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Biological applications of Mixed ligand Complexes: A Review

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ABSTRACT

A heteroleptic or mixed ligand complex refers to a coordination compound where two or more distinct types of ligands are bound to a central metal atom or ion, creating a structure composed of diverse ligands with varying chemical compositions attached to the metal center. These complexes offer an extensive range of properties due to the synergistic combination of complementary ligands, resulting in superior electronic characteristics, improved catalytic efficiency, and enhanced bioactivity relative to simpler analogs. Representing a key subset of coordination compounds, they play vital roles across multiple disciplines, particularly in biological contexts, where the chelate effect—promoting exceptional stability via multidentate ring formation—the unique chemistry of individual ligands, and their lipophilicity enable strong interactions with physiological systems. Consequently, these complexes exhibit a broad spectrum of bioactivities, encompassing anti-inflammatory and analgesic effects, antioxidant capabilities, anticancer properties, and antidiabetic potential.

Keywords: Mixed-ligand complex, bioactivity, chelate effect, amtidiabetic potential.

INTRODUCTION

Mixed ligand complexes exhibit a remarkably broad spectrum of biological activities within biomedical applications, far surpassing the capabilities of simpler mononuclear systems due to their exceptional structural versatility and tunable properties.This versatility arises from the coordination of central metal ions with multiple distinct ligand typessuch as bidentate or polydentate chelators alongside monodentate groupswhich enables precise modulation of steric hindrance, electronic distribution, and hydrophobicity around the metal center. The chelate effect, resulting from multidentate ligands forming highly stable five- or six-membered rings through entropy-driven ring closure, dramatically enhances thermodynamic stability and resists dissociation in physiological environments; meanwhile, the lipophilic effect, imparted by hydrophobic ligand substituents like aryl or alkyl chains, promotes efficient permeation across lipid bilayers, superior cellular uptake, and enhanced bioavailability when compared to unbound ligands or single-ligand analogs.

These synergistic attributes drive a wide array of therapeutic and pharmacological mechanisms, including competitive enzyme inhibition at active sites, DNA intercalation or groove binding to disrupt replication, generation of reactive oxygen species for oxidative stress induction, and structural mimicry of native metalloproteins, thereby facilitating potent applications in anticancer therapies (through apoptosis and mitochondrial targeting), anti-inflammatory and analgesic responses, antioxidant defense and antidiabetic insulin-mimetic effects. Some of the biologically active mixed ligand complexes were shown in fig 1-4

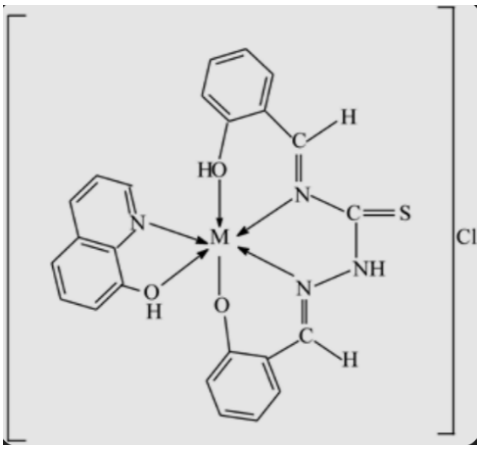
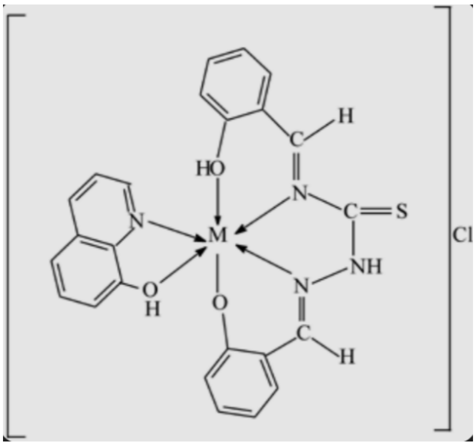


Fig 1



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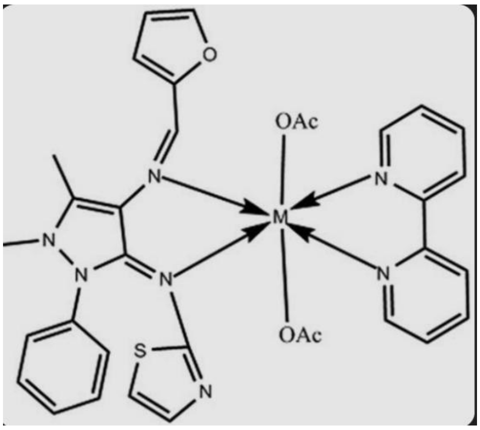


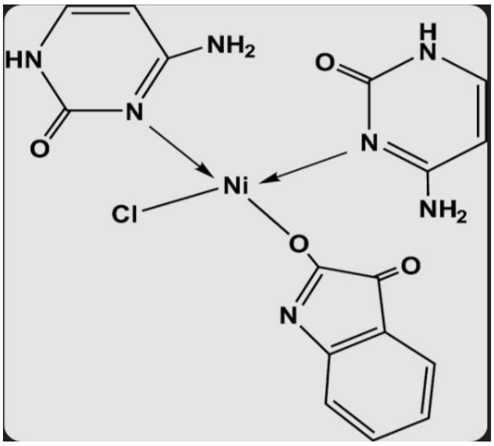


Fig 3 Fig4

Biological phenomena of mixed-ligand complexes

Antioxidant activity

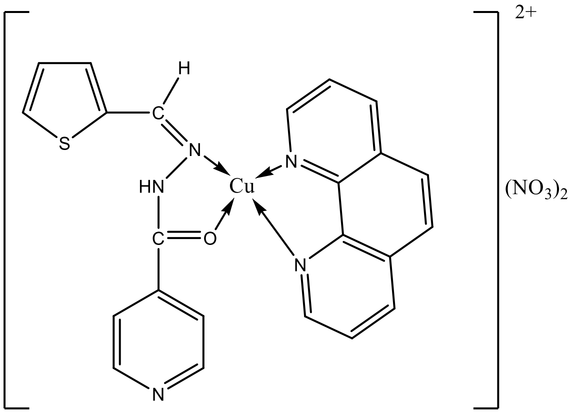
Numerous biochemical reactions occur constantly in our bodies, leading to the creation of different types of biomolecules. Some extremely reactive and perhaps harmful chemical compounds, including as superoxide anions even so hydrogen peroxide had been devised among these beneficial moieties[1]. Some 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[2]. 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[3]. 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[4].

Schiff base complexes exhibit variable antioxidant activity, which becomes partly related to their coordination environment and redox properties[5]. Typically, the degree of chelate ring unsaturation, axial ligation and ring size each impact the redox characteristics of the metal complexes[6]. 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[7].

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[8]. 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[9].

SOD is a well known and most useful antioxidant enzymes which is known for its conversion of superoxide into H_2O_2 and oxygen[10]. 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[11].



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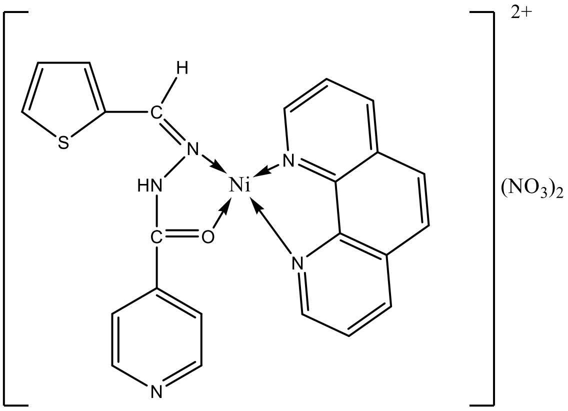

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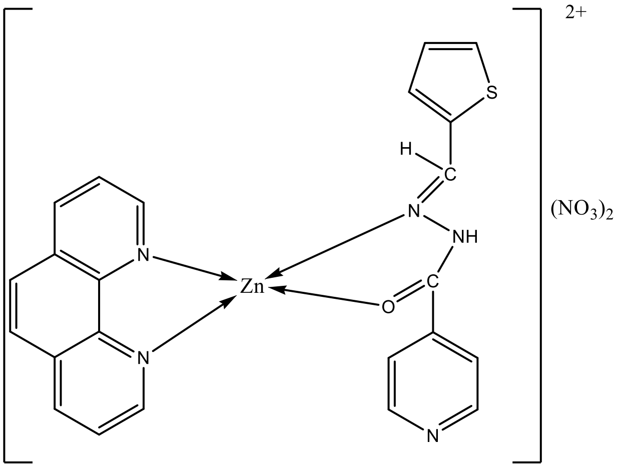

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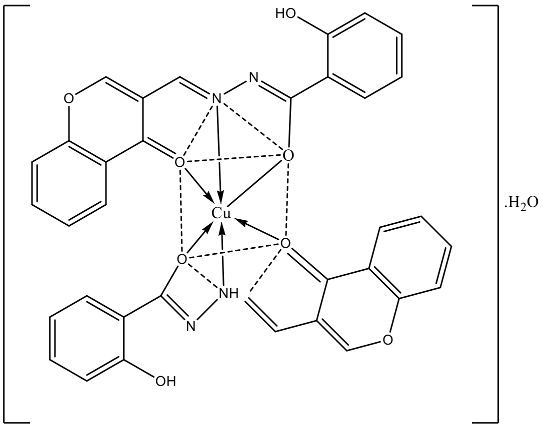

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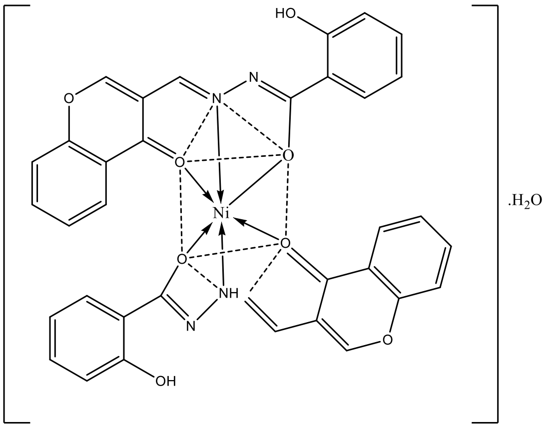

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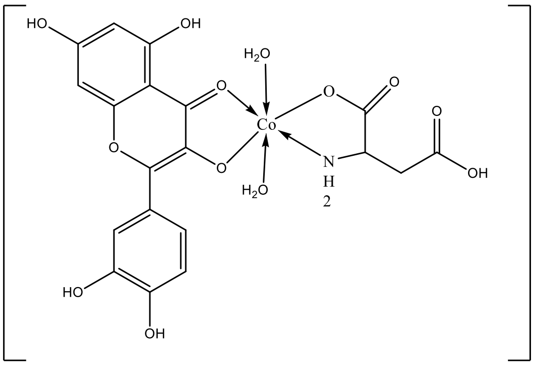

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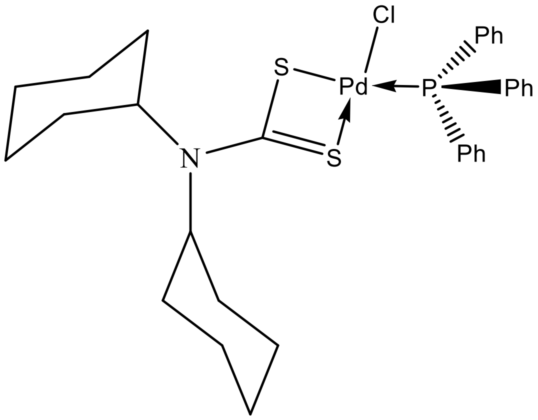
Fig 5: Antioxidant activity of Copper, Nickel, Zinc and cobalt complexes.

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[12]. Histamin and serotonin mediate the initial phase of the inflammatory response, kinins and prostaglandins mediate the second phase[13]. 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[14]. 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[15]. 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[16].

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[17]. 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[18]. 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[19].

The technique for analgesic action was utilized using Acetic acid-induced writhing in the mice[20,21]. The copper complexes exihibited higher analgesic activity at lower concentration[22]. 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)[23].



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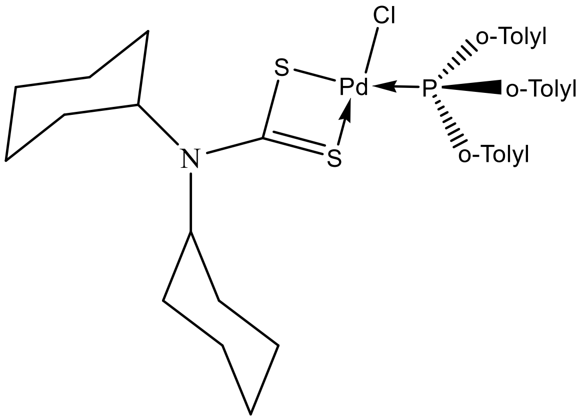

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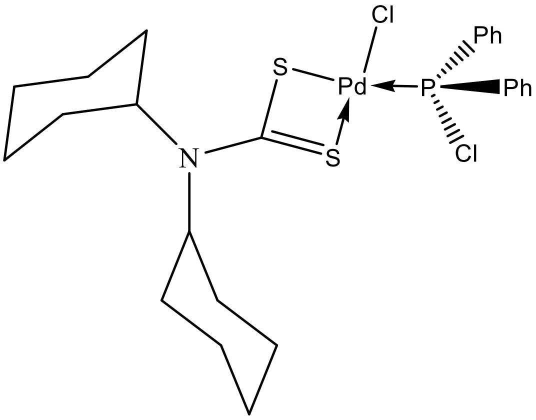

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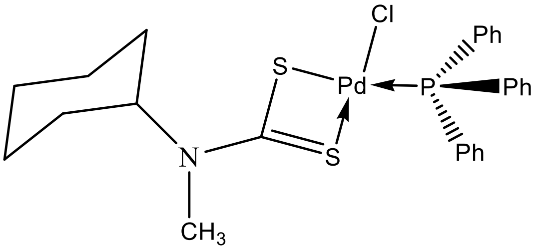

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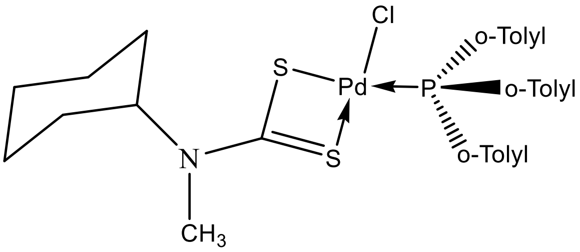

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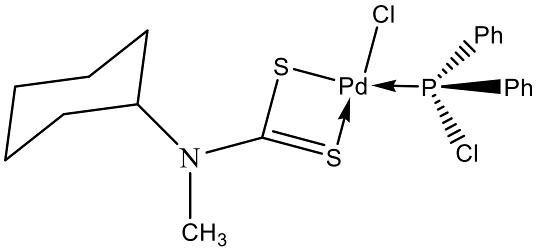

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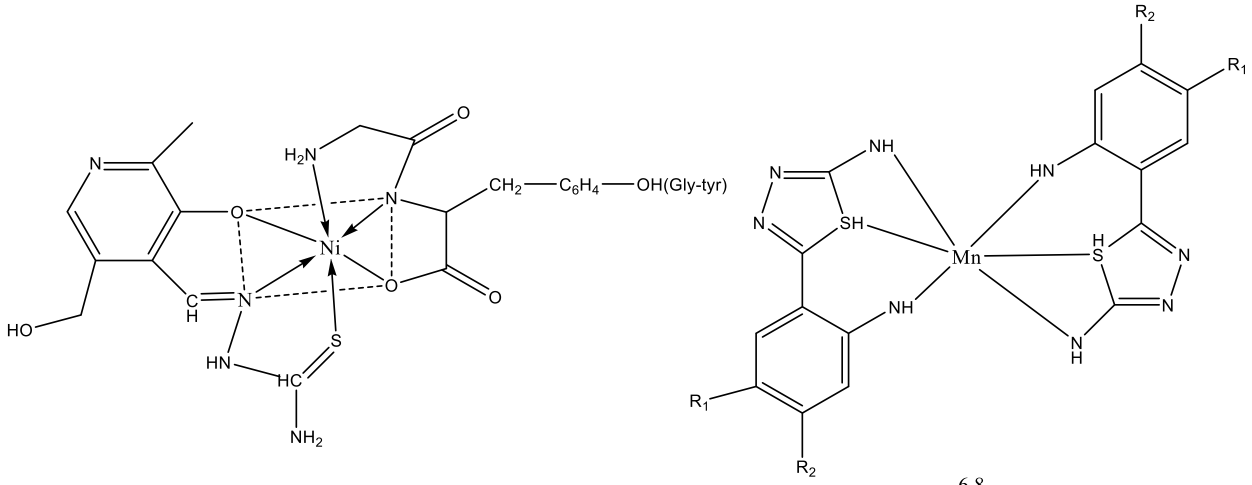

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Fig 6: Anti-inflammatory and Analgesic activity of complexes.

Anticancer activity

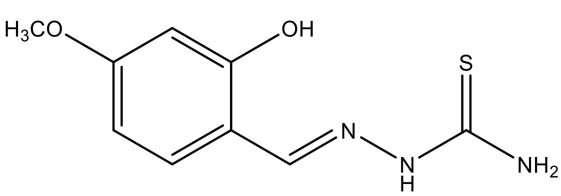
The metal ions through enzymatic activity are crucial for the treatment of cancer cells apart from their mechanism in normal cells. Particularly, transition metals such as Fe and Cu are considered as cancer risk factors[24-27].

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[28-30]. 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[31-33]. 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)[34]. 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[35,36]. The efficient anticancer drug, 5-Fluorouracil (5-FU, 30µM) was utilized as a positive control[37]. 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[38].

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[39]. 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[40]. 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[41]. 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[42]. The anticancer activity of different cell lines was significantly influenced by Ru(II)-polypyridine complexes with an auxiliary bpy/phen ligand[43]. 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[44]. 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[45].



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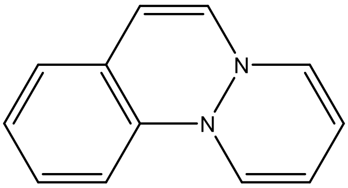

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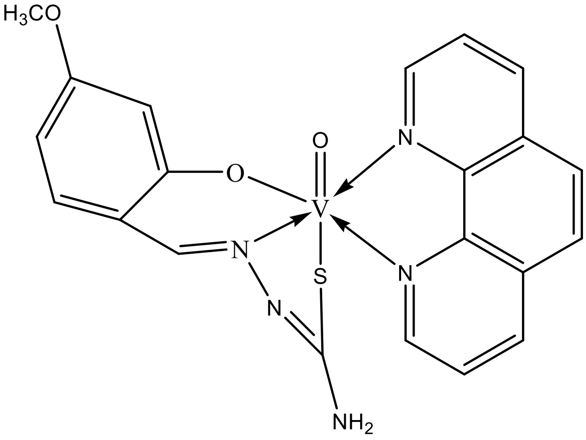

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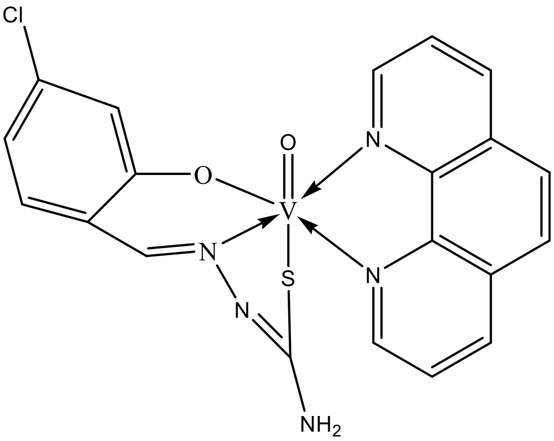

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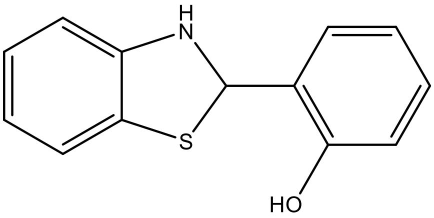

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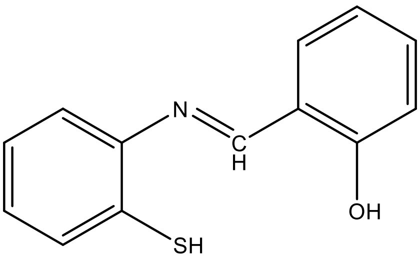

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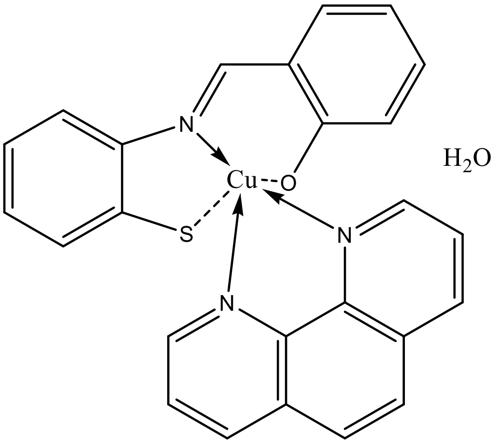

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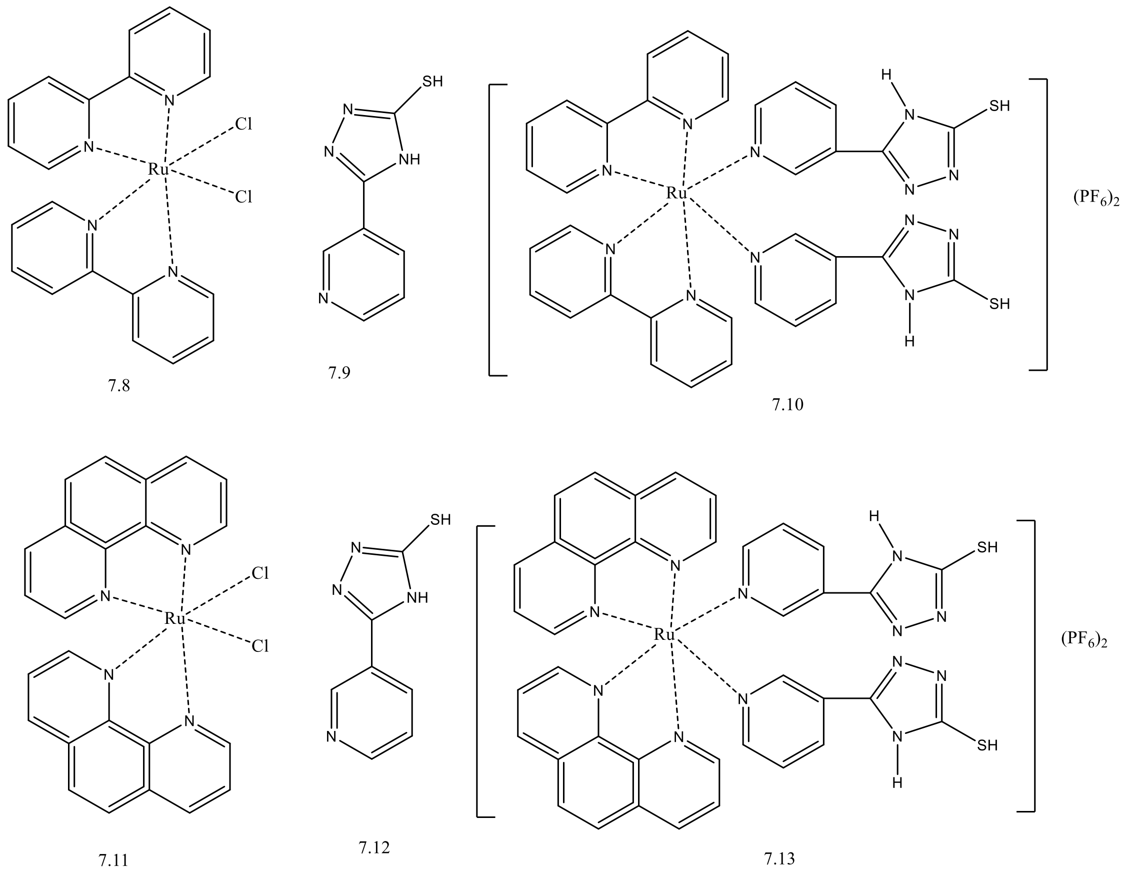

Fig 7: Antitumor activity of mixed ligands and its complexes

Antidiabetic activity

Diabetes mellitus(DM) is a metabolic degenerative sickness that is predominant around the world and is characterized by elevated blood glucose levels[46,47]. 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[48]. 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[49]. An essential enzyme breakdown of carbohydrates is α-glucosidase, which facilitates the breaking down of monosaccharides emerging via disaccharides with oligosaccharides[50]. Mammals utilize α-glucosidase for carbohydrate digestion in the intestine from food, maturation and folding of glycoproteins, and destruction of glycogen[51]. Furthermore, drugs for diabetes and other degenerative illnesses are treated in large part by inhibiting α-glucosidases and related enzymes[52].

The complexes having 2,2' bipyridyl {[Hg(6-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[53]. 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[54,55]. 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[56]. 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[57]. 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[58].

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)[59,60] and resveratrol (IC_{50} = 12.70 µM)[61,62] 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[63].

It was mentioned that study results on artificial or natural α-glucosidase inhibitors has significantly grown in the past few years[64,65]. Furthermore, it has been disclosed with the range of IC50 results for α-glucosidase inhibitiory action of complexes was from 2.910to >600 µM[66].

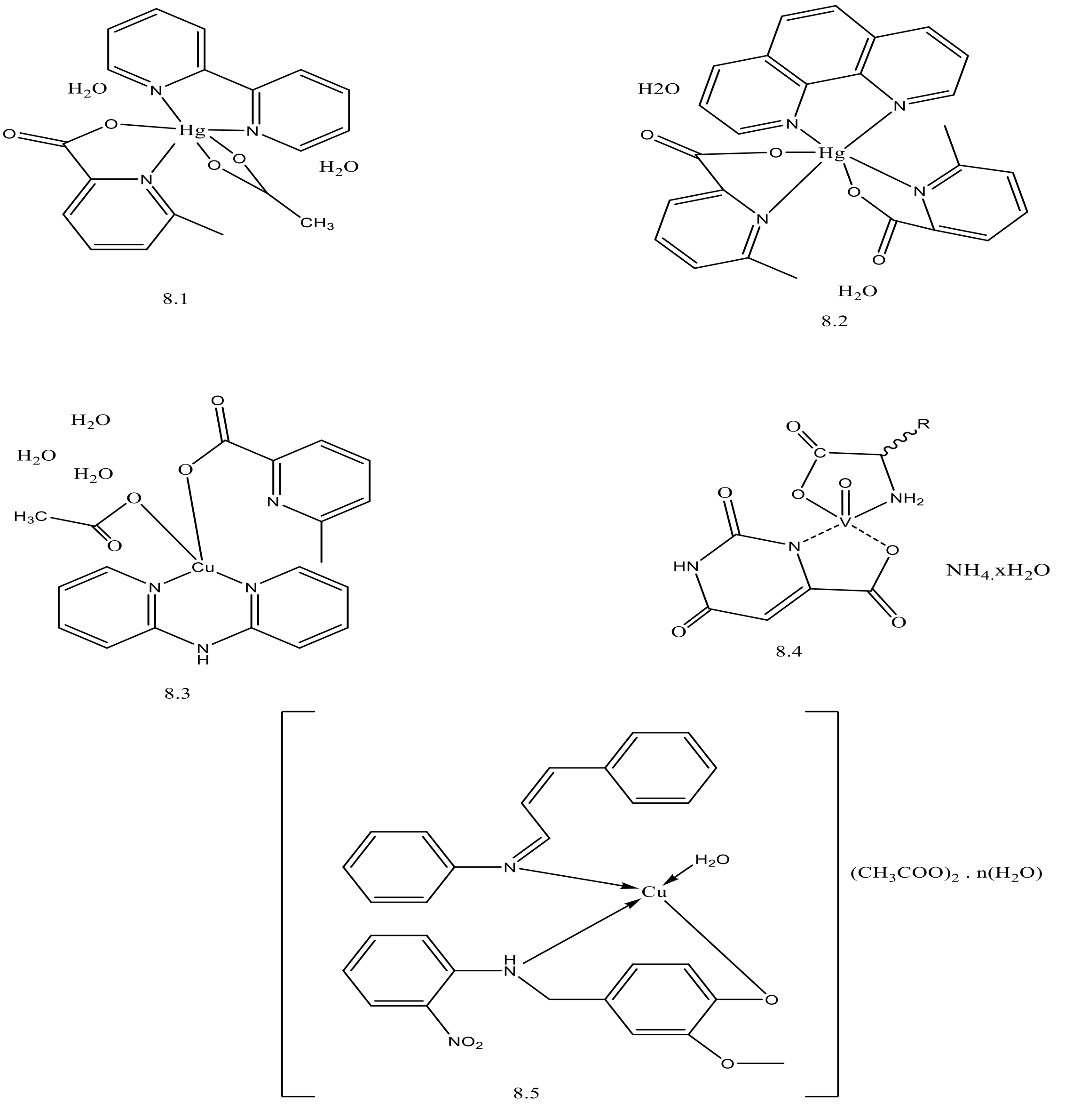

Fig 8: Anti diabetic activity of Mercury, Copper and Vanadium complexes.

CONCLUSION

Mixed ligand complexes exhibit a broad spectrum of biological activities in biomedical applications, far exceeding those of simpler systems, due to their unique structural versatility arising from coordination with multiple distinct ligand types that enable precise steric and electronic tuning. The chelate effect, stemming from multidentate ligands forming stable five- or six-membered rings, significantly enhances thermodynamic stability and metal-ligand bond integrity, while the lipophilic effect—conferred by hydrophobic moieties—facilitates superior cellular uptake, membrane permeability, and bioavailability compared to free ligands alone. These properties underpin diverse therapeutic and pharmacological actions, including enzyme inhibition, DNA intercalation, reactive oxygen species generation, and biomolecular mimicry, manifesting in applications acrossanticancer (via apoptosis induction), anti-inflammatory, analgesic, antioxidant, antidiabetic (through insulin-mimetic effects), and antitubercular domains. Consequently, ongoing advancements in mixed-ligand designs—incorporating motifs such as Schiff bases, amino acids, or phosphines—hold immense promise for bioinorganic chemistry, paving the way for innovative metal-based therapeutics to combattumors and neglected tropical diseases in future clinical pipelines.

Conflict of interest

All authors declare no conflict of interest..

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