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Physiological and Biological phenomena of Mixed Ligand Transition Metal Complexes: A Review

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Abstract:

A coordination compound that has two or more dissimilar type of ligands attached to the central metal atom or ion which is termed as mixed ligand complex or heteroleptic complex. The complex is made up of several ligands with varied chemical identities bound to a metal center. A vast array of features are feasible for these complexes. Due to the general combination of interrelated ligands, these complexes display key traits like higher electronic properties, enhanced catalytic efficiency with greater bioactivity. As these complexes seem to be the significant category of coordination compounds, they have been implicated in various fields. Owing to the chelate effect, the chemistry of certain ligands and lipophilicity of the mixed-ligand complexes they have good activity of biological systems. These complexes have diverse bioactivites such as antibacterial activity, antitubercular activity, antimalarial activity, antifungal activity, anti-inflammatory and analgesic activity, antioxidant activity, anticancer activity and antidiabetic activity.

Keywords: Mixed-ligand complex, chelate effect, lipophilicity, bioactivity.

INTRODUCTION:

In contrast to conventional complexes, mixed ligand complexes consist of a minimum of two distinct ligand types connected to a single metal ion within the complex. The probability of a complex deviating from its predicted features increases when multiple ligand types are present. This sparks the researchers curiosity in creating mixed ligand complexes because of their structural variation that play an integral role in biological systems[1]. Due to the mixed chelation, these complexes form unique structure to connect the diffusion and conservation of active ingredients across membranes[2]. The relevance of synthesizing and characterizing complexes continues to expand frequently. Therefore, it had been amply proven the fact that certain complexes are biologically effective against a range of harmful bacteria[3,4].

Mixed ligand complexes were indeed employed as replicas of metallo enzymes. Additionally, they stimulate enzymes and implemented in transportation and storage of active substances[5]. Those metal ions attached with the ligands hold a crucial position in the biological process[6,7.] Since all such complexes come under the significant category in aspects of organometallic compounds, it was generally applied for the assessment of biological properties[8]. The challenge has drawn the lay emphasis of researchers owing to the numerous possibilities in the medical field[9,10]. The bioactivities and inhibitory action of the mixed-ligand complexes will be explored in this review.

Biological phenomena of Mixed ligand complexes:

Antimicrobial activity:

The antimicrobial characteristics of mixed ligand complexes encompassing antibacterial and antituberculosis showed enhancement in activity.

Antibacterial activity:

The complex with mixed ligands of 4-(Benzeneazo)salicylaldehyde and 2-amino-4-nitrophenol (See 1.1, Fig 1) demonstrated antibacterial action in opposition to the range of bacterial pathogens. .With an inhibitory zone

ranging in diameter from 18 to 24 mm, the Cu(II) complex demonstrated impactful wide ranging action in opposition to Bacillus subtilis, Pseudomonas aeroginosa, Staphylococcus aureus and Escherichia coli. The bacterial lawn plate utilized for the comparison analysis showed the zone diameter represented percentage inhibition when positive control tetracycline was employed. There was no distinctive inhibitory effect against most of negative control of the pathogen tested[11]. The antibacterial resistance feature of gram positive/gram negative bacterial species were conducted out for palladium metal(II) ofloxacin drug and amino acid protein ligands (See 1.2,1.3,1.4, Fig 1) The palladium complexes illustrated significantly increased level against Klebsiella and Escherichia coli[12]. The enhanced antimicrobial activity of palladium complexes against the bacterial strain is imputable to the concept of chelation. The subsequent sharing of positive charges throughout the ligands and the metals, along with the potential of π-electron delocalization through the formation of a more lipophilic metal complex that makes the system for accurate penenetration of the lipid coating for the microorganisms[13].

Oxovanadium(IV) complex of 8-hydroxy quinoline and 3-acetyl-6-methyl-2H-pyran-2,4,(3H)-dione (See 1.5, Fig 1) was screened for the antibacterial effectiveness against E.coli (MTCC16799) and S.pyogenes (MTCC1925) at a concentration of 300-µg cm^3 in DMSO by the agar well diffusion method. The complex is less active against E.coli but shows considerable activity against S. pyogenes in comparison with the drug[14].

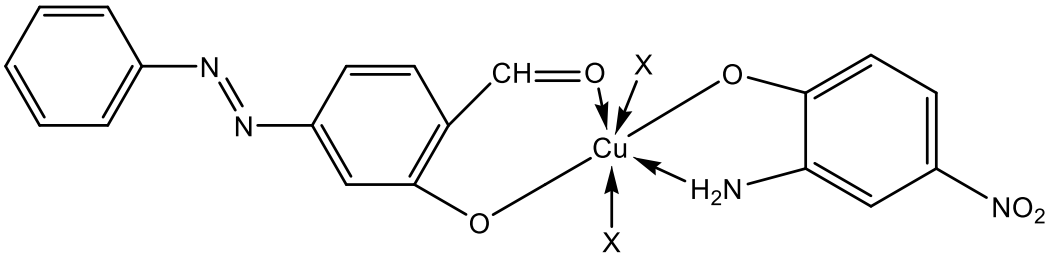
Complexes of Ni(II) with triphenyl phosphine (pph_3), imidazole, 4-picoline and bipyridine containing 4-(p-phenyl)thiosemicarbazones of salicylaldehyde have been assessed in comparison to E.coli and the complex containing imidazole (See 1.6, Fig 1) was observed to be most intensive[15]. The anti bacterial activities of Zn(II) complexes of 2-acetylpyridine-4-phenylsemicarbazone and N and S containing hetero ligands such as thiophene, pyridine, picoline, aniline and ammonia were evaluated against S. aureus, and B. anthracis. The most active complexes were thiophene and aniline[16].

The mixed ligands of 2,6-pyrimidinedicarboxaldehydebis(o-hydroxyphenylimine), 2,6-pyridinedicarboxaldehydebis(p-hydroxyphenylimine) and 2-aminopyridine with Ni(II) and Zn(II) metal ions showed moderate activity towards Pseudomonas aeroginosa similar to that of Ampicillin antibiotic[17]. The more electron donating group (OMe) of the [RuCl(CO)($C_{17}H_{16}ON$)(py)(pph_3)] complex showed higher inhibition action against E.coli and Salmonella typhi of 1% and 2% DMSO solution in potato dextrose agar medium. Elevation in the accumulation of the compounds increases the inhibition activity[18]. This is consistent with Tweedy's theory of chelation, which states that partial sharing of the positive charge and potential π-electro delocalization throughout the entire ring are the main justifications of the decrease in chelation with the mutual opposition of the metal atom. This enhances the lipophilic depiction of the metal chelates, which enables them to more easily infiltrate the lipid folds of the bacterial membranes[19]. The copper complex with mixed bipyridine and phenanthroline (See 1.7, Fig 1) showed increasing activity as attributed to the free metal ion. The complexes with mixed ligands represented greater antibacterial activity contrasted to the uncoordinated ligand and free metal ion and hence they are more potent antimicrobial agents[20,21]. The mixed ligands of ciprofloxacin and 4'-(4-benzyloxyphenyl)-2,2':6',2"- terpyridine with Copper chloride (See 1.8, Fig 1) exhibited more activity against E. coli, P. aeruginosa, S. marcescens, B. subtilis and S. aureus and the MIC data of these complexes featured that the Cu complex had absolute capacity than ciprofloxacin[22]. The good antimicrobial activity was examined with the chelate effect, aspect of the ligands, the total charge of the complex, the aspect of the ion neutralizing the ionic complex, the nuclearity concerning the metal center in the complex[23,24].

The isatin monohydrazone with 2-hydroxynapthaldehyde and 8-hydroxy quinoline as primary and secondary ligands (See 1.9, Fig 1) combined with the copper metal displayed maximum inhibitory zone of 24 mm limiting the expansion of P. medocina with MIC of 3.12 µg/mL. The variability concerning the effectiveness of distinct biocidal entities against diverse species is interdependent upon the impermeability of the cell, metal ion size and dipole moment, which may change as a potential outcome of metal ion presence[25]. The

Copper complex of imino-oxalato mixed ligands (See 1.10, Fig 1) exhibited higher antimicrobial efficacy in comparison to Cobalt, Nickel and Zinc complexes and have MIC values of 1.7-2.8 µg/mL and it may be contributed as a outcome of the atomic radius and the electronegativity of Cu(II) ion[26]. Larger atomic radii and higher electronegativity reduce the effective positive charges on the metal complex molecules, facilitating their interaction with the charged particle and extremely sensitive biological membranes[27].

Novel Mn(III) mixed ligand complexes of ciprofloxacin with various bis-pyrazolone based bidentate ligands (See 1.11, Fig 1) possess increase in cell permeability and hence they are more potent bacteriostatics. Only lipid soluble substances may passs through the lipid membrane that envelops the cell and liposolubility is anticipated to be a key element in regulating antimicrobial action[28]. The overtone concept suggests that the chelation reduces the core atom's polarity mostly due to potential electron delocalization along the whole chelation ring and partial positive charge sharing with the contributing groups and this makes the core manganese atom to be lipophilic, which facilitates its penetration of the lipid folds of the cell membrane[29,30.]



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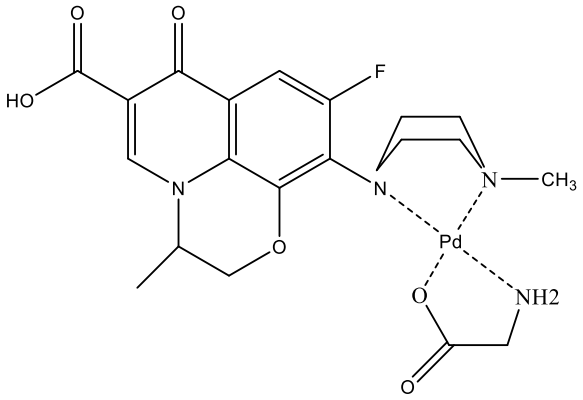

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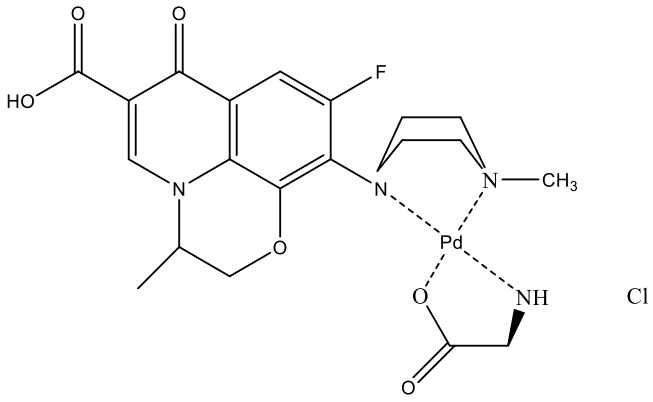

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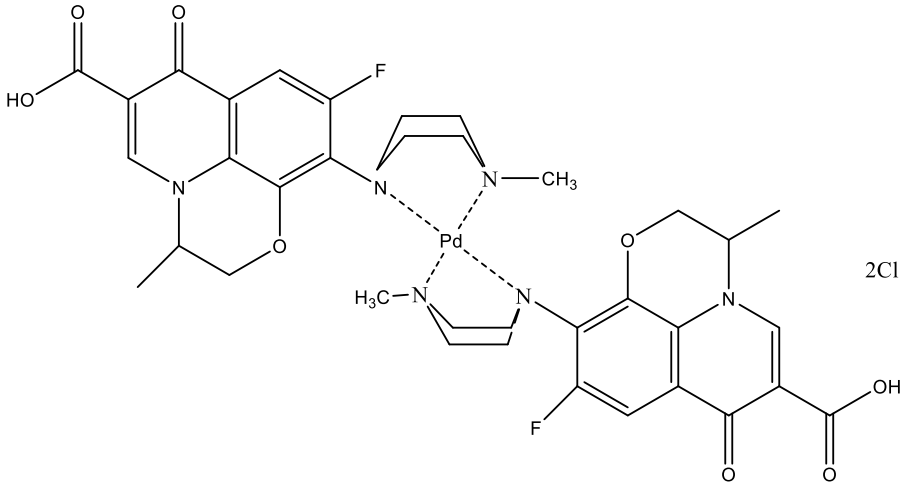

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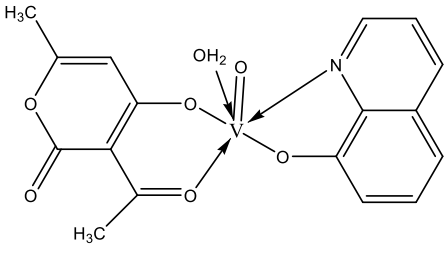

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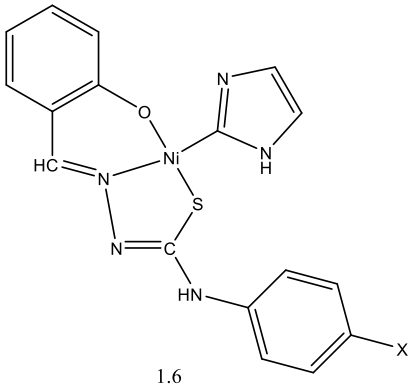

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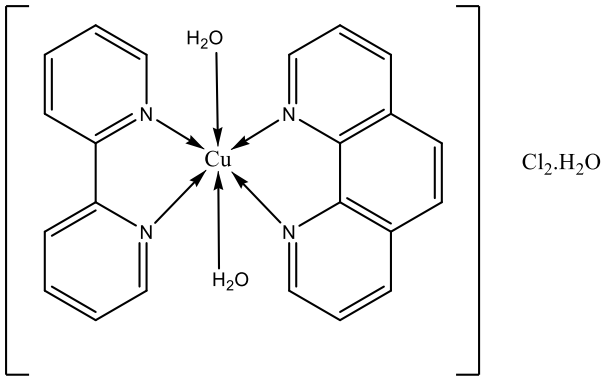
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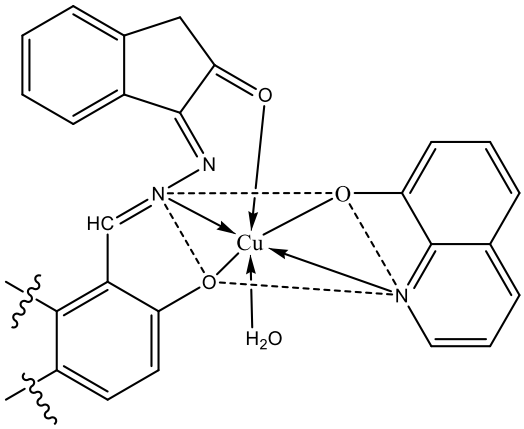
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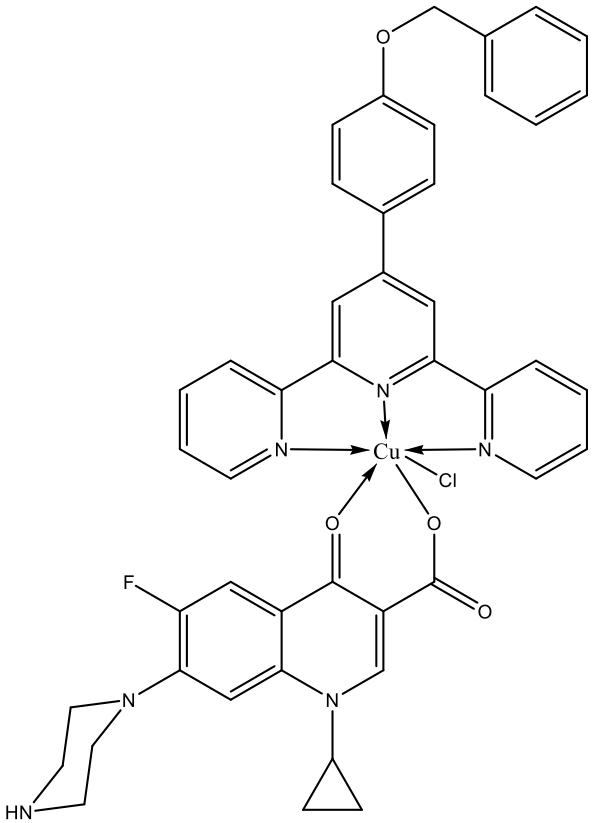
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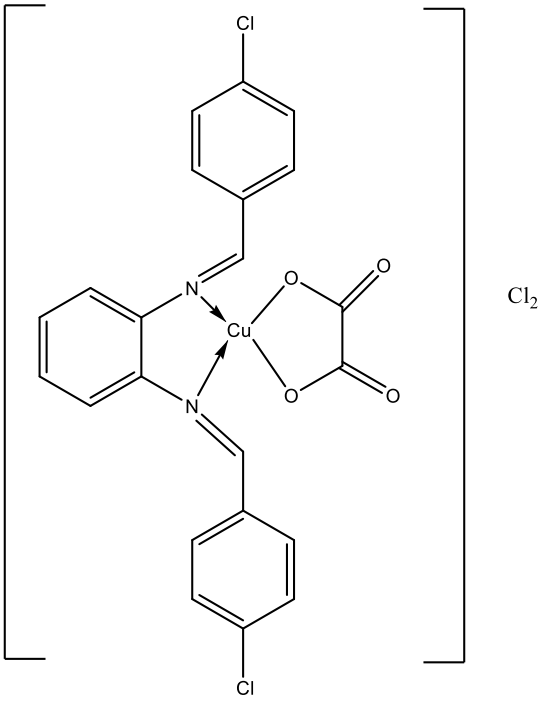
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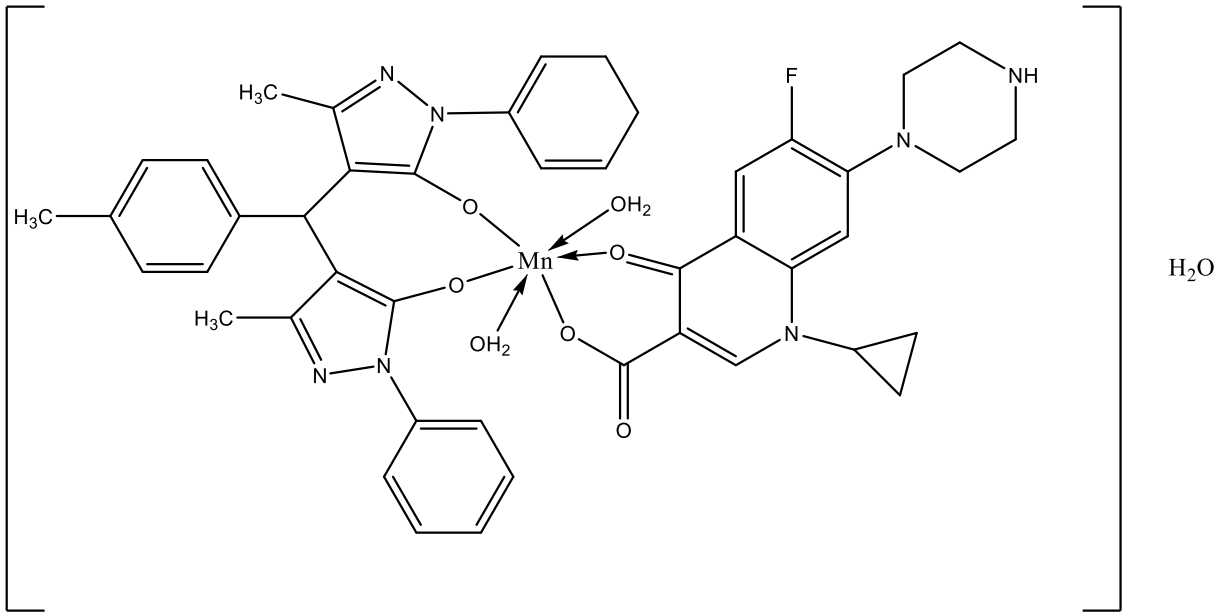

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Fig 1: Antibacterial activity of transition metal complexes.

Antitubercular activity:

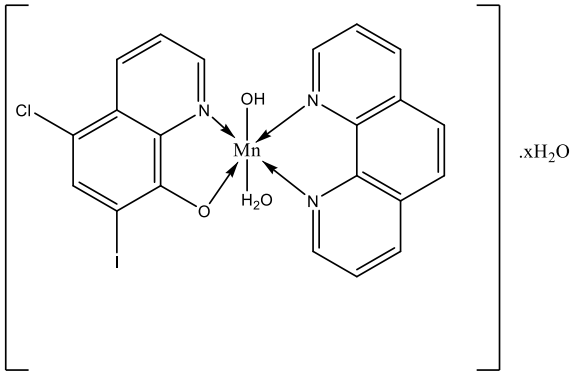
Latent tuberculosis, also known as non replicating Mycobacterium tuberculosis, is more resistant to most anti tuberculosis medications than replicating TB and necessitates a longer course of treatment[31].

It was found that 5-chloro-7-iodo-8-hydroxy quinoline metal complexes displayed anti tubercular activity. In particular, many derivatives of mixed ligand complexes are indeed developed and examined for the anti tubercular property. The complex interconnected with metal ions embracing 1,10-phenanthroline and 5-chloro-7-iodo-8-hydroxy quinoline as ligands. The Mn(II) complex (See 2.1, Fig 2) had equivalent MIC values of 45μg/mL and 40 μg/mL to the conventional medicine rifampicin, against tuberculosis (TB) (MTCC200). On the other hand, the Co(II) complex (See 2.2, Fig 2) shown more potent activity, with a MIC that was 6.4 times lower than that of rifampicin. Based on this study, metal complexes and free ligands have more antitubercular efficacy than metal salts[32].

The silver(I) complex of thiosemicarbazide, 2-(propan-2-ylidene)hydrazinecarbothioamide and thiazolidine-2-thione shows better activity against M. tuberculosis when compared with the second-line drugs of tuberculosis[33]. The clioquinol with (E)-2-(3-(4-chlorophenyl)acryloyl)-3H-benzo[f]chromen-3-one as primary and secondary ligands with Cu(II) complex (See 2.3,2.4,2.5 Fig 2) have shown enhancement in activity with MIC of 3.125 μg mL^{-1} was emerged as the most promising anti-tubercular element due to its superior action especially compared to streptomycin[34].

Vanadium complexes like [$V^{V}O$(L-pheolnaph-im)(5-Cl-8HQ)], [$V^{V}O$(OMe)$(8HQ)^{2}$] and [$V^{IV}O$(pic)(8HQ)] (See 2.6,2.7,2.8, Fig 2) are more active than the currently used drugs such as p-aminosalicylic acid (0.5-2.0 μg/mL), ethinamide (0.63-1.25 μg/mL), gentamicin (2.0-4.0 μg/mL), ethambutol (0.94-1.88 μg/mL).

tobramycin (4.0-8.0 µg/mL), clarithromycin (8.0-16 µg/mL) in comparison with the molar basis[35]. Mixed ligand Cu(II) complexes (See 2.9, Fig 2) based on bromo-coumarins with clioquinol has an enhancement of activity and it showed that the complexation of ligand with Cu(II) metals has doubled its activity[36].



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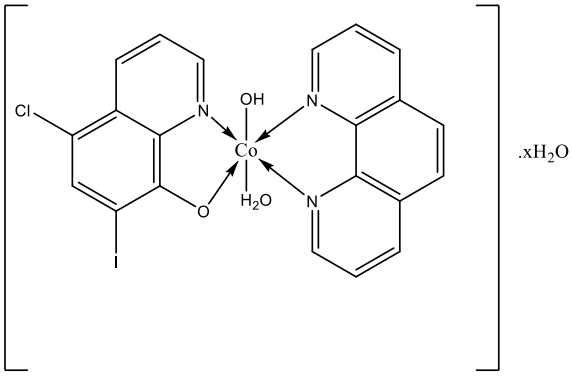

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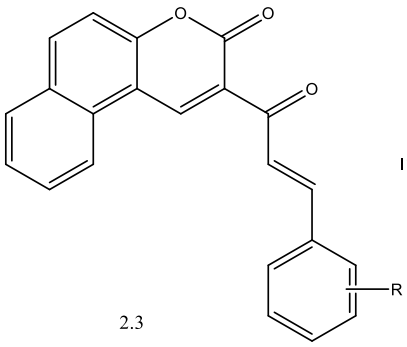

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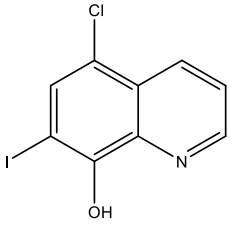

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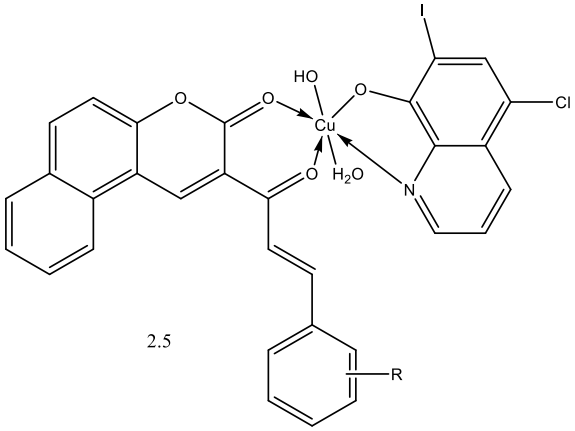

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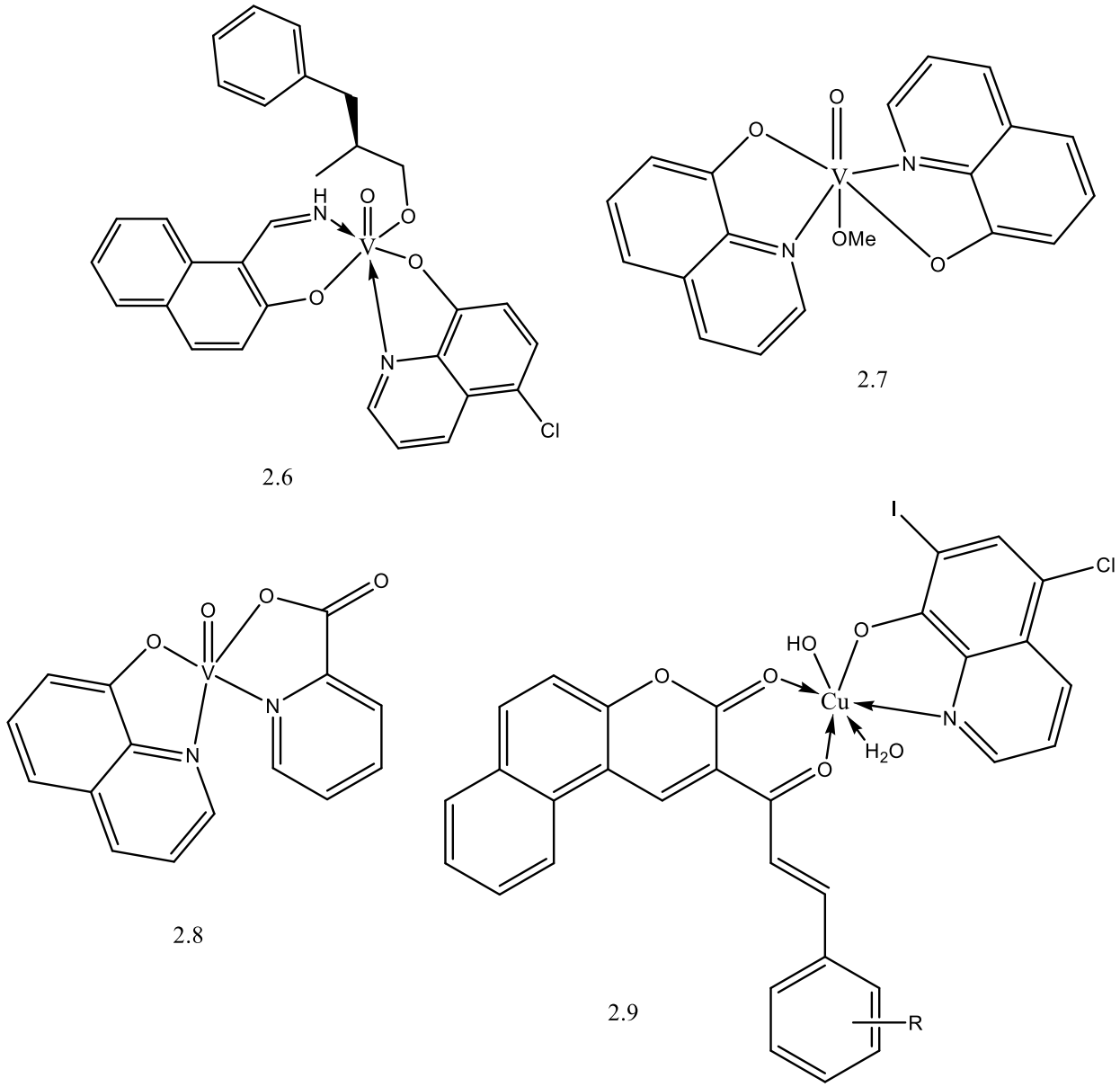


Fig 2: Anti-tubercular activity of Manganese, Cobalt, Vanadium and Copper complexes.

Antiparasitic activity:

The persistence of parasitic illness as a highly prevalent concern was attributed to the growing resistance to be readily accessible complexes which were applied for preventing the growth of the parasites.

Antimalarial activity:

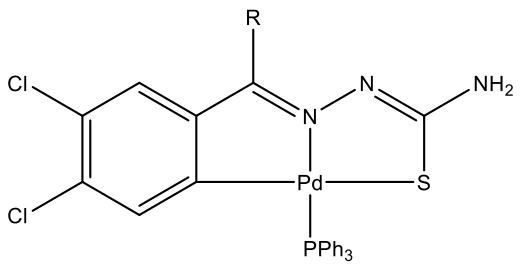
Globally, Malaria was regarded as a potentially fatal infectious disease[37]. Mixed-ligand complexes were highly useful in treating malarial disease. The chelating capacity of the compounds was shown to be closely related to their capacity for limiting the proliferation of Plasmodium falciparum[38].

It was identified that the mixed ligand complexes of melfloquine hydrochloride and chloroquine phosphate with cobalt(II) and Iron(II) would be a better therapeutic drug for malaria. This can be explained by testing the complexes with mixed ligands and their outcomes were shown as in comparison with the

control, the serum ALP activities significantly ($p<0.05$) increased when represented with fluoxetine, chloroquine and $[Ni(Mef)(CQ)]Cl_3$, but the activities of the $[Co(Mef)(CQ)]Cl_2$ and $[Fe (Mef)(CQ)]Cl_3$ groups decreased. In conversely to such control group, kidney ALP activity considerably higher in the $[Co(Mef)(CQ)]Cl_2$ therapeutic group and decreased ($p<0.05$) in the mefloqine and chloroquine therapeutic groups. Hence the mixed ligand complexes $[Co(Mef)(CQ)]Cl_2$ and $[Fe(Mef)(CQ)]Cl_3$ can be utilized as a therapeutic drug for malaria[39].

The Palladium complex (See 3.1,3.2, Fig 3) was tested against 3D7 (chloroquine-sensitive) and K1 (chloroquine and pyrimethamine resistant) P. falciparum strains. The mixed ligand complex of Pd(II) exhibited greater activity in the treatment of malaria[40]. The lowest minimal concentration of 0.11 μM/L was obtained for zinc complex of 4-acyl pyrazolones (See 3.3,3.4,3.5, Fig 3) against P. falciparum[41]. The synthesis of hemozoin, also known as β-hematin was a distinct process that Plasmodium species uses to detoxify free heme. The majority of well known antimalarial medications currently in use have confirmed this target and it was assumed be an ideal location to target potential antimalarial medications[42].

Numerous recent studies have offered proof for a quantitative relationship between the strength of β-hematin formation and antiparasitic activity against the malarial parasite Plasmodium falciparum[43-46]. The efficiency of $[Zn(nap)_2(2\text{-ampy})_2]$ (See 3.6,3.7,3.8, Fig 3) in averting the development of β-Hematin was 75% with the range of concentration between 1-0.6 mg/ml[47]. Platinum(II) complexes of 2,2'-bipyridyl and 1,10-phenanthroline benzoylthiourea inhibit β-hematin development heavily and hence it will comprise the secondary family of platinum antiplasmodials[48]. The cytotoxic effects of $[Ag_2(dppf)(3\text{-benzyl-}1,3\text{-thiazolidine-}2\text{-thione})_2].(NO_3)_2$ complex was assessed to determine the selectivity index to biological activity(SI) and the antiplasmodial activities of the complexes were considered to be specific and safe when the SI was more than 10[49,50]. Due to the highest SI value(more than 12.4) the silver complex can be used for the emergence of antimalarial drug[51].



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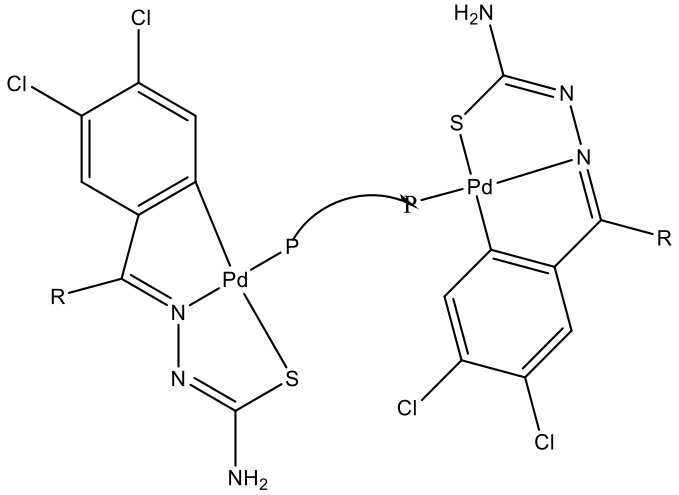

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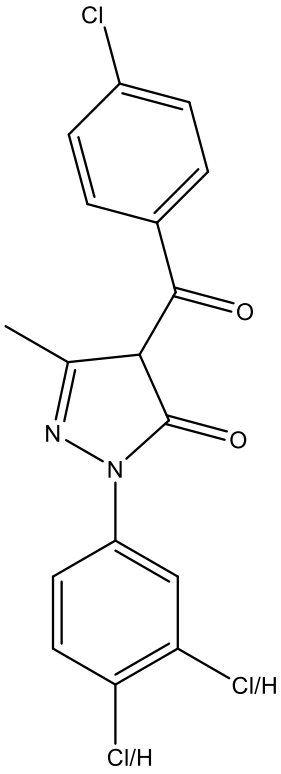

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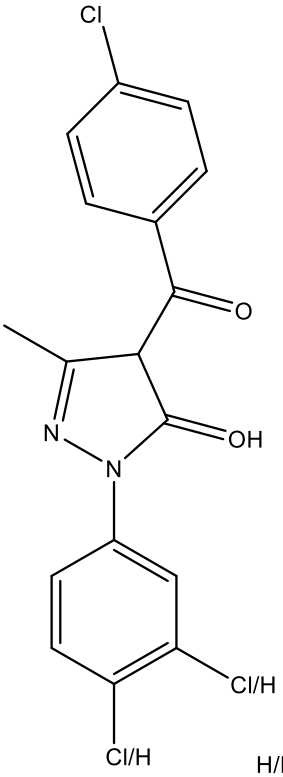

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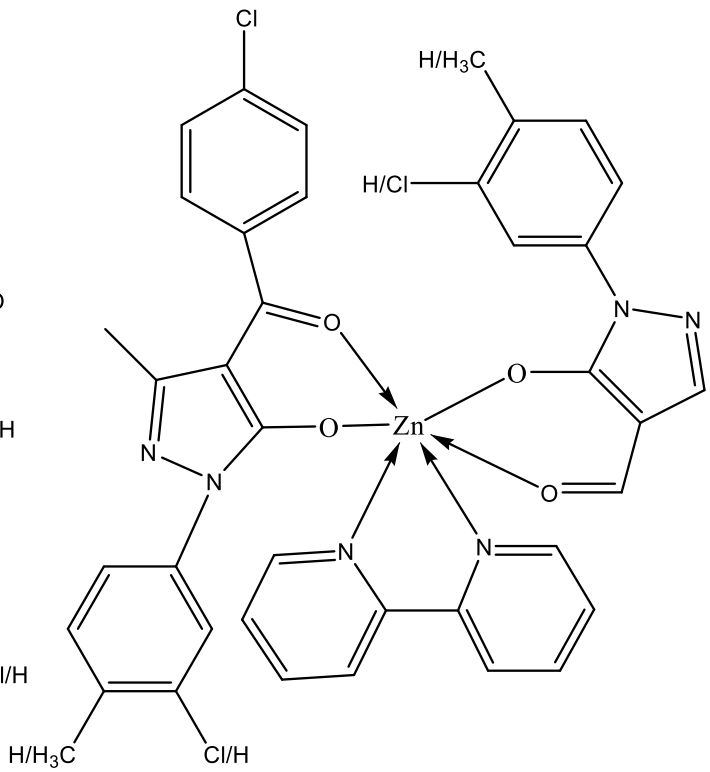

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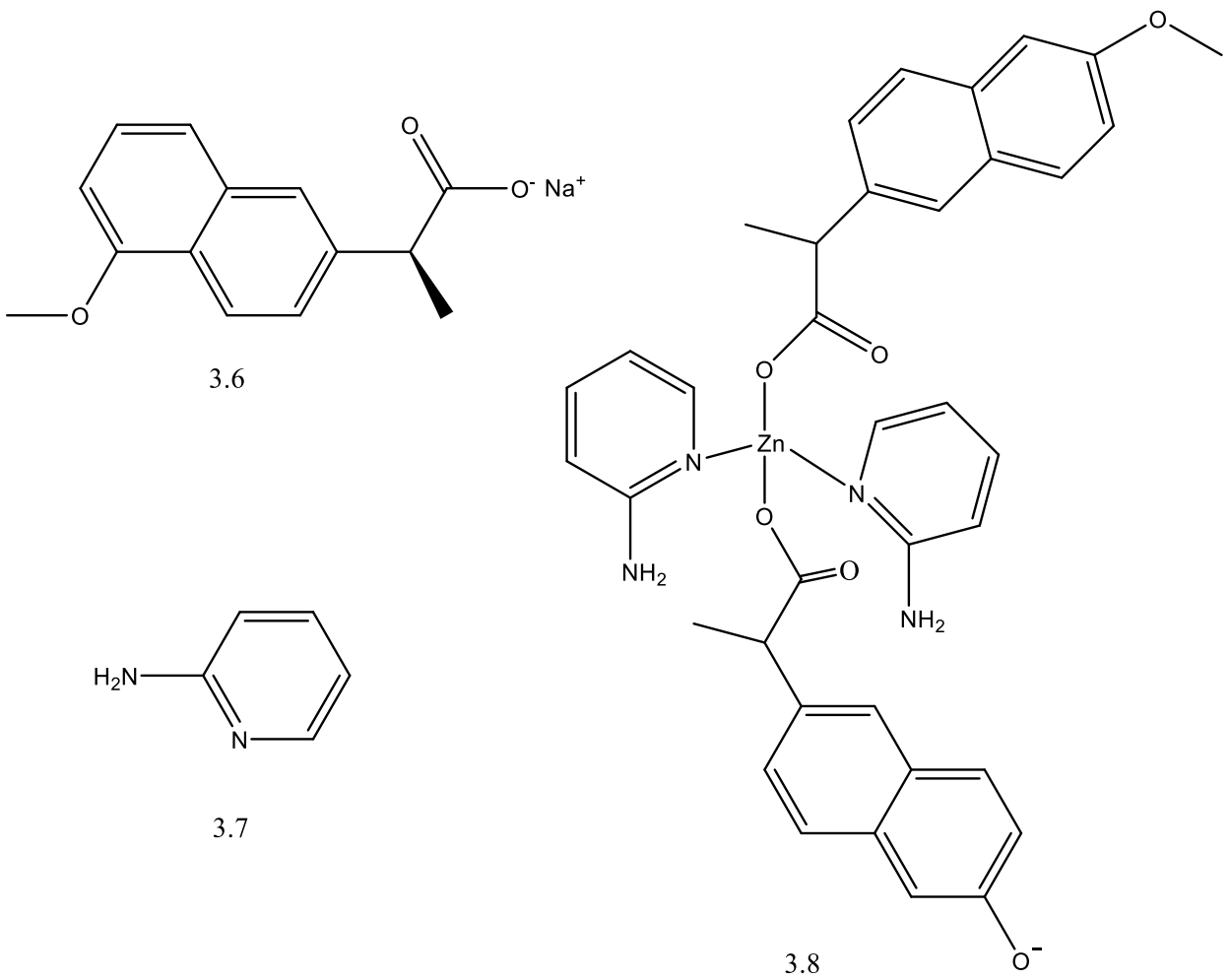


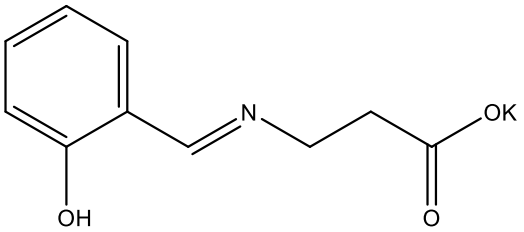
Fig 3: Antimalarial activity of transition metal complexes with its mixed ligands.

Antifungal activity:

Mixed ligand complexes had been shown to exhibit greater fungal toxicity compared to their initial organic component(ligand). According to reports, the antifungal action can be significantly associated to the chelation of chemicals[52]. Antifungal action is not just dependent on chelation rather it is a complex combination of various parameters including the kind of metal and ligand, the morphology of the metal compounds, lipophilicity, the availability of co-ligands, steric interactions and pharmacological components[53]. The metal complexes of fluoroquinolone drug enrofloxacin and glycine containing ligands (See 4.1,4.2,4.3, Fig 4) were evaluated against C. albicans and the sequence of activity is greater for Nickel than Chromium and Copper, through blocking the active sites of the microorganisms, the greater antifungal activity of the mixed ligand complexes prevents the microbes from taking the average[54].

The coordination complexes of 2-hydroxyacetophenone with L-Tyrosine and 4-dimethylaminobenzaldehyde with 2,4-dinitrophenylhydrazine of Fe(III) displayed significant antifungal activity compared to certain complexes when resolved with A. niger, A. flavus, A. alternate and R. stolonifer (See 4.4,4.5,4.6, Fig 4)[55]. The antifungal activities of Mn(III) of mixed ligand complexes were investigated against C. herbarium and A. flavus. In comparison to the complexes using the standard drug fluconazole, $[Mn(acac)_2(NCS)SH_2]$ displayed the maximum percentage of suppression against these fungal strains. This high antifungal activity is described

in view of the existence of thiocyanato group[56]. The other complexes $[Mn(acac)_2(Cl)SH_2]$, $[Mn(acac)_2(Br)SH_2]$ and $[Mn(acac)_2(N_3)SH_2]$ showed 49%, 50% and 52% preventing mycelial growth in opposition to C. herbarium respectively[57].



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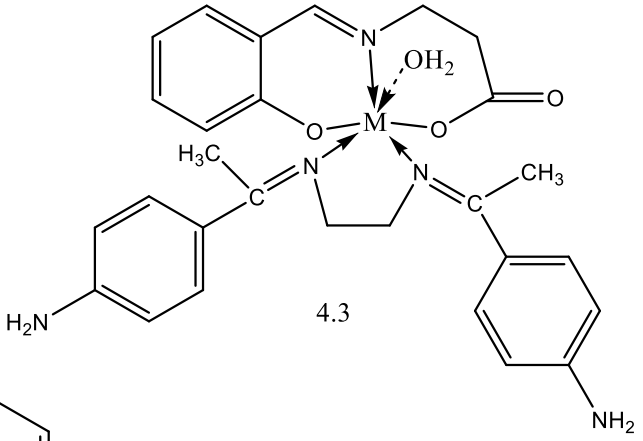

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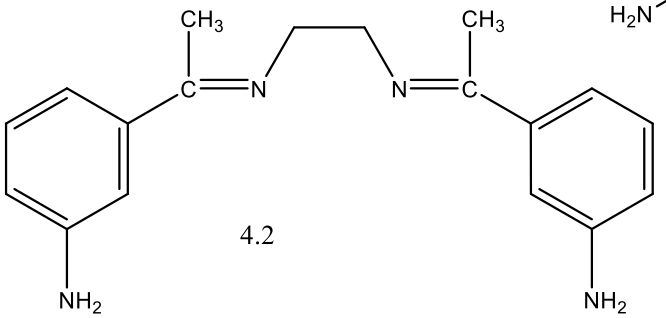

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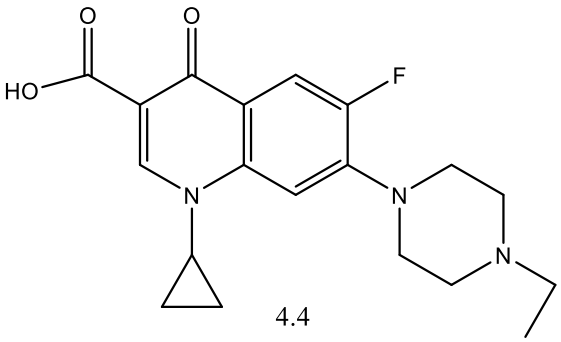

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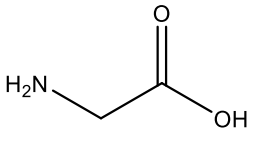

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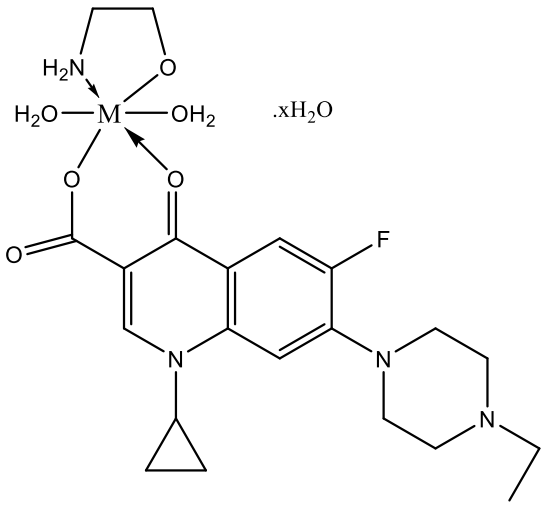


4.6

Fig 4: Antifungal activities of mixed ligands and its metal complexes.

Antioxidant activity:

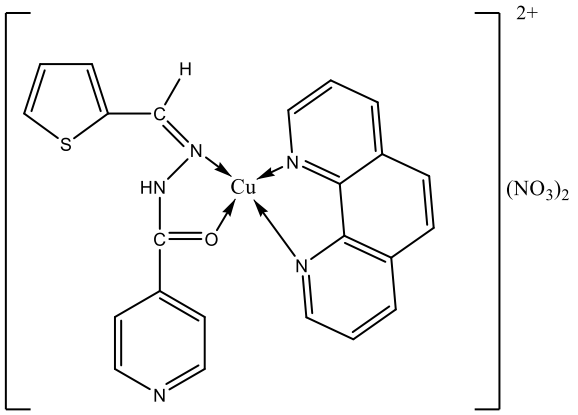
Numerous biochemical reactions occur constantly in our bodies, leading to the creation of different types of biomolecules. Some extremely reactive and perhaps harmful chemical compounds, including as superoxide anions even so hydrogen peroxide had been devised among these beneficial moieties[58]. Some serious chronic diseases such as cancer, coronary heart disease, etc can be caused by these reactive oxygen species(ROS) by changing the structure of lipids, fats, proteins and various biomolecules[59]. To lead a healthy life these ROS are trapped by some natural antioxidants within the body but that could be artificially incorporated by synthetic drugs. There are variety of mixed ligand complexes synthesized in the laboratory act as antioxidants to prevent these free radicals.

The free radical molecule 2,2- diphenyl-1-picryl hydrazyl (DPPH), and butylated hydroxytoluene(BHT) as a standard were utilized to test the antioxidant action of the mixed ligand metal complexes of IsonicotinamidoThiophene-2-Carbaldimine and 1,10-phenanthroline with Cu(II), Ni(II) and Zn(II) ions (See 5.1,5.2,5.3, Fig 5). When DPPH, which is violet in color was dissolved in DMF, it turned pale[60]. According to the findings, all the metal complexes had scavenging of DPPH radical which was moderately high. In comparison to the conventional BHT, Cu(II) complexes displayed the highest antioxidant activity of all the investigated substances, surpassing Ni(II) and Zn(II) complexes[61].

Schiff base complexes exhibit variable antioxidant activity, which becomes partly related to their coordination environment and redox properties[62]. Typically, the degree of chelate ring unsaturation, axial ligation and ring size each impact the redox characteristics of the metal complexes[63]. The high reducing capacity of Cu^{2+} and its proton donation feature, where Cu^{2+} focused as a super oxide scavenging center, are listed to the Cu(II) complexes (See 5.4, Fig 5) beneficial antioxidant activity as opposed to other developed complexes. The moderate antioxidant action of Ni(II) complexes (See 5.5, Fig 5) may have emerged as a consequence of geometric structure-induced steric hindrance, which prevented DPPH from approaching active complex centers in a radical manner. Moreover, Zn(II) has less activity since it is most likely not a transition metal and cannot take part in electron transfer reactions[64].

The mixed ligand complex of Quercetin and Aspartic Acid with Cobalt(II) exhibited greater antioxidant activity due to the considerable change in the chemical properties of Co(II) metal ion. In reaction of quarcetin to DPPH radical, a H atom is abstracted from the $[CoQAA(H_2O)_2]$ to give a semiquinone complex (See 5.6, Fig 5) which is stabilized by the metallic center and by conjugation with the 3-OH group[65]. The complexed quercetin have increased antioxidant activity as appealed to the uncomplexed metals due to the decline in the oxidation potential of metal complexation with flavonoids[66].

SOD is a well known and most useful antioxidant enzymes which is known for its conversion of superoxide into H_2O_2 and oxygen[67]. The results for the antioxidant action of the mixed ligand complexes using 8-HQ, 5-iodouracil and 5-nitrouracil as ligands showed that the 5-iodouracil-Mn-8HQ complex exerted the highest activity with a IC_{50} of about 3-fold less compared to those pertaining the free ligand 8-HQ. Hence, it was proved that perhaps the advancement of SOD activity is mainly because of the coordination of metal into the free ligand[68].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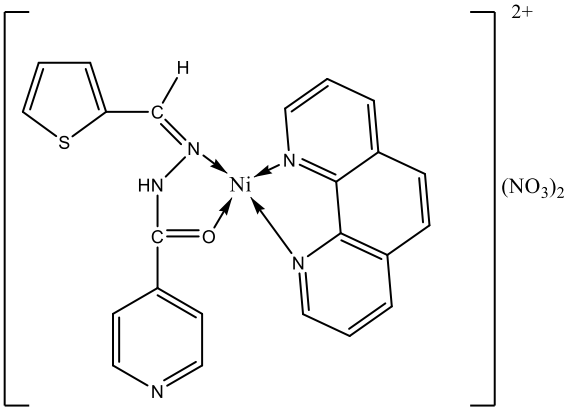
H
C
S
N
HN
Cu
N
C
O
N
N
(NO3)2

5.1


2+
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Ni
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C
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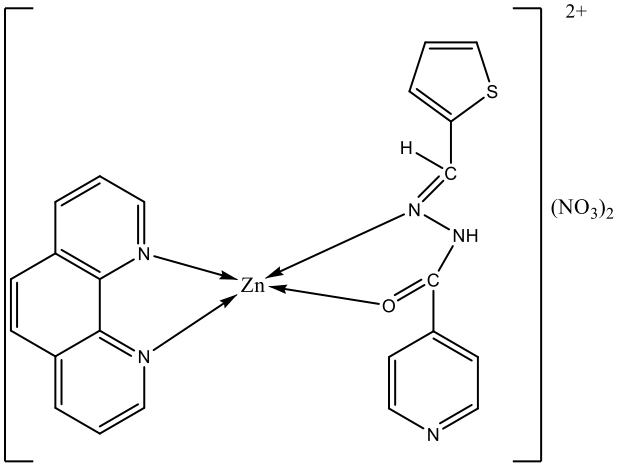
5.2


2+
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H
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N
NH
N
Zn
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C
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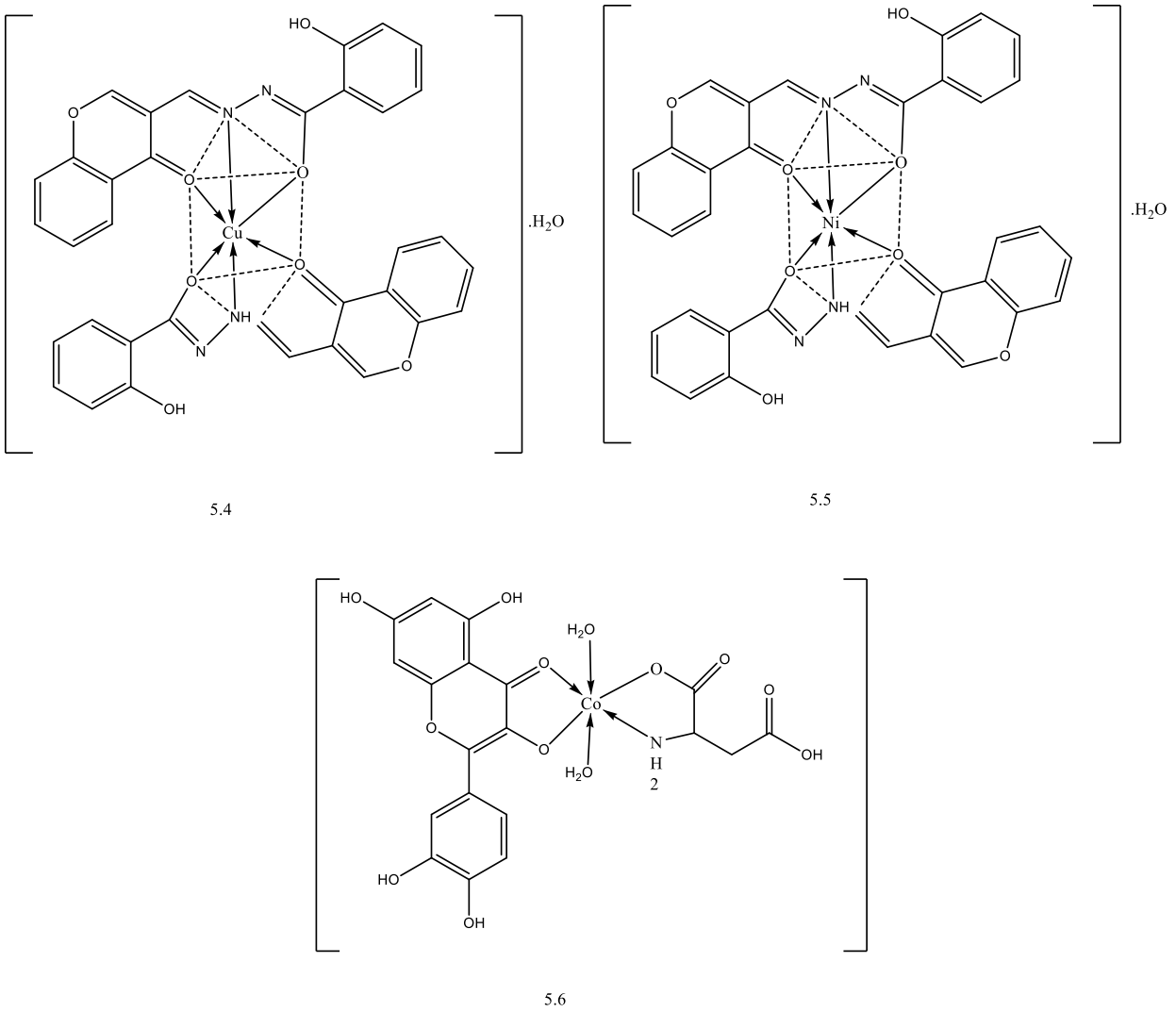
N
(NO3)2

5.3



5.4 5.5 5.6

Fig 5: Antioxidant activity of Copper, Nickel, Zinc and cobalt complexes.

Anti-inflammatory and analgesic activity:

The implications of non-steroidal anti-inflammatory drugs(NSAIDS) are widely varied. Furthermore, there were also speculations that some of these variations in tolerability and efficacy are caused by variations in their physicochemical aspects, although this can manage their distribution throughout the body and their capacity to penetrate and enter the interior of membranes[69]. Histamin and serotonin mediate the initial phase of the inflammatory response, kinins and prostaglandins mediate the second phase[70]. The rat paw is injected with carrageenan to release bradykinin, which then triggers the building of prostalglandlin and other autacoids, which are in charge of creating the inflammatory exudate[71]. Hence, it is mandatory that the prostaglandin synthesis may be related to the manner in which the compounds as described for the anti-inflammatory mechanism of potassium diclofenac in the inhibition of the inflammatory process induced by carrageenan[72]. Therefore, Pd(II) complexes with organophosphines and dithiocarbamates derivatives of α-amino acids($C_{31}H_{36}ClNPPdS_2$) (See 6.1,6.2,6.3,6.4,6.5,6.6, Fig 6) was compared with the standard drug Diclofenac at 10mg kg^{-1}, which inhibited the odema by 74% after 4hrs as a more potent anti-inflammatory

complex[73].The mixed-ligand complexes of Diclofenac and acetaminophen were interrogated for in-vitro anti-inflammatory activity using protein denaturation by egg albumin assay. The Cu complex has 45.17% inhibition when compared to 58.24% for diclofenac potassium salt (standard) all at a concentration of 200 ppm[74]. The ternary complexes anti-inflammatory properties suggested a modest reduction of the denaturation of bovine serum albumin. In comparison with the reference medication, [Ni(PLTSC)(gly-tyr)] (See 6.7, Fig 6) was the complex with the greatest inhibitory effectiveness of the complexes involving Pyridoxalthiosemicarbazone and dipeptides[75]. The anti-inflammatory activity was studied for the mixed-ligand Cu(II) complexes of Me_5dien and heterocyclic acids and to access their inhibition activity values against soybean lipogenase. Out of these complexes, [Cu(Me_5dien)(fa)](BPh_4) had the highest IC_{50} result of 100µM exhibited higher activity of anti-inflammation[76]. The technique for analgesic action was utilized using Acetic acid-induced writhing in the mice[77,78]. The copper complexes exihibited higher analgesic activity at lower concentration[79]. The most potent analgesic drug of the mixed-ligand complex is developed with the molecular formula $C_{16}H_{12}MnN_{10}O_4S_2$ which is compatible with conventional diclofenac sodium owing to the existence of an electron withdrawing group and a halogen atom (See 6.8, Fig 6)[80].

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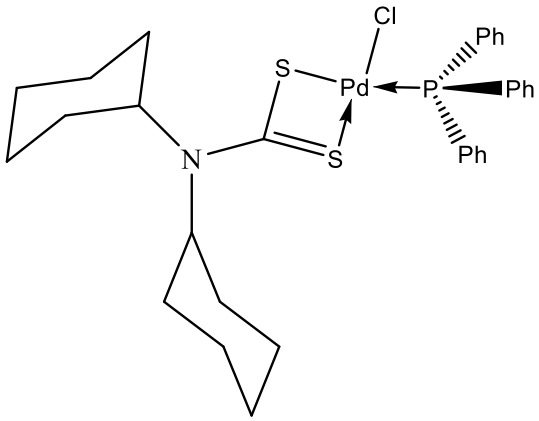

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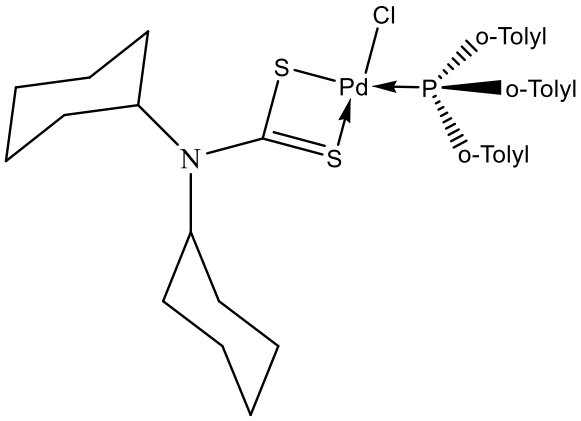

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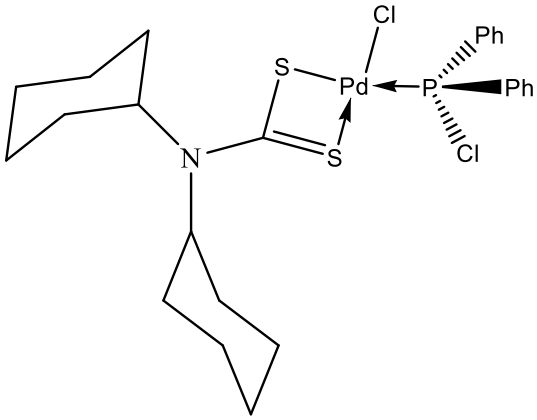

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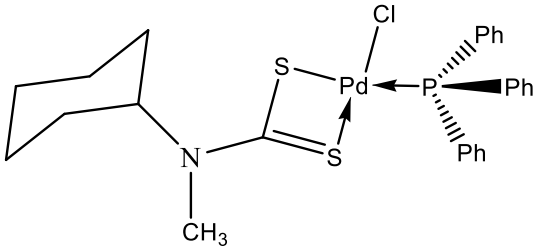

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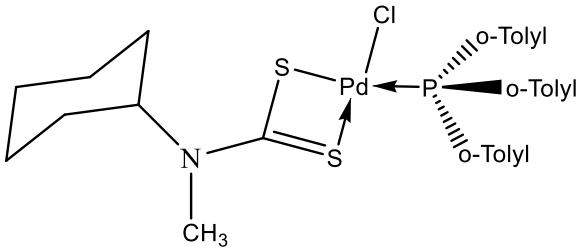

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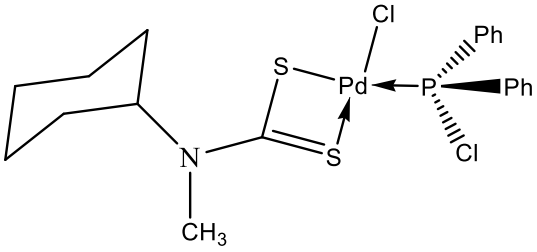

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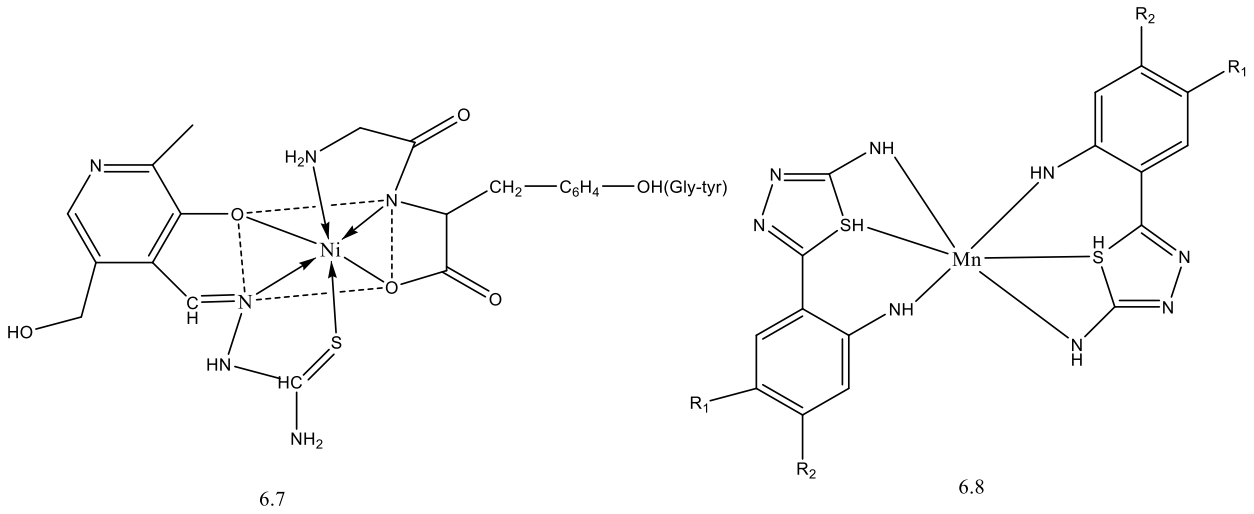


Fig 6: Anti-inflammatory and Analgesic activity of complexes.

Anticancer activity:

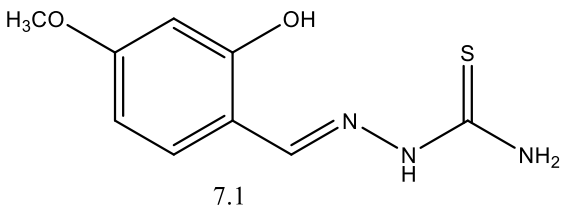
The metal ions through enzymatic activity are crucial for the treatment of cancer cells apart from their mechanism in normal cells. Particularly, transition metals such as Fe and Cu are considered as cancer risk factors[81-84].

The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide) assay was applied in evaluating the cytotoxic activity for Mn(II), Co(II), Ni(II), Zn(II) with phenanthroline and tropolone as mixed ligands against SKOV3, T24, MGC80-3. HeLa, A549, Bel-7402, Hep-G2 and human normal hepatocyte HL-7702 cells. Numerous findings suggest that incorporating phenanthroline to metal complexes might increase their anticancer action most likely because of its heteroaromatic ring, which lacks electrons and could be an efficient DNA intercalent[85-87]. But Mn(II) with phenanthroline and tropolone ligands has the most anticancer effect on HeLa cells with an IC50 value of 15.86 μm comparable to cisplatin, which is most widely used drug in cancer treatment in just a few decades[88-90]. The most intriguing aspect is that the Mn complex exhibited minimal cytotoxicity to healthy cells, which gets around the insufficiently high toxicity (IC50= 4.8±0.6μm) Copper complex that blocks the typical human cells (HL-7702)[91]. It indicates that the combination of certain metal ions regulates anticancer activity and selectivity in a particular way.

Oxovanadium(IV) complexes (See 7.1,7.2,7.3,7.4, Fig 7) were analysed in depth to prevent the occurrence of BEL-7402, HUH-7 and HepG2 hepatoma cell lines in humans using MTT assay since they were described as an appropriate model for hepatoma assessment in vitro toxicity[92,93]. The efficient anticancer drug, 5-Fluorouracil (5-FU, 30μM) was utilized as a positive control[94]. Both methoxy and chlorine substituted complex exhibited significant induced apoptosis in BEL-7402 cells and displayed typical morphological apoptotic characteristics. Due to the depolarization of the mitochondrial membrane, the chlorine substituted oxovanadium complex showed higher antitumor activity[95].

The mixed ligands of mononuclear Copper(II) complex (See 7.5,7.6,7.7, Fig 7) was examined for the anticancer activity. The cytotoxicity studies of HeLa cell line illustrated that their IC50 values for 48 hours (9.98-18.72 μM) were especially relatively small than that of Cisplatin (35.25 μM). They were retrieved to trigger apoptosis through the ROS-mediated mitochondrial pathway and activate the Bcl2 family of proteins[96]. In the presence of ascorbate or H_2O_2, Cu(II) complexes of mixed heterocycle ligands demonstrated strong DNA cleavage activity subsequently intercalative interaction with DNA[97]. The complexes show great possibility of advancement for antitumor agents, owing to in vitro examines conducted on B16 melanoma tumor cells.

The IC50 values obtained for $[Ru(bpy)_2(pytrzSH)_2](PF6)_2$ (See 7.8,7.9,7.10, Fig 7) and $[Ru(phen)_2(pytrzSH)_2](PF6)_2$ (See 7.11,7.12,7.13, Fig 7) on SK-MEL-28 cancerous cell line were found to be 27.444 and 40.721 µg/ml and for non-tumoral L6 cells were 25.869 and 38.425 µg/ml. The inclusion of the Ru(II)-bpy/phen moiety in each of the complexes which can reduce the steric hindrance in the course of their exchanges with their biological targets and perhaps lead to increased anticancer activity[98]. The similar complex of Ruthenium-polypyridyl having (2-(4-(diethoxymethyl)-1H-imidazo[4,5-f]-[1,10]-phenanthroline) intercalating ligand performed on HeLa cell line with the IC50 values of 39±4.6mM, 44.3±6.3mM and 49±8mM respectively[99]. The anticancer activity of different cell lines was significantly influenced by Ru(II)-polypyridine complexes with an auxiliary bpy/phen ligand[100]. It was also because of the intercalating pytrzSH ligand that these complexes exhibit anticancer behavior. When the S-H bond was homolytically cleaved at 87 kcal mol^{-1}, the thiol group in the triazole molecule easily forms thiyl radicals[101]. Because of its high reactivity and low dissociation energy of the S-H bond, the thiyl groups of the complexes operate as a chain transfer agent and maintain an intracellular equilibrium. The complexes seem to have stronger anticancer activity despite to the triazole ring which connects to the pyridine substituent as well as the –SH group was substituted to the triazole nucleus[102].



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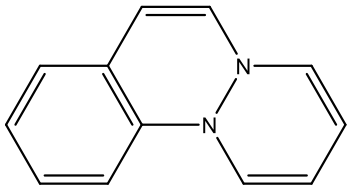

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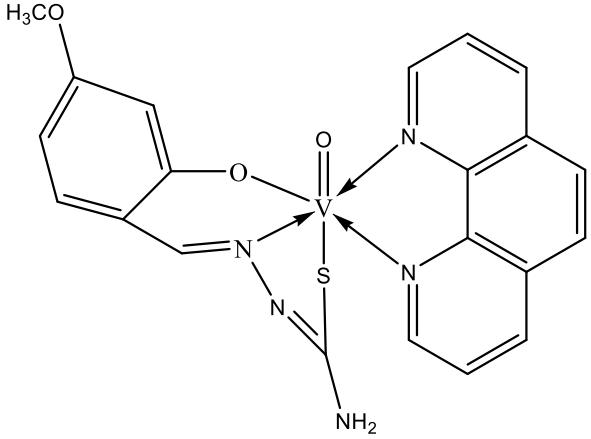

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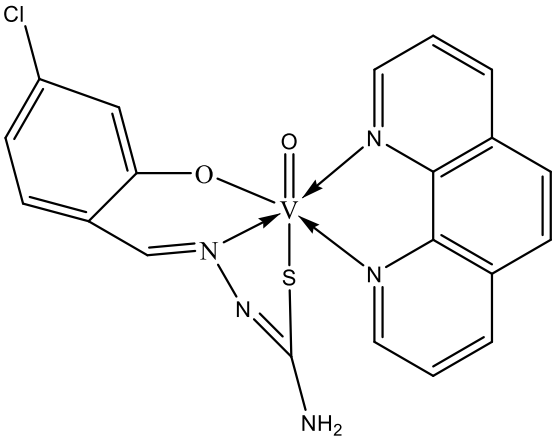

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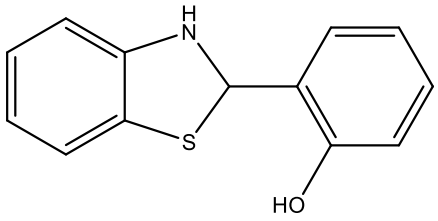

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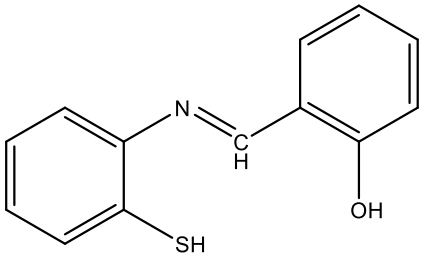

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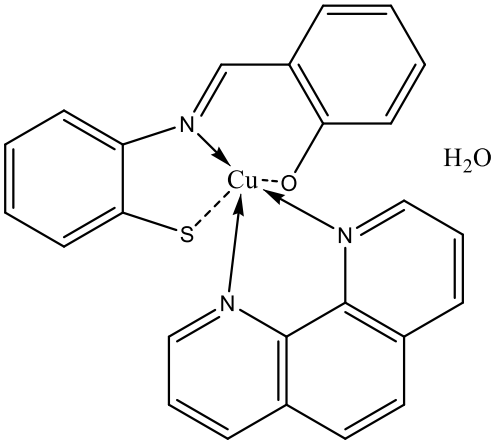

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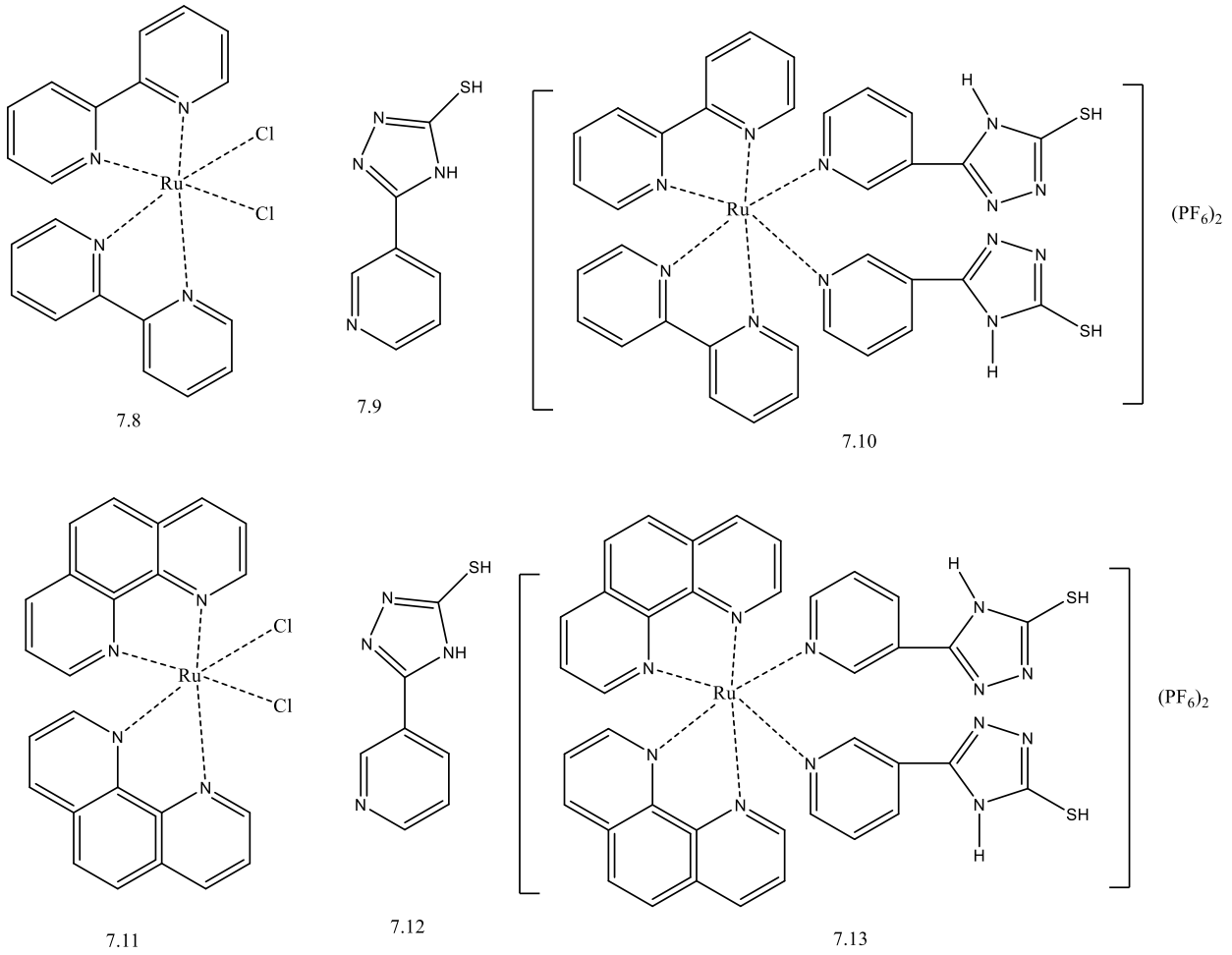

Fig 7: Antitumor activity of mixed ligands and its complexes

Antidiabetic activity:

Diabetes mellitus(DM) is a metabolic degenerative sickness that is predominant around the world and is characterized by elevated blood glucose levels[103,104]. Insulin resistance is the foremost common reason of diabetes. It is anticipated that the worldwide predominance of diabetes would rise to a extent influencing individuals of all ages[105]. Glucose management is a impactful diabetes treatment since many anti diabetic medications target reducing metabolism levels. It is commonly recognized with α-glucosidase, a carbohydrate hydrolase, selectively hydrolyzes 1,4-α-glucopyranosidic correlate to liberate glucose[106]. An essential enzyme breakdown of carbohydrates is α-glucosidase, which facilitates the breaking down of monosaccharides emerging via disaccharides with oligosaccharides[107]. Mammals utilize α-glucosidase for carbohydrate digestion in the intestine from food, maturation and folding of glycoproteins, and destruction of glycogen[108]. Furthermore, drugs for diabetes and other degenerative illnesses are treated in large part by inhibiting α-glucosidases and related enzymes[109].

The complexes having 2,2' bipyridyl {[$Hg(6\text{-}mpa)_2(bpy)(OAc)].2H_2O$ have the greatest inhibitor activity (IC_{50}=0.184 μM) (See 8.1,8.2, Fig 8) than the Co, Mn, Ni and Fe metals[110]. This is because of the atomic size of Hg metal especially in comparison to that indeed other complexes, Hg complex is bulkier and exhibits much Van der Waals interrelations more with amino acid sequences in enzyme molecule. It is evident that coordination context and these have a direct impact on α-glucosidase inhibition[111,112]. The Copper complex

of (1E,2E)-N,3-diphenylprop-2-en-1-imine and (Z)-2-methoxy-4-(((2-nitrophenyl)imino)methyl)phenol ligands (See 8.3, Fig 8) displays more potent inhibition against α-amylase having IC_{50} value of 33.26 µg/mL The medicinal strategy could lower the blood sugar level after nourishment in by preventing α-amylase enzymes from working, which can be applied as a crucial tactic in the control of blood sugar levels[113]. The IC_{50} values for oxovanadium (IV) complex (See 8.4, Fig 8) is 14.75 µM, and hence it is a moderate α-glucosidase inhibitor. Insulin sensitivity has been explained to be improved in animal models by a variety of inorganic and organo vanadium compounds[114]. Although organic ligands on vanadium can modify the bioavailability of the vanadium ion, carefully crafting organic ligands on vanadium can have a major impact on their bioactivities suitable and most accurate for clinical medicinal purposes in the medications of diabetes[115].

The α-glucosidase inhibition of [Cu(6-mpa)(dipya)(OAc)].$3H_2O$ (See 8.5, Fig 8) has the IC_{50} value of 513.10 µM which is 1.77 fold higher and 40.40 lower than those of acarbose (IC_{50} = 906 µM)[116,117] and resveratrol (IC_{50} = 12.70 µM)[118,119] well-known α-glucosidase inhibitors, respectively. The Cu(II) complex have a distorted trigonal geometry whereas Co(II) and Zn(II) complexes have a distorted octahedron geometry and the difference of coordination shows small alteration of enzyme action hence Cu(II) complex has the highest level of inhibition against α-glucosidase[120].

It was mentioned that study results on artificial or natural α-glucosidase inhibitors has significantly grown in the past few years[121,122]. Furthermore, it has been disclosed with the range of IC50 results for α-glucosidase inhibitiory action of complexes was from 2.910 to >600 µM[123].

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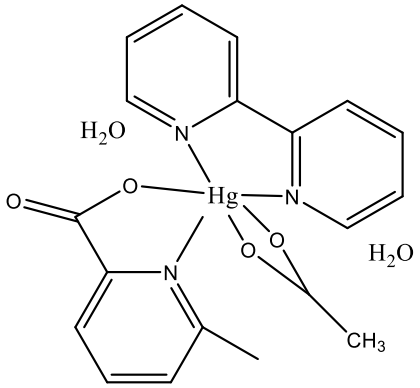

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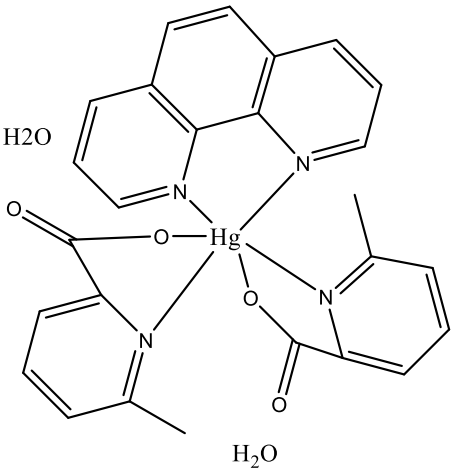

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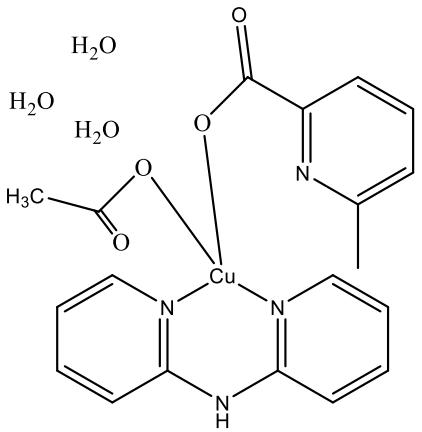

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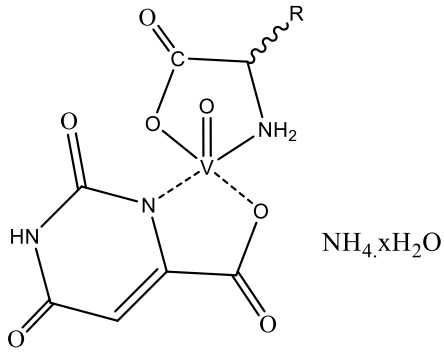
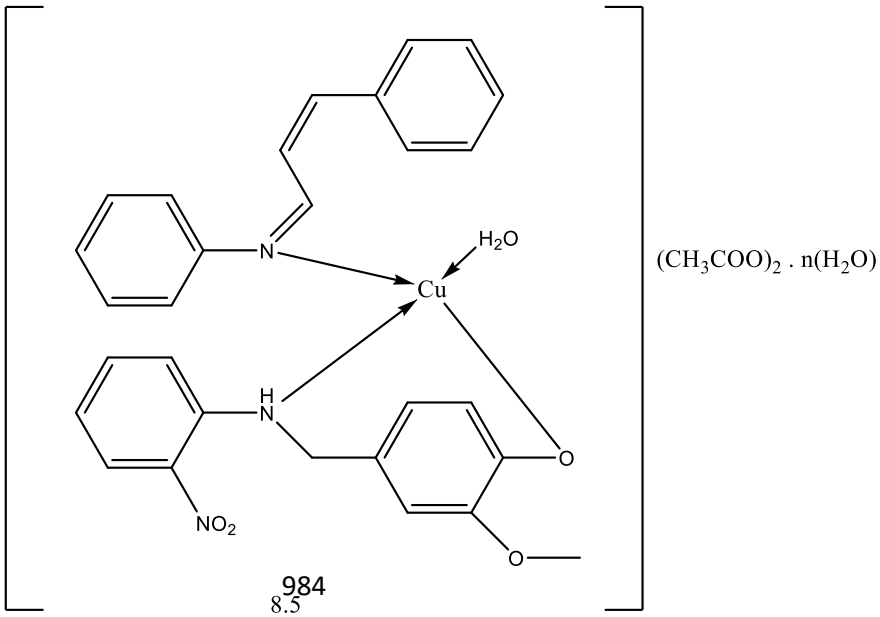


$NH_4.xH_2O$

8.4



$(CH_3COO)_2 . n(H_2O)$

8.5

Fig 8: Anti diabetic activity of Mercury, Copper and Vanadium complexes.

Table 1: Bioactivity and distinct mechanisms of Mixed-ligand metal complexes

Mixed-ligand complex	Activity	Mechanism
Cu complex	Anti-bacterial	Inhibiting the growth of bacteria
	Anti-tubercular	Complexation of ligands
	Anti-oxidant	High reducing capacity with proton donation feature acting as a super oxide scavenging center.
	Anti-cancer	Trigger apoptosis through the ROS- mediated pathway and activate BCl_2 family of proteins
	Anti-diabetic	Lower the blood sugar level by inhibiting α-amylase enzyme
Fe complex	Anti-fungal	Restricts microbes from multiplying by obstructing their active sites
Co complex	Anti-tubercular	Metal-binding increases the activity
	Anti-oxidant	Considerable alteration with the chemical characteristics of the ion
Ni complex	Anti-bacterial	Facilitating interaction with the charged particle and extremely sensitive biological membrane
	Anti-inflammatory	Modest reduction of denaturation of bovine serum albumin
Zn complex	Anti-malarial	Inhibiting the formation of β-hematin
Pd complex	Anti-bacterial	Concept of chelation
	Anti-malarial	preventing the proliferation of P. falciparum
	Anti-inflammatory	Inhibiting the odema
V complex	Anti-bacterial	Prevents the growth of bacteria
	Anti-cancer	Significant induced apoptosis in BEL-7402 cells
	Anti-diabetic	Improved insulin sensitivity and moderate α-glucosidase inhibition
Ag complex	Anti-tubercular	Limiting mycobacteria from synthesizing proteins in the ribosome
	Anti-malarial	Enzyme inhibition
Mn complex	Anti-bacterial	Liposolubility with increase in cell permeability.
	Anti-fungal	Inhibition of mycelial growth

	Anti-oxidant	Enhancement of SOD activity because of the coordination bond with metal and free ligand.
	Anti-cancer	Inhibit cancer cells and minimal toxicity to healthy cells

CONCLUSION:

Mixed ligand complexes possess more range lists of biological action in biological field. The Lipophilic effect and chelate effect of metallic complexes were the outcome of the diverse therapeutical and pharmacological activites. Due to the mechanism and action of these metal complexes, it has been used in various biological area of activity(Table 1). The development of mixed-ligand complexes could be enhanced in the bioinorganic field for the medications of diseases in future.

Conflict of interest:

All authors declare no conflict of interest.

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