significant DNA damage in accompanying hydrogen peroxide as a mediator or an initiator. Additionally, the ability to get attached to proteins, which is essential for a therapeutic to function as an anticancer agent, has been studied.

A range of Cu (II) metal ions containing artificial metallo-nucleases (AMNs) has been tested for DNA damaging characteristics and *in vitro* cytotoxicity toward human pancreatic cancer cell lines (Torres Martin de Rosales et al., 2010). The minor groove binding of guanine-cytosine (G-C) which is abundant in sequences has been discovered using Cu-DPA-dipyridophenazine(DPPZ), a combination of a

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polypyridyl ligand that is tris-chelating, DPA, and a DNA intercalating phenanthrene moiety. These act as agents that capture superoxide and hydroxyl radicals and can help avoid oxidative DNA damage in the minor groove. Cu-DPA-DPPZ, specifically, has outperformed the therapeutic Pt(II) medicine oxaliplatin *in vitro* in human pancreatic tumor cells.(Fantoni et al., 2021).

A DPA-alendronate has been synthesized and investigated, which is a readily generated and quite well bifunctional bisphosphonate that creates a single crystal, defined isostructural Tc(I) and Re(I) tricarbonyl complexes that aggregate quickly inside bone tissues *invivo*. $^{188}Re(CO)_3$-DPA-alendronate surpasses the clinically approved bisphosphonate, ^{188}Re- HEDP, in terms of locating and concentrating in regions with higher metabolic bone function while maintaining a very small soft-tissue absorption, according to in vivo imaging and biodistribution studies (Osawa et al., 2021).

Utilizing the selectively concentrated state of the DPACu, a methacrylate (MA)-aligned polymer with dipicolylamine copper complexes DPACu(II)MA polymer was produced to improve catalytic activity towards hydrogen peroxide breakdown (Biswas et al., 2017). The obtained DPACu(II)MA polymer showed a rapid generation of reactive oxygen species from hydrogen peroxide and, in particular, enhanced hydroxyl radical generation, which could be a good potential property for antitumor and antibacterial drug applications when particularly in comparison to the monosubstituted dipicolylamine copper complex (DPACu(II)–OH. The DPACu(II)MA polymer demonstrated substantially greater antibacterial action towards E. coli than the DPACu(II)–OH at lower DPACu(II) molar ratios. These findings demonstrate that leveraging the polymer chain's regionally concentrated state to facilitate copper complex redox activity and increase its application is an option.

Early identification, diagnosis, and medication of prostate cancer in people with potentially aggressive diseases can save their lives. The human prostate accumulates the most zinc relative to just about any other soft tissue in the body. Tumor cells' inability to collect zinc, on the other hand, has been associated with the formation of deceases, leading to a substantial decline in the zinc concentration of prostate gland tissues. A dipicolylamine-coumarinchlorambucil-associated system (DPA-Cm-Cmbl) that may operate as a sensing and detecting tool as well as a photo detective drug delivery system has been created and evaluated (Storr et al., 2005). The DPA-Cm-Cmbl system, a single crystal component framework, used intracellular zinc level as a biomarker to locate the sick region and then used external stimulating light to release anticancer medication chlorambucil on-demand. DPA-Cm-Cmbl has been proven to have excellent features *in vitro*, including the ability to detect prostatic cancers, photo-detected drug delivery in a controlling way, and biocompatibility with overall efficacy.

3.2 Metal-dpa complexes as potential fluorescent imaging agents

Fluorescent cell imaging, which is useful in diagnostics and biomedical research, relies on the ability to stimulate a cell sample and detect the produced light using confocal microscopy. To investigate the relationships of single molecules to whole organism research, light emission either from native fluorophores or external fluorescent probes to detect the surrounding environment can be used. The use of fluorescent probes in optical imaging is a relatively new medical imaging approach. It offers cost savings, portability, and real-time capabilities. Fluorescence imaging has been proposed many times in medicine for the detection of diseases or specific physiological situations. In recent years, polypyridyl ligand families related to organometallic complexes, which have been complexed with rhenium, rhodium, platinum, zinc, and copper, have been used *in vivo* fluorescent cell imaging. These compounds all have the proper photophysical characteristics for intracellular excitation and detection of sufficient biological compatibility and luminescence tunability, which is crucial for evolution in this field of applied bioinorganic chemistry.

A succession in carbohydrate-attached dipicolylamine ligands coupled to the $M(CO)_3^+$ where M is either ^{99m}Tc or Re center was synthesized, characterized, and solid-state characteristics were described. To connect the dangling carbohydrate groups to the DPA moiety, an ethylene spacer molecule was employed (Storr et al., 2005). Radiolabeling with a carbohydrate attached DPA ligands with the tagging precursor $[^{99m}Tc(H_2O)_3(CO)_3]^+$ generated compounds that were essentially identical to their Re counterparts, according to HPLC comparison. After 24 hours, the radiolabeled compounds are stabilized in ligand exchange when there is an accumulation of cysteine or histidine. These findings have given rise to new ideas for imaging agents in the future. Glucosamine appended DPA compound as a ligand with the $M(CO)_3^+$ core has been explored and used to generate stable carbohydrate-appended imaging agents (Mikata et al., 2009). Because the main amine serves as a functionalization site, glucosamine is an appealing carbohydrate scaffold. Furthermore, emerging evidence in the studies indicates that N-functionalized glucosamines are active *in vivo* in terms of transport and accumulation in tumors.

The ability of radioactively labeled Zn(II)-DPA coordination compounds to monitor apoptosis *in vivo* has been investigated (Smith et al., 2011). The radioactively labeled Zn(II)-DPA coordination complexes via $^{99m}Tc(CO)_3^+$ or HYNIC have been used to generate $[^{99m}Tc(CO)_3]^+$ and ^{99m}Tc-HYNIC compounds, respectively. According to the hepatic cell death model, both $[^{99m}Tc(CO)_3]^+$ and ^{99m}Tc-HYNIC target dead cells. In two animal models, the capacity of a synthetic near-infrared fluorescent probe to detect cell death was studied. A Zn(II)-DPA affinity ligand in the molecular probe targets exposed phosphatidylserine on the membrane of dead and injured cells (Smith et al., 2010). Rats were given dexamethasone to promote thymic atrophy in the first animal model. In two different xenograft animal models, a chemically produced luminous near-IR imaging probe with an associated Zn-DPA specificity ligand can determine the amount of aggregation in prostate and mammary cancers. *Ex vivo* biodistribution and histopathological investigations indicate that the probe aims at the dead tissue sections of cancer cells, and *in vitro* microscopy shows selective targeting of the anionic membrane surfaces of dead and injured cells, which is consistent with *ex vivo* biodistribution and histopathological investigations (Tsuchido et al., 2018). Visualizing probes that can noninvasively identify the quantity and kind of induce apoptosis in tumors could be beneficial in evaluating tumor etiology's clinical prognosis. The probe is to be tested in future trials to see if it can be used to non-invasively detect cancer cell death caused by anticancer therapy. Zn-dpa based NIR probes with sensor groups ought to be possible to build, allowing for cancer deep tissue monitoring in patients.

Dipicolylamine-modified fluorescent silica nanoparticles have been made via depositing a thin layer of silica nanoparticles with amines as the terminal group and then coating the surface of the silica nanoparticles with dipicolylamine. The selectivity for metal ions and phosphate anions of dipicolylamine-hydroxycoumarin carbonate (DPA-HCC) and DPA-HCC/fluorescent silica nanoparticles (FSiNP) has been investigated (Tsuchido et al., 2018). The DPA-HCC surface assembly effect has revealed a new selectivity in the dipicolylamine-modified silica nanoparticles when they were exposed to Pb(II) and triphosphate. Surface-modified luminescent silica nanoparticles could be employed as a detector for biological and environmental purposes, according to the researchers. Cu-DPA-HCC fluorescent silica nanoparticles produced massive accumulation with *S. aureus* in less than 10 minutes, which were visible to the naked eye (Tsuchido et al., 2018).

The complex (di-(2-picolyl)amino)quinazolines, a new fluorescent sensor has been developed and evaluated for use in measuring ATP levels (Aoki et al., 2020). Using fluorescence quenching, copper ions and the corresponding copper complexes have been precisely detected. It has also been demonstrated that

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the fluorescence rises in the presence of phosphoric acid associated products. On the whole, 2-amioquinazolines have greater fluorescence intensities which can be used as sensitive, versatile, and broad-ranging probes or detectors for a variety of purposes, such as on-time or real-time tracking of intracellular ATP concentrations to aid in the understanding of important biological occurrences. When paired with a phenylboronic acid-modified g-cyclodextrin as well as a realistic multipoint recognition system, this fluorescence on-off approach allowed highly sensitive fluorescence monitoring of ATP.

^{18}F-FB-DPAZn$_2$, a synthetic bis(zinc(II)-dipicolylamine) coordination compound with ^{18}F labeling, could be used to image sterile inflammation *in vivo*, but additional research is needed to establish how well it works in bacterial infection models. Compared to ^{18}F-2-deoxy -D-glucose (^{18}F-FDG), ^{18}F-radioactively labeled ^{18}F-FB-DPAZn$_2$ demonstrated quick radioactivity removal from the kidney and little absorption in most organs (Choi et al., 2009). Decreased radioactivity concentrations in the brain and heart, as well as increased uptakes in the liver, lungs, and intestines, have been seen in ^{18}F-FBDPAZn$_2$ biodistribution. ^{18}F-FDG showed a much higher tumor and inflammatory absorption than ^{18}F-FBDPAZn$_2$ in the fibrosarcoma animal model and the sterile inflammation animal models.

To monitor sulfide ions, a new chemical signaling system associated with an easy combination of fluorescein and dipicolylamine has been developed. The compound showed a unique turn-on signaling response at 100 percent aqueous solution in response to sulfide ions in the presence of Cu(II) ions (Sakamoto et al., 2009). The excellent trapping of complexed and dynamic Cu(II) ions because of the persistent complexation with sulfide ions formed the basis for targeted signaling, which could be exploited in biological and environmental samples for sulfide sensing.

3.3 Metal-dpa complexes as a potential phosphate anion chemo sensor

All living cells contain phosphate anions and its relevant derivatives, which play an important role in a range of biological activities. Phosphate anions are used by the biological system as bioactive entities in interacting and reacting with other biomolecules, as well as a crucial structural component in anchoring biomaterial units through phosphodiester linkages. A promising analytical technique for analyzing phosphate-related biological processes is a molecule-based fluorescence chemo sensor. This is a simple and adaptable approach that allows for on-time or real-time monitoring of phosphorylated biological molecules in biological contexts with high sensitivity and quick reaction time. As a result, phosphorylated biomolecule-targeting artificial receptors and chemo sensors have attracted a lot of attention.

The strong binding sensitivities or excellent sensing capabilities of a dimeric Zn(II)–DPA complex have been used to construct and characterize it as a universal protein complex for phosphate anion analogs (Ishida et al., 2009). The phosphatase, kinase, and glycosyltransferase processes, as well as a phosphoprotein–protein interfacial surface inhibition assay, have been successfully developed using this complex. A new fluorescent phosphorylated peptide chemo sensor consisting of a rigid *trans*-4,40diazastilbene and two Zn(II)-DPA units selectively binds to a bis-phosphorylated peptide sequence and shows with dual fluorescence alteration (Roy et al., 2011). The simple but rigid molecular design of Zn(II), which entails straight conjugation of the Zn(II)-DPA sites to the stiff fluorophore with limited structural flexibility, enabling this sensing selectivity and signal change. To make two mononuclear Zn(II) and Cu(II) complexes, a DPA ligand was molded onto a naphthol analog of a push-pull fluorophore (Mito-oka et al., 2001). Each of these complexes exhibits a little degree of fluorescence, but it is only activated when pyrophosphate and other anions such as phosphate are present. In an aqueous solution, the zinc and copper complexes selectively detect Pyrophosphate (PPi) beyond ATP.

Due to many implications for peptide sensing and medicinal application, synthetic sensors for biologically active peptides are being actively devoted to the development of contemporary molecular recognition chemistry. A technique for creating artificial peptide receptors. Artificial receptors that may

precisely bind a peptide/protein interface to limit or enhance function must be produced on a surface in an aqueous solution. A flexible dinuclear Zn (DPA) complex has been created, which contains a molecular motif for binding peptides via two histidine at certain locations (Jeong et al., 2018). It is the first illustration of manufactured receptors that may selectively bind peptides with two histidine in the distance of two or three-helix pitches in an aqueous solution. This motif can be combined with other binding motifs to create artificial receptors that are more specific and efficient when it comes to a certain peptide or protein.

The influence of the metal ion on the degradation of organophosphorus compounds in metal-DPA complexes shows that this is a pseudo-first-order kinetics process. Dipicolylamine complexes of Cu(II), Co(II), Zn(II), Fe(II), and Ni(II) have been studied for its ability to degrade diisopropyl fluorophosphate, a nerve intriguing component for surrogate molecules.(Jeong et al., 2018). The reaction kinetics of the Cu(II)DPA complex were the fastest, whereas Zn(II)DPA and Ni(II)DPA were the slowest. Theoretical calculations and Fluorescence Minus One (FMO) tests of mediator nucleophilicities were utilized to explain reactivity trends, confirming the important influence of metal ions on hydrolysis kinetics. Inspections associated with academic ideational research provide a useful foundation for designing and forecasting the performance of innovative transition metal-organic ligand complexes as an accelerator for decomposition and cytotoxicity reduction of organophosphorus nerve medicines.

4. Conclusion

In conclusion, metal-dipicolylamine complexes are formed and described in a wide range of structural variety due to the multiple coordination mechanisms of transition metals and the large range of dipicolylamine ligand derivatives that are synthetically accessible. In theory, high flexibility, high conjugation, and substitutional inertness can be used to create a wide range of forms, physicochemical properties, and reactivities, all of which can be tweaked to increase the therapeutic and diagnostic effectiveness of this class of molecules.

In the search for connections among magnetic, spectroscopic, structural, and coordination geometries, DPA-containing metal complexes have gotten a lot of interest. Several mononuclear metal-DPA complex crystal structures with four, five, or six coordinated metal centers have been synthesized and described as a result of this interest. The coordination geometries of the metals Pt, Re, Zn, and Cu were reviewed. In comparison to the coordination number of metal centers, bond lengths, and bonding nature, unique structural characteristics and coordination geometries have been addressed.

DPA derivatized ligand-associated metal complexes have been synthesized and utilized as prospective therapeutic agents for malignancies, microbial and fungal inflammations, and as potential diagnostic agents for fluorescence imaging and radiopharmaceuticals. Due to the capacity to arrange ligands in a three-dimensional form, metal-containing complexes have benefits over traditional carbon-based molecules. This allows for group functionalization that is customized to a certain molecular target. Transition metals with partially filled *d* orbitals have interesting electronic properties that can be used as a probe in the design of anticancer agents. In recent years, polypyridyl ligand families related to organometallic complexes, which have been complexed with rhenium, rhodium, platinum, zinc, and copper, have been used *in vivo* fluorescent cell imaging. These compounds all have the proper photophysical characteristics for intracellular excitation and detection of sufficient biological compatibility and luminescence tunability. Fluorescence chemo sensor-based sensing systems are reported to be promising analytical appliances for studying phosphate-related biological processes. Several versatile metal-DPA complexes have been reported to be potential chemo sensors. All these findings

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suggest that there is still more to be explored in this research niche as metal-DPA complexes shed some light on synthesizing and developing novel therapeutic and diagnostic agents in the biomedical field.

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