CHAPTER – I

INTRODUCTION

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1.1 INTRODUCTION

A Lewis acid-base reaction product of organic ligand and metal ion via co- ordination bond is known as metal complex. Here bases are ligands and metal ions are acids. The metal complexes are known as co-ordination compounds and their physical/chemical properties are almost different from parent ligands & metal ions.

1.1.1 History

Metal complexes are known from beginning of chemistry, the dye Prussian blue is known from 1800s and it is well recognified by C. Blomstrand (1869)[1]. He established the theory of metal complexes and later on Jorgensen[2] improved the theory. He claimed that the ammonium ion binds directly to metal ion in solution. Werner[3] established the metal complexation theory. He explained that two possible ions could be located in co-ordination sphere. The ions bound directly to metal ions within co-ordination cluster. The spatial arrangement of ligands and metal ions in coordination sphere was also discussed.

1.1.2 Geometry

The structures of coordination compounds can be established by their coordination numbers (Number of ligands coordinated to central metal ions). They are mostly 2 to 9. The numbers are dependent on size, charge and electronic configuration of metal ions and the ligands. The possible geometries of coordination compounds are given in the Table 1.1.

Table 1.1: Geometrics of coordination compounds

Geometry	Coordination number	Examples
Linear	2	$[Ag(NH3)2]^{+}$
Trigonal planar	3	$[Cu(CN)3]^{2-}$
Tetrahedral square planar	4	$[NiCl4]^{2-}$
Square pyramidal	5	$[VO(CN)4]^{2-}$
Octahedral	6	$[CoCl6]^{3-}$
Pentagonal	7	$[ZrF7]^{3-}$
Square antiprismatic	8	$[ReF8]^{2-}$
Tricapped trigonal prismatic	9	$[ReH9]^{2-}$

The main Structure of the metal chelates are Square Planar, Octahedral and Tetrahedral (Fig. 1.1).

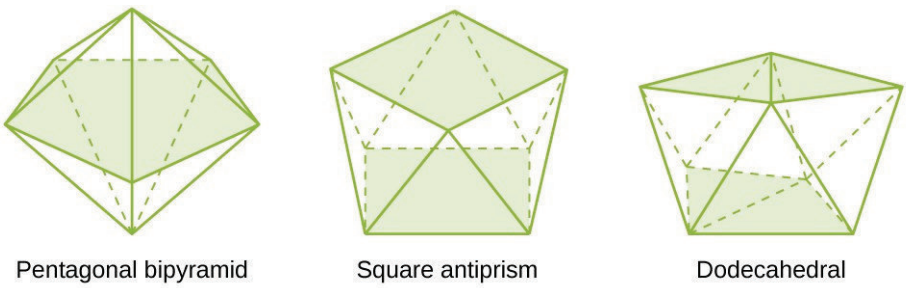


Fig. 1.1: Some Common Sphere of Complexes

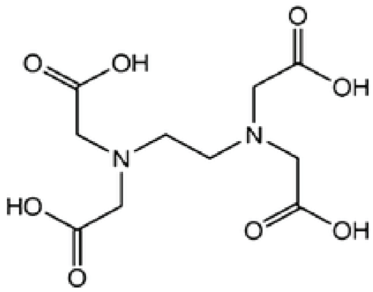
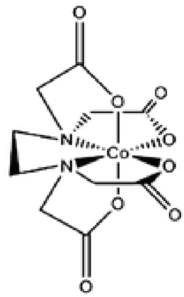
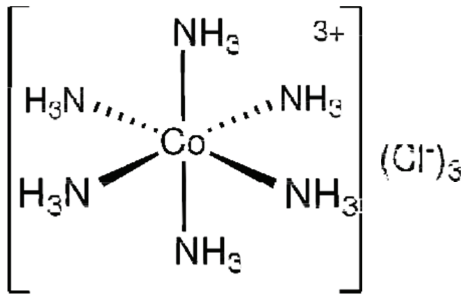
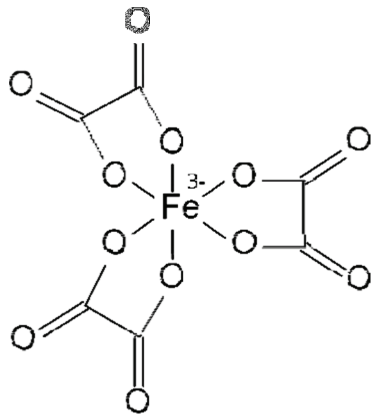
Stereoisomerism is there in certain cases. These are cis- and trans- isomerism.

1.1.3 Classification

The co-ordination complexes are classified as follow:

(a) Classical or Werner complexes

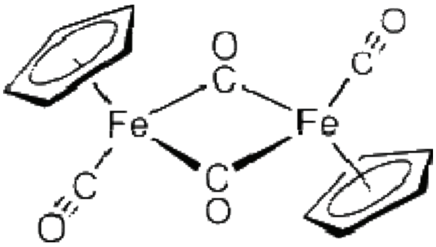
In this structure metal binds by ligand via lone pair of electrons. e.g., H_2O, NH_3, Cl^-, CN^-. Some examples are:

Example	Structure
Cobalt-EDTA complex	 
Hexamminecobalt(III) chloride	
Ferrioxalate	

(b) Organo-metallic compounds

Alkenes / alkynes, cycloalkyls with phosplines, hydride, CO, etc.

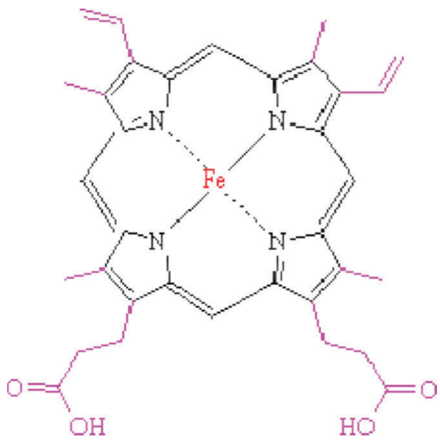
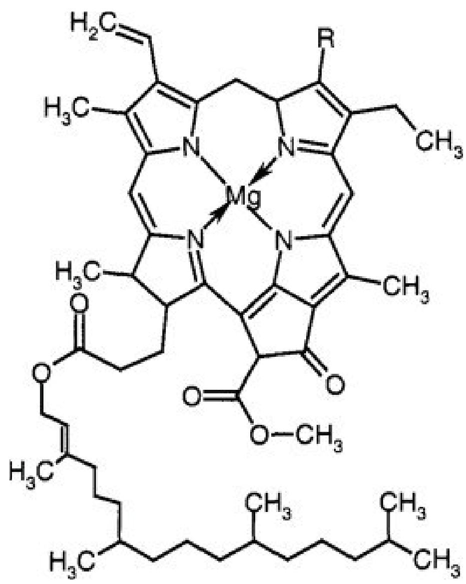
Cyclopentadienyliron dicarbonyl dimer is a good example

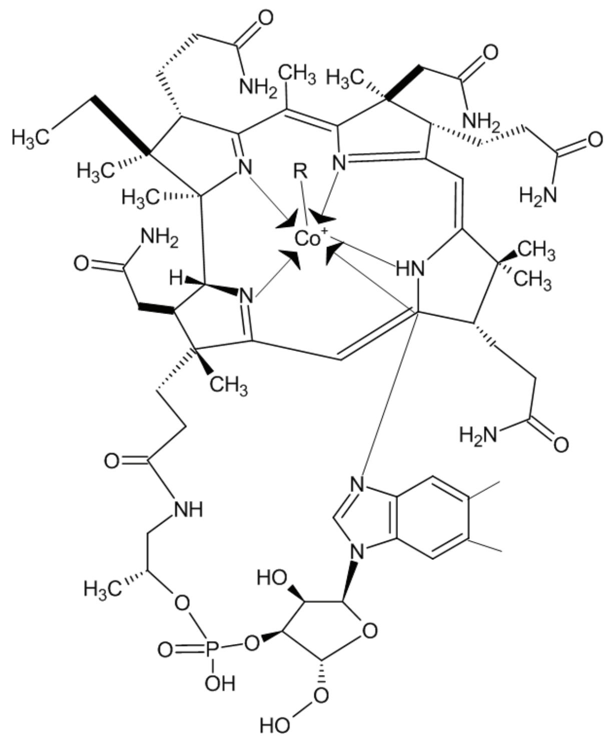
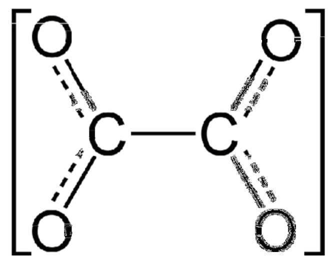


(c) Bioinorganic complexes

These complexes are obtained naturally. It includes side chains of amino acids, co-factors, porphyrins, etc.

Some examples are:

Example	Structure
Hemoglobin – Fe complex	
Chlorophyll – Mg complex	

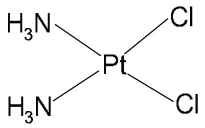
Vitamin B12 – Co complex	
Calcium oxalate – Ca complex	

All these complexes are most important for our human life.

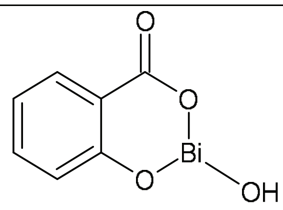
1.2 METAL COMPLEXES IN PHARMACEUTICALS

Metal ions play a pivotal role in humans deficiency of some metal created diseases like anemia, growth retardation, heart disease, etc. So, metal complexes in form of drug become an important platform in medicinal chemistry. It is known that transition metal complexes can be used as drug to cure several human diseases[4-6]. Metal like platinum, gold, lithium, zinc, silver, copper, lanthanium, bismuth, barium, mercury, etc. are useful for drug applications.

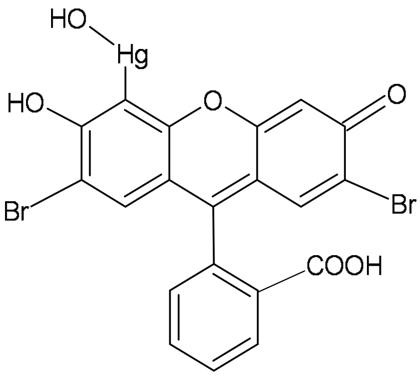
Some important metal complexes are used (Anticancer agents). These metal complexes are well known for their use as *in vivo* and *in vitro* anticancer activities[7-10].



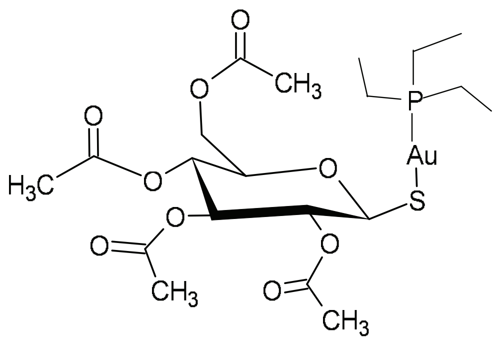
Cisplatin



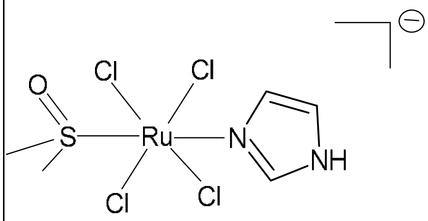
Bismuth subsalicylate



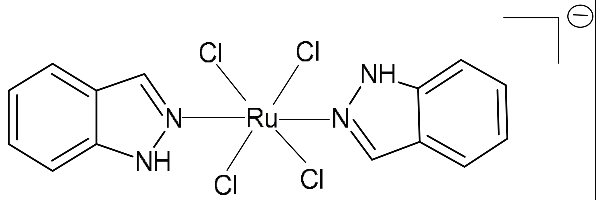
Merbromin



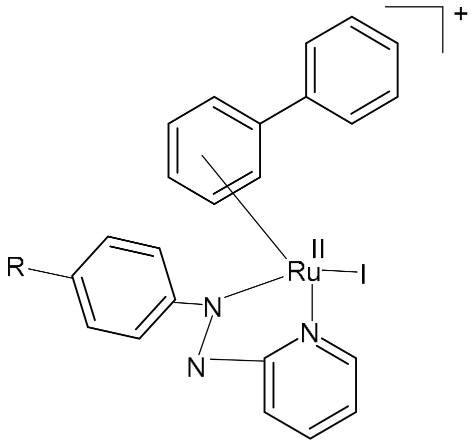
Auranofin



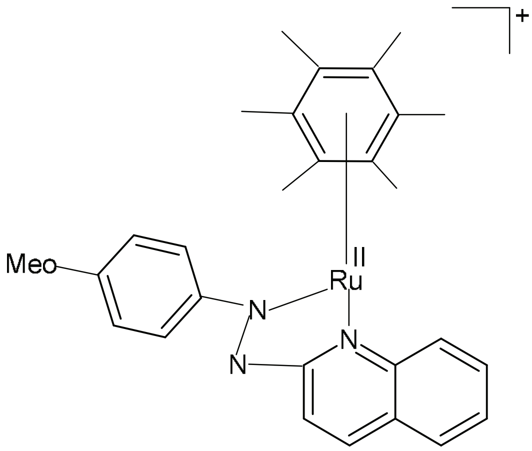
NAMI-A



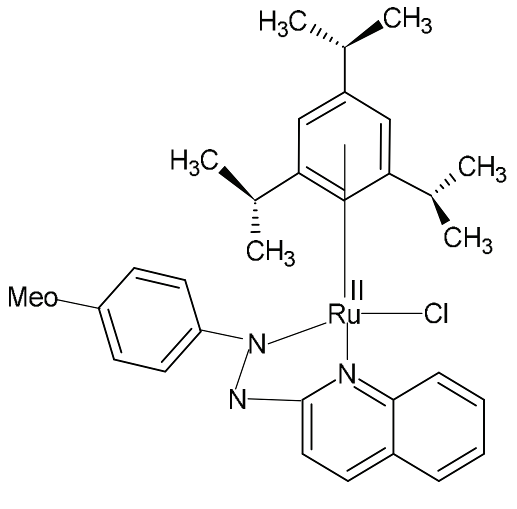
KP1019



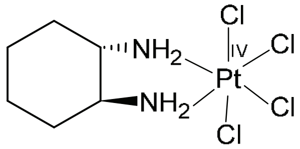
[Ru(h^6-bip)(p-azpy-R)I]$^+$
R=N$(CH_3)_2$OH



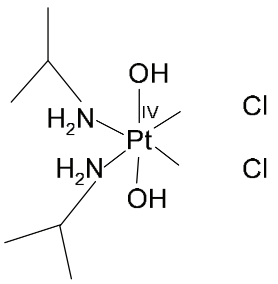
RAS - 1H



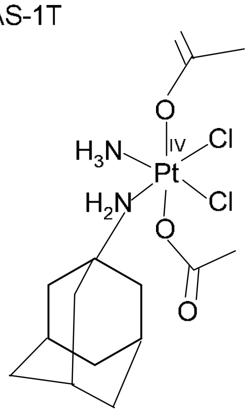
RAS-1T



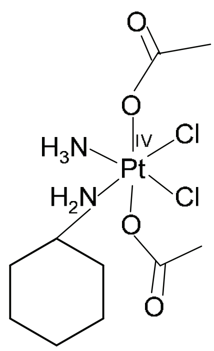
Tetraplatin



Iroplatin



LA-12



Starplatin

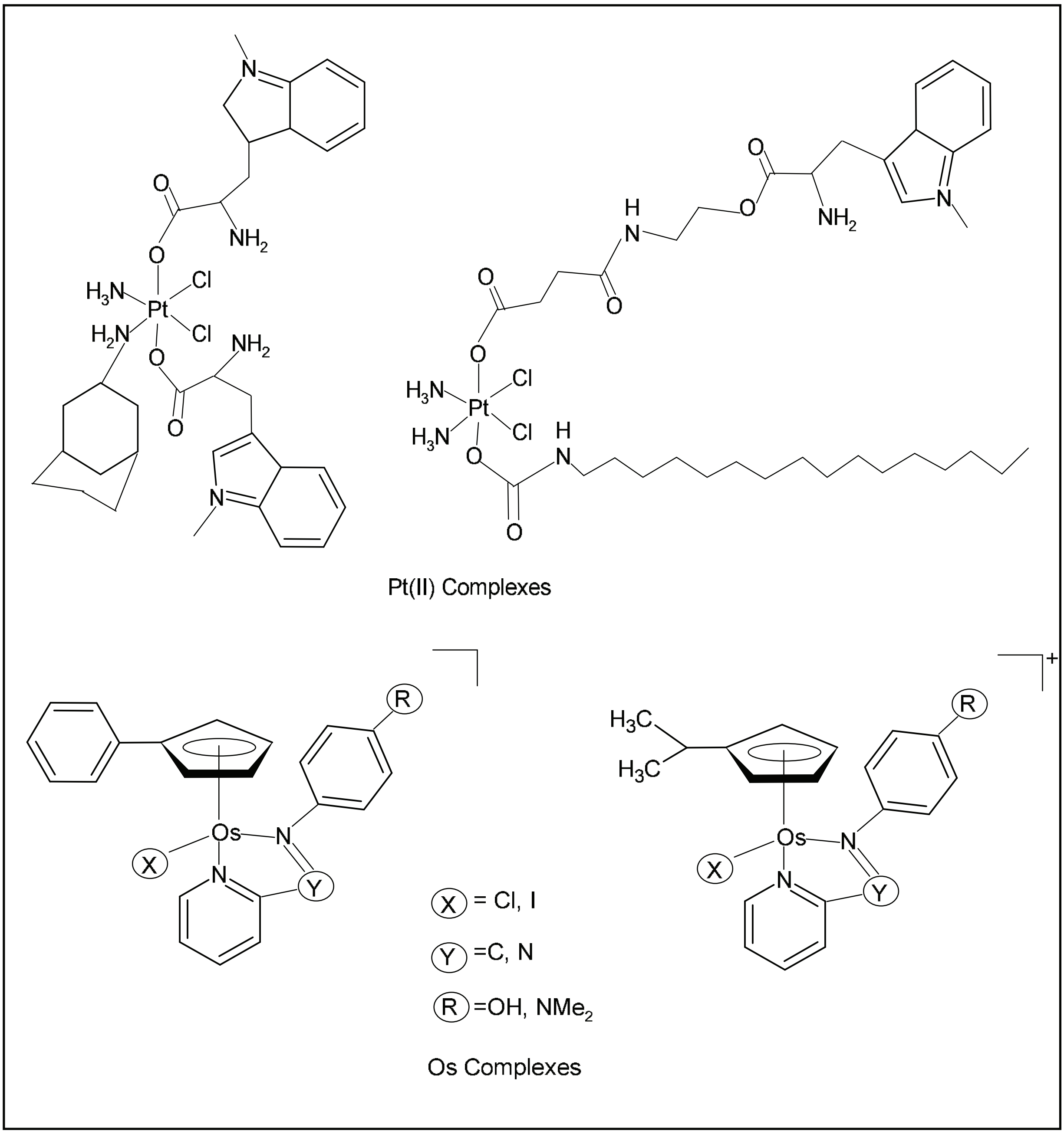


Fig. 1.2: Some Co, Ru, Pt and Os metal complexes exhibiting redox mediated anticancer activity

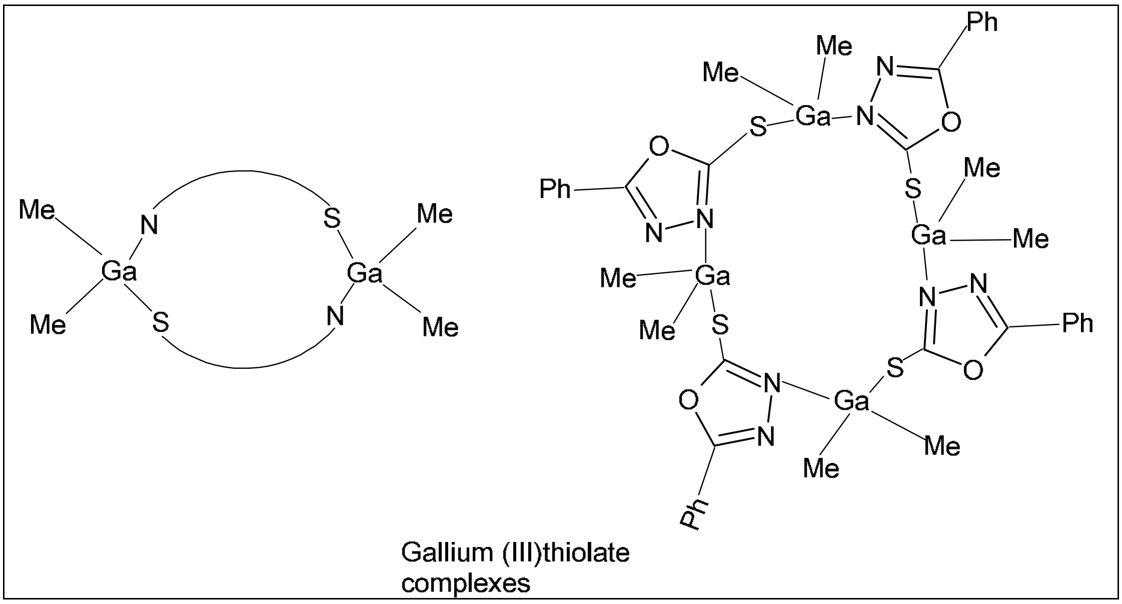


Fig. 1.3: Heterocyclic thiolate polynuclear gallium (III) derivatives with anticancer activity.

Many metal complexes[11-24] solved the problem created in insulin injection for diabetic patients.

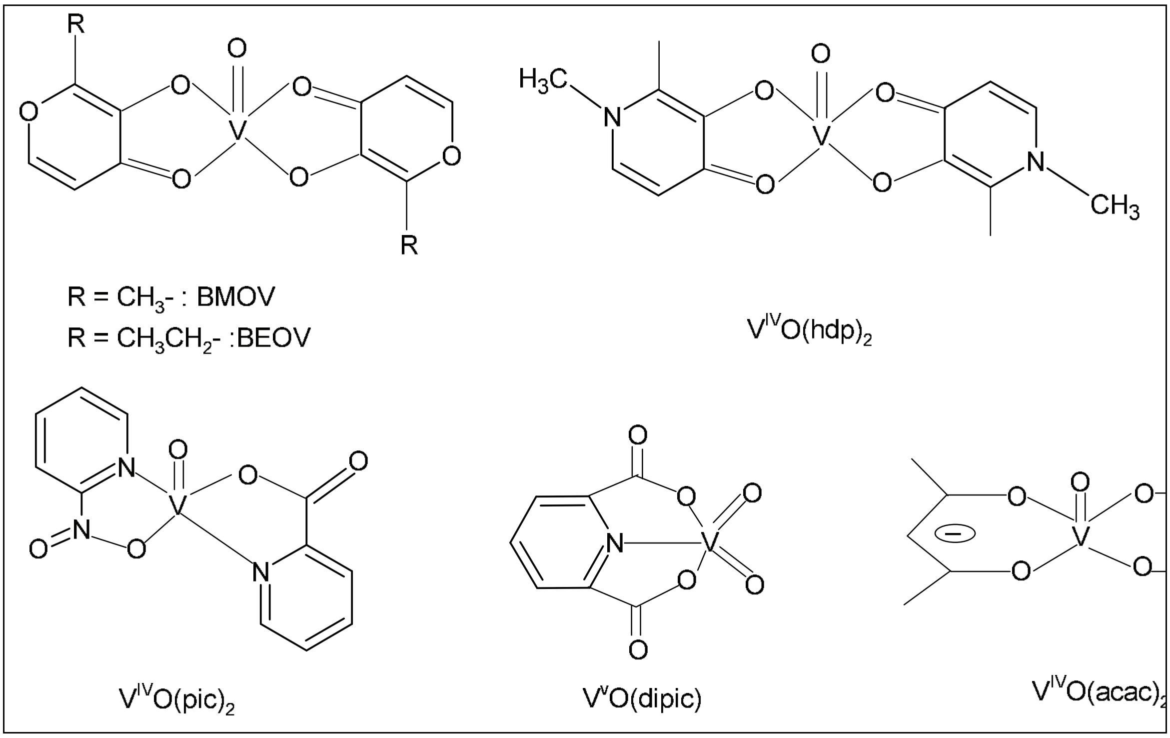


Fig. 1.4: Structures of some insulin mimetic vanadium complexes.

The amyloid β-targeted metal complexes bear excellent anti Alzheimer's diseases[25].

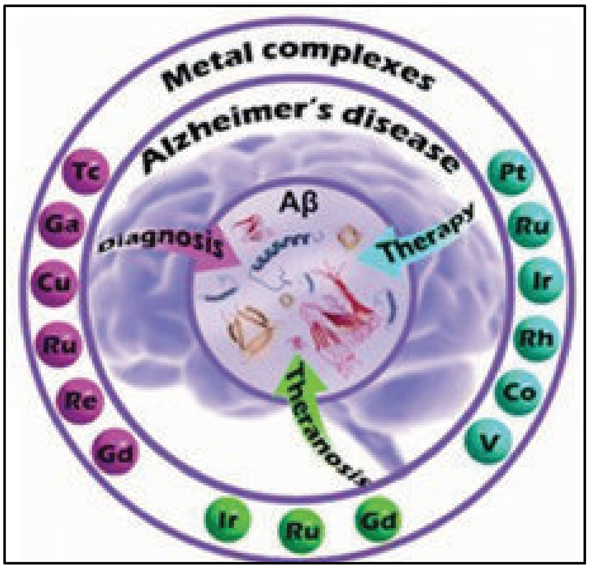
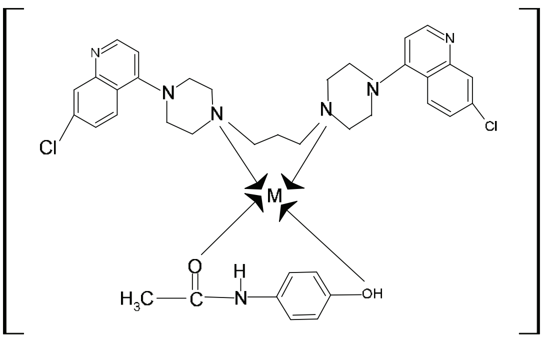


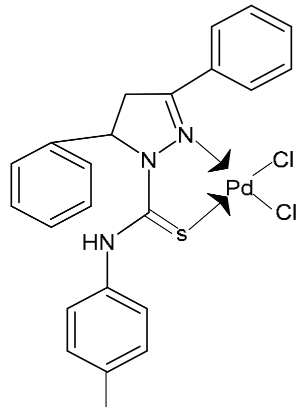
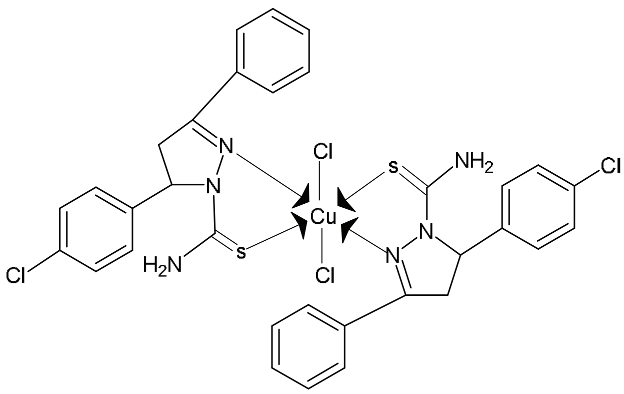
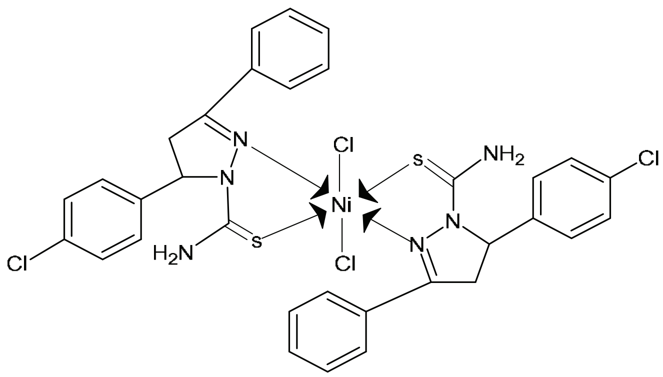
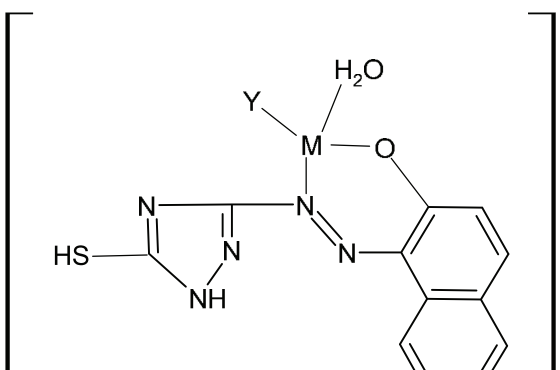
Fig. 1.5: Metal complexes for potential applications in Alzheimer's disease

Number of metal complexes of zinc, silver, mercury, etc. are used commonly as:

Antimicrobial:

The complexes with their antimicrobial activity[26-32].

Structure	Activity
 Y.x H_2O Y= 2Cl, SO_4,or 2(CH_3COO)	*Escherichia coli* and *Staphylococcus aureus*

	*Entamoebahistolytica*
 	*Candida strains*
 .X H_2O	*Escherichia coli, Staphylococcus aureus, Aspergillus flavus*and *Candida albicans*

Anticancer:

These complexes of Ti and Cu display anticancer activity[33-36].

<table>
<tr><th>Structure</th></tr>
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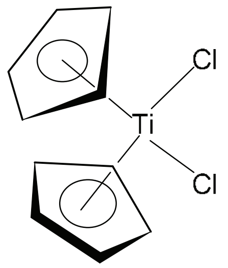
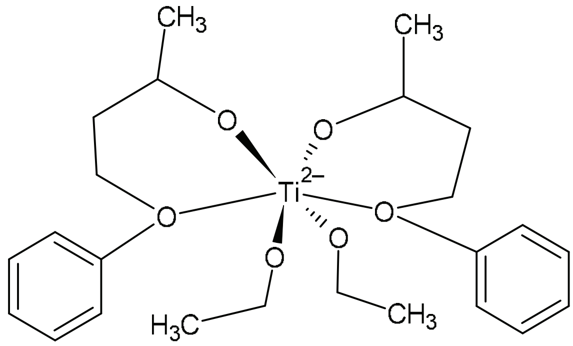
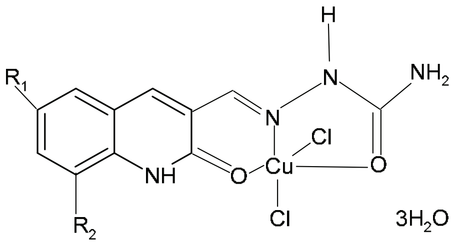
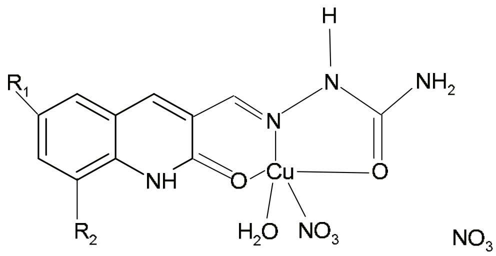


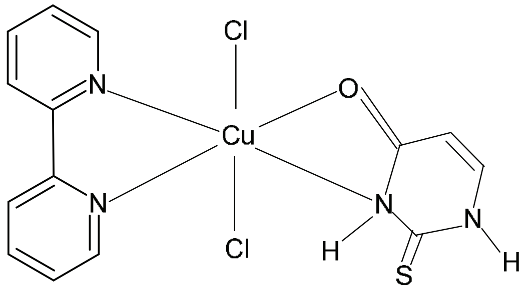
Titanocene dichloride



Budotitane
</td></tr>
<tr><td>


R_1= 6 Me
R_2= 8Me



Cu (II) complexes
</td></tr>
<tr><td>


Cu(II) complex
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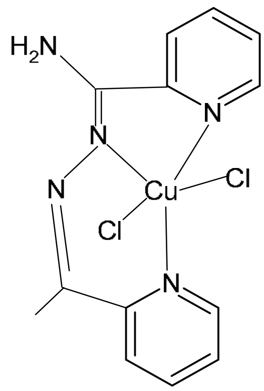
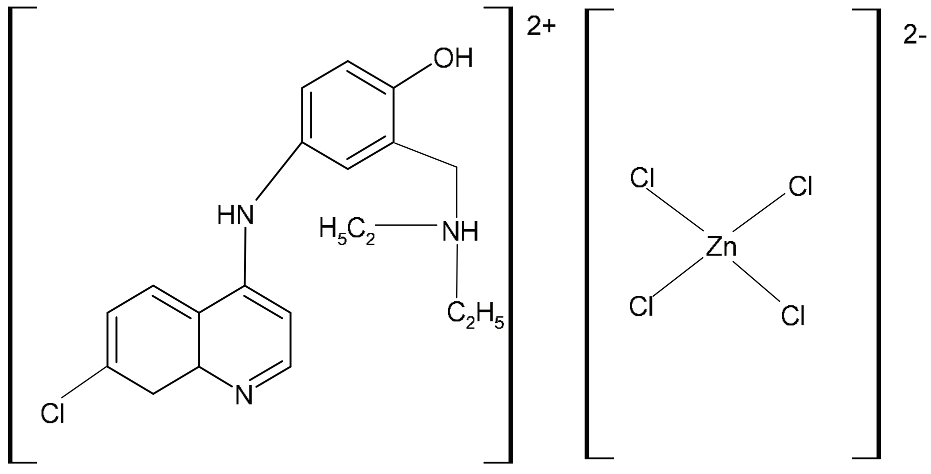
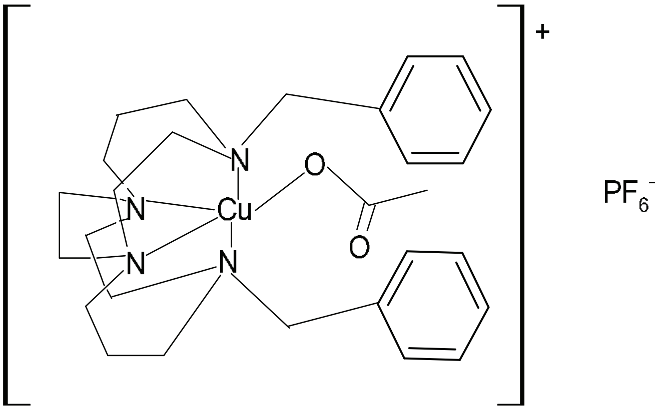


Cu(II) complex

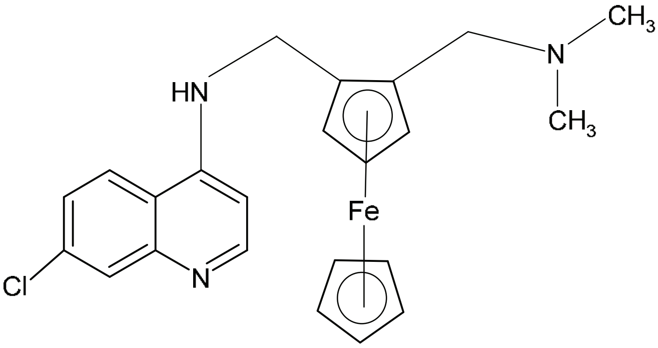
Antimalarial:

Some metal chelates such of gold, ruthenium, cobalt, rhodium, copper, cobalt, zinc, osmium and palladium show effective antimalarial activity[37-45].

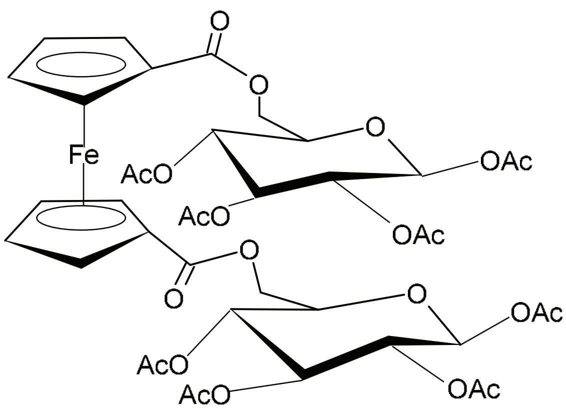
Structure
 Zn(II) with amodiaquine



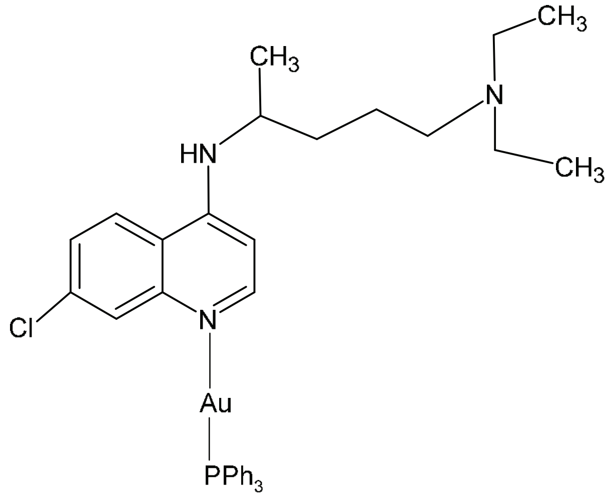
Cu(II) Complex



Ferroquine(7-chloro-[2-N,N-dimethyl-aminomethyl) ferrocenylmethylamino]quinolone



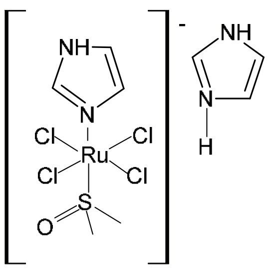
Ferrocenyl carbohydrate conjugate



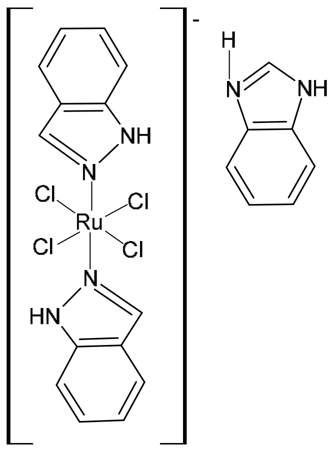
Gold chloroquine

Anti-Alzheimer:

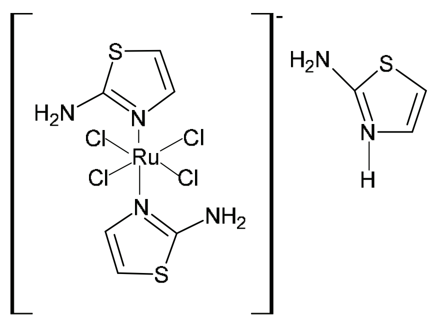
These metal complexes exhibited ability in blocking β-amyloid aggregation and scavenging its toxicity. Some complexes of ruthenium (III) exhibited significant role as anti-Alzheimer agents such as NAMI A, KP1019 and PMRU20[46].



NAMI A



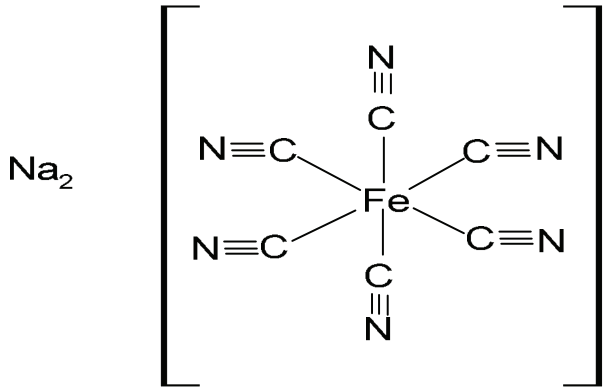
KP1019



PMru20

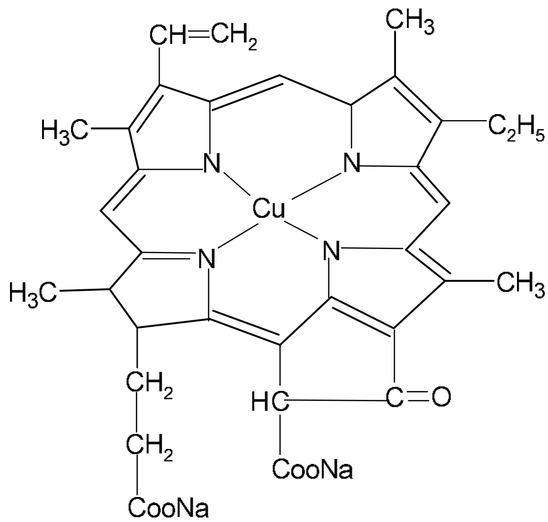
Antihypertensive:

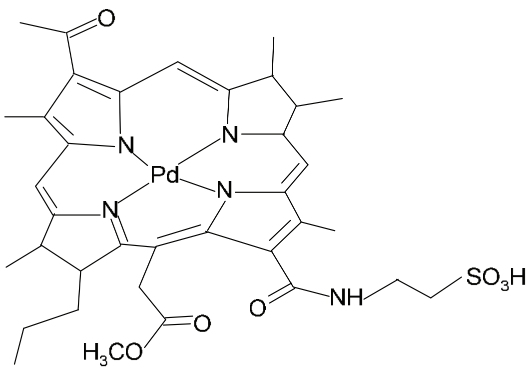
Sodium nitroprusside was below used for lowering blood pressure.[47-52]



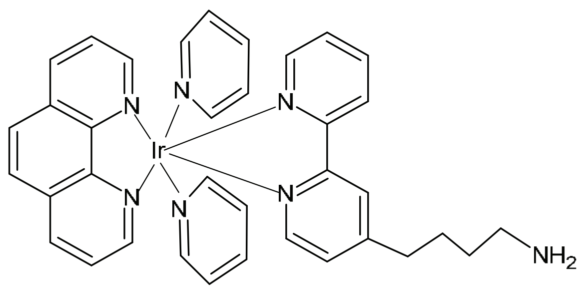
Sodium nitroprusside

Some metal complexes also find utility in cosmetics, photodynamic therapy more particularly Covid-19 virus.[52-56]

Structure
 Copper chlorophyllin



Bacteriochlorin

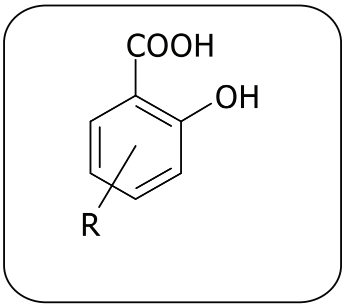


Iridium

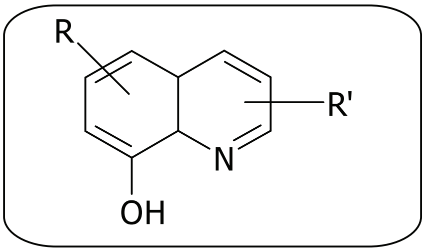
1.3 COMMON AROMATIC LIGANDS

Some of aromatic ligands used mostly are bidentate and these are;

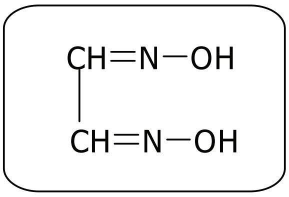
- Salicylic acid



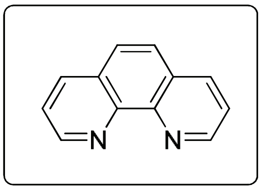
- 8-Hydroxy quinoline



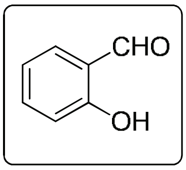
- Dimethylglyoxime



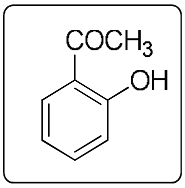
➢ 1,10-Phenanthrene



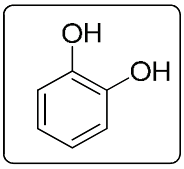
➢ Salicylaldehyde



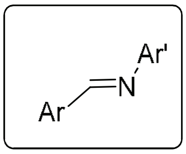
➢ o-Hydroxy acetophenone



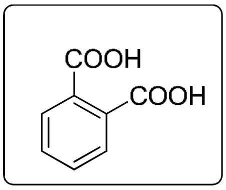
➢ Catechol



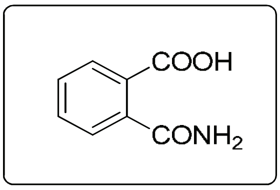
➢ Schiff base



➢ Phthalic acid



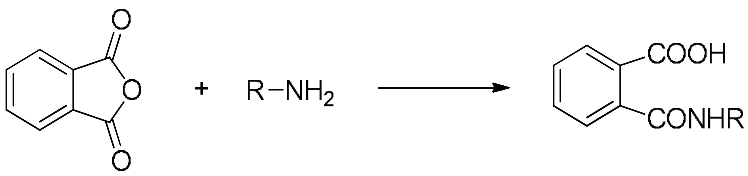
➢ Phthalamic acid



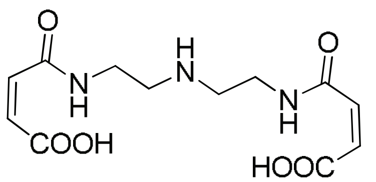
1.4 POLYDENTATE LIGANDS OF AMIDE GROUPS

Over the past few decades, revealed that peptides (Amides) have stability, versatility, optical properties and ease of their availability and in modification[57]. Their transition metal complexes have prominent application as catalyst is organic synthesis. As metal complexes of such ligands are more stable under physiological conditions, and they also received attraction in the field of physics, biology and medicines[58-96].

The amide groups are based on acid-amine reactions. The easy reaction between anhydride and amine afforded amide.



Such amide can display metal complexing capacity. Vishwanathan and Krishnan[97] studied the metal complexation of such amides prepared from maleic anhydride and diamine.

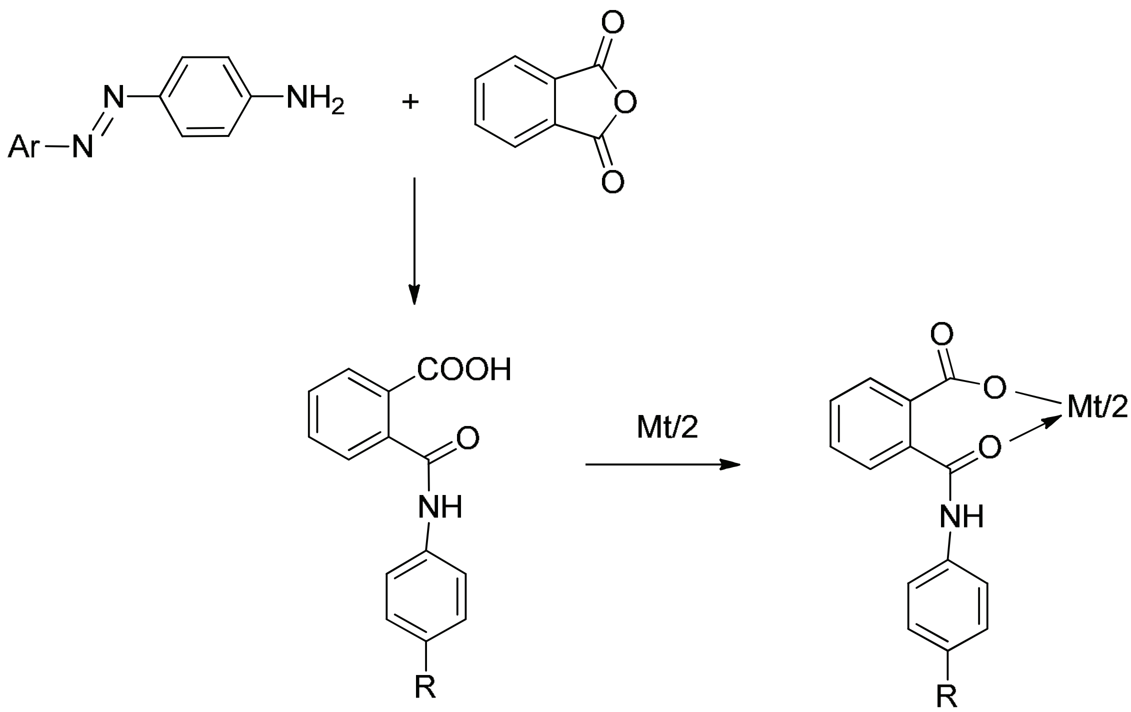


Polydentate lignd

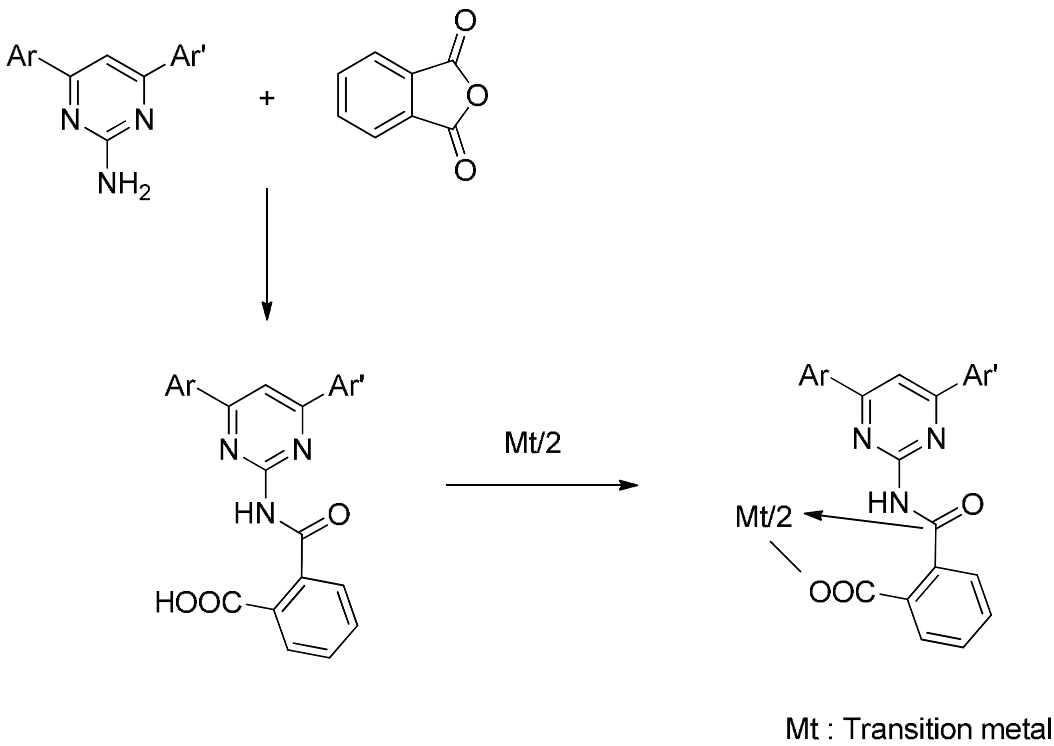
The structure as $Mn^{2+,}$ Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and VO^{4+} complexes have been studied.

Patel and Patel[98] prepared ligand from the reaction between an azo dye/ aminopyrimidine and phthalic anhydride. They also prepare complexes of this ligand with metal ions.

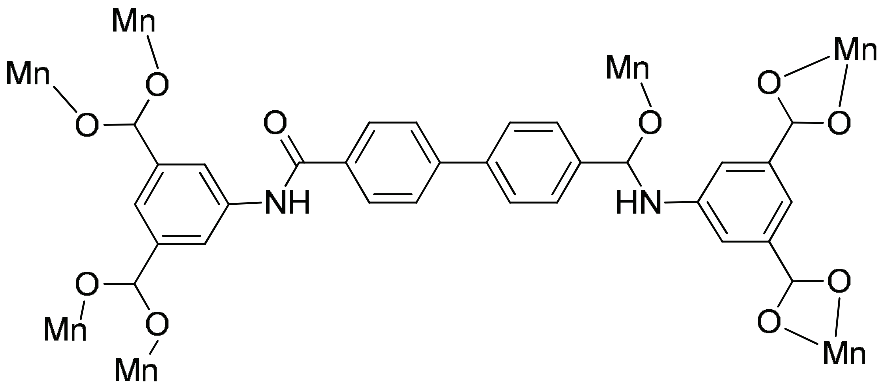
Basic azo dyes + Phthalic anhydride



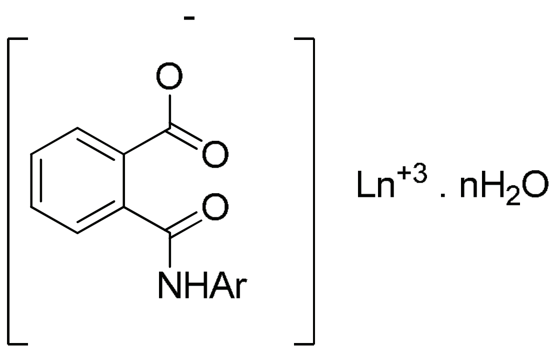
Amino Pyrimidine + Phthalic anhydride



Zhu et al.[99] Synthesized the ligand from amino isophthalic acid and biphenyl acid. The Mn^{+2} complex of this ligand was prepared and characterized by X-ray diffraction, IR spectroscopy and thermogravimetry.

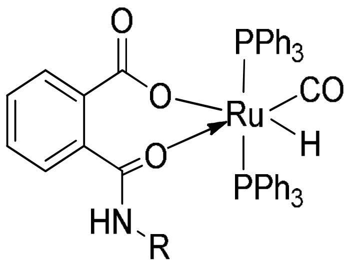


Chernyshova et al.[100] Synthesized and used it for preparation of complexes of europium, terbium and gadolinium derivatives. They also studied their luminescent behavior. It was also indicated that Eu^{3+} and Tb^{3+} complexes bear luminescence.



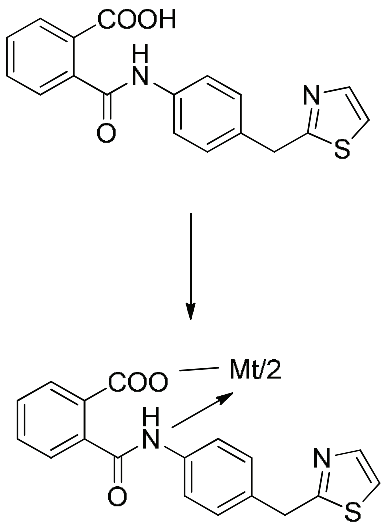
Where, $Ln^{3+}= Eu^{3+}$, GD^{3+} and Tb^{3+}

Deyakar and Lingaiah[101] reported ruthenium complexes of phthalamic acid and observed their physicochemical properties. Ashok et al.[102] also reported Ru^{3+} complexes at phthalamic acid and reported their catalytic activity.



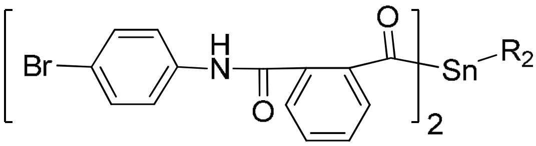
R = Phenyl, 2-Benzimidazolyl, 1-Naphthyl

Edozie et al.[103] used sulfathiazole containing phthalamic acid as ligand. They prepared Fe^{2+} and Mn^{+2} complexes and observed charge transfer intensity and antibacterial activity. It was found that complexes show very good antibacterial activity.



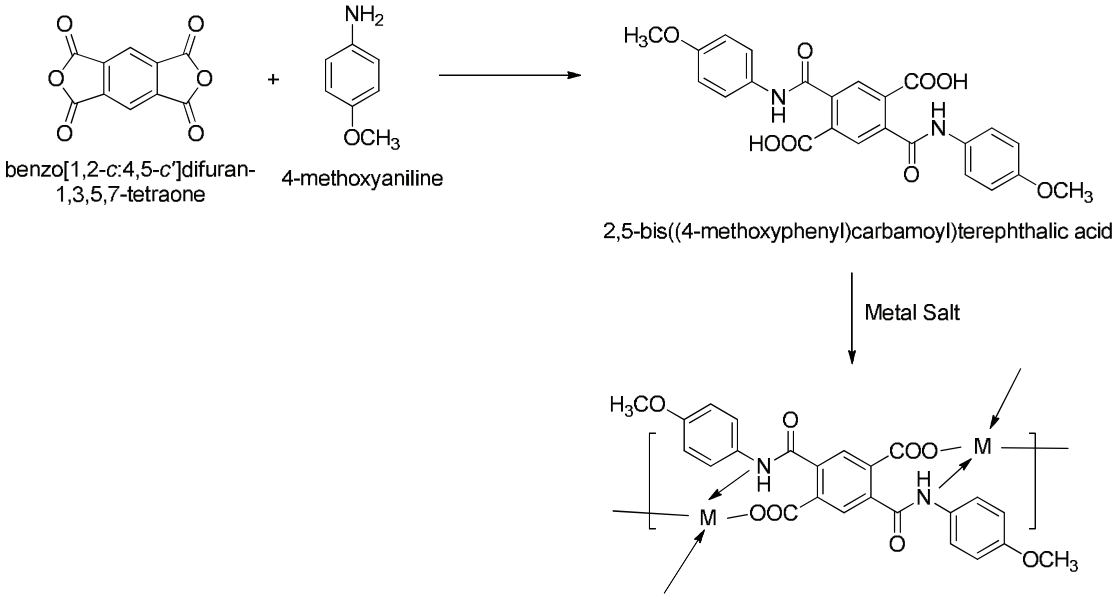
Where, Mt/2 = Fe^{+2} & Mn^{+2}

Shahid et al.[104] synthesized organo tin complexes of phthalamic acid and characterized these.



R = Me

Patel et al.[105] reported the coordination polymer based on bistype phthalamic acid. They synthesized ligand containing terephthalic acid with orthoarylaminocarbonyl derivatives.



Various ligands have been utilized from time to time to form complexes of metal ions. These were found biologically active. There is great scope in making some new ligands to prepare metal ion complexes and investigate their antimicrobial activity.

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