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SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL, CNS AND ANALGESIC STUDIES OF 2-[N-(4-chloro-2-{[1-(2-hydroxyphenyl) ethylidene] amino}phenyl) ethanimidoyl] phenol AND ITS COMPLEXES

M. Phill Dissertation submitted to

PERIYAR UNIVERSITY

In partial fulfillment of the requirements

For the award of the degree of

MASTER OF PHILOSOPHY IN CHEMISTRY

BY

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This is to certify that the project work dissertation entitled **"SYNTHESIS,CHARACTERIZATION ANTIMICROBIAL, CNS AND ANALGESIC STUDIES OF 2-[*N*-(4-chloro-2-{[1-(2-hydroxyphenyl)ethylidene]amino}phenyl)ethanimidoyl]phenol AND ITS COMPLEXES"** submitted in partial fulfillment of the degree of **MASTER OF PHILOSOPHY IN CHEMISTRY** to **PERIYAR UNIVERSITY, in MUTHAYAMMAL COLLLEGE OF ARTS AND SCIENCE RASIPURAM,** is bonafide record of the project work carried out by **DEIVANAYAGAM.P., Reg No: 12CAF1035** under my guidance and supervision and I certify that this work is original and has not been submitted elsewhere for any degree.

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Submitted for the Viva Voce examination held on:

EXAMINERS: 1)

2)

DECLARATION

DECLARATION

I hereby declare that the project work entitled **" SYNTHESIS,CHARACTRIZATION ANTIMICROBIAL, CNS AND ANALGESIC STUDIES OF 2-[*N*-(4-chloro-2-{[1-(2-hydroxyphenyl)ethylidene]amino}phenyl)ethanimidoyl]phenol AND ITS COMPLEXES** in partial fulfillment of the requirements for the award of MASTER OF PHILOSOPHY IN CHEMISTRY in record original research done by me under the supervision and guidance of **Mr.R.PA.BHOOPATHY,M.Sc.,MPhil.,** Assistant professor, **DEPARTMENT OF CHEMISTRY,MUTHAYAMMAL COLLEGE OF ARTS AND SCIENCE,RASIPURAM.** This work has not been submitted earlier in full or parts for the award of any degree/ Diploma/ Associate ship/ Fellowship other similar title of any university.

Place: **RASIPURAM** Signature of the candidate

Date: **(DEIVANAYAGAM.P)**

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DEIVANAYAGAM.P

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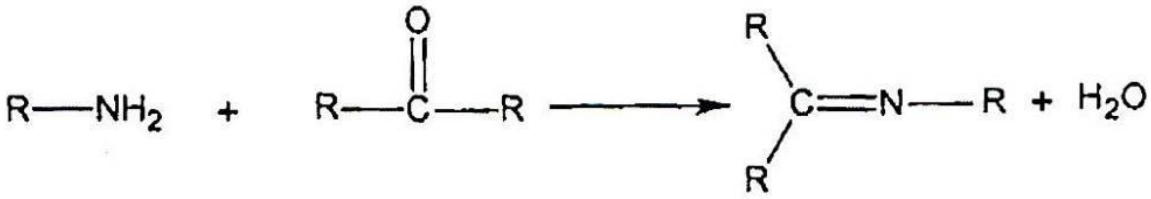
CHAPTER I

INTRODUCTION

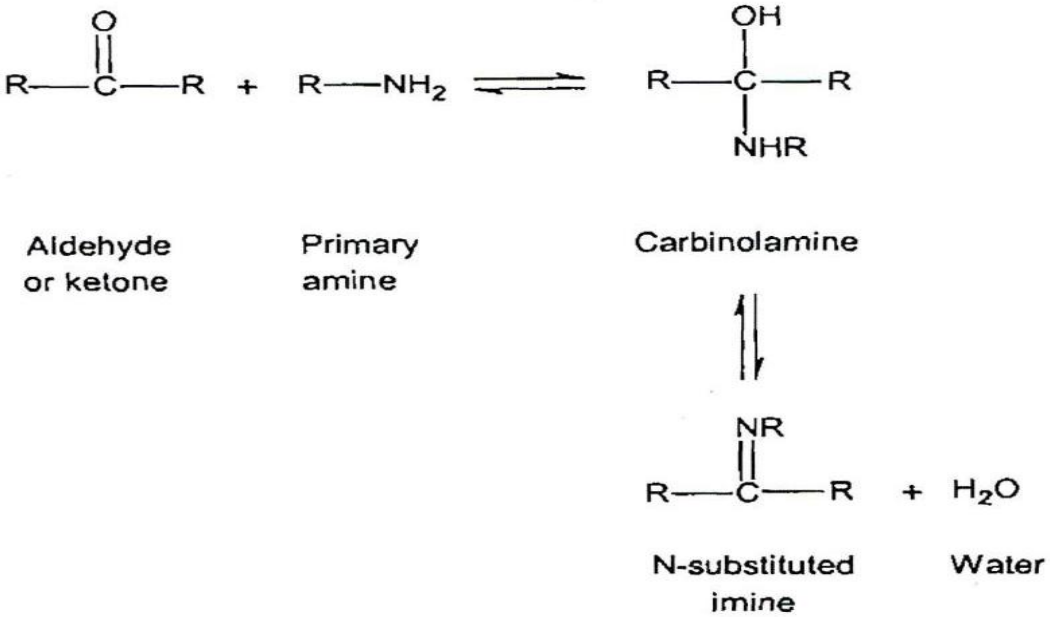
A Schiff base is a nitrogen analog of an aldehyde or ketone in which the C=O group is replaced by C=N-R group. It is usually formed by condensation of an aldehydes or ketones with a primary amine according to the following scheme:



Primary amine Aldehyde or ketone Schiff base

Where R, may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable while those of aromatic aldehydes having effective conjugation are more stable

The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating.

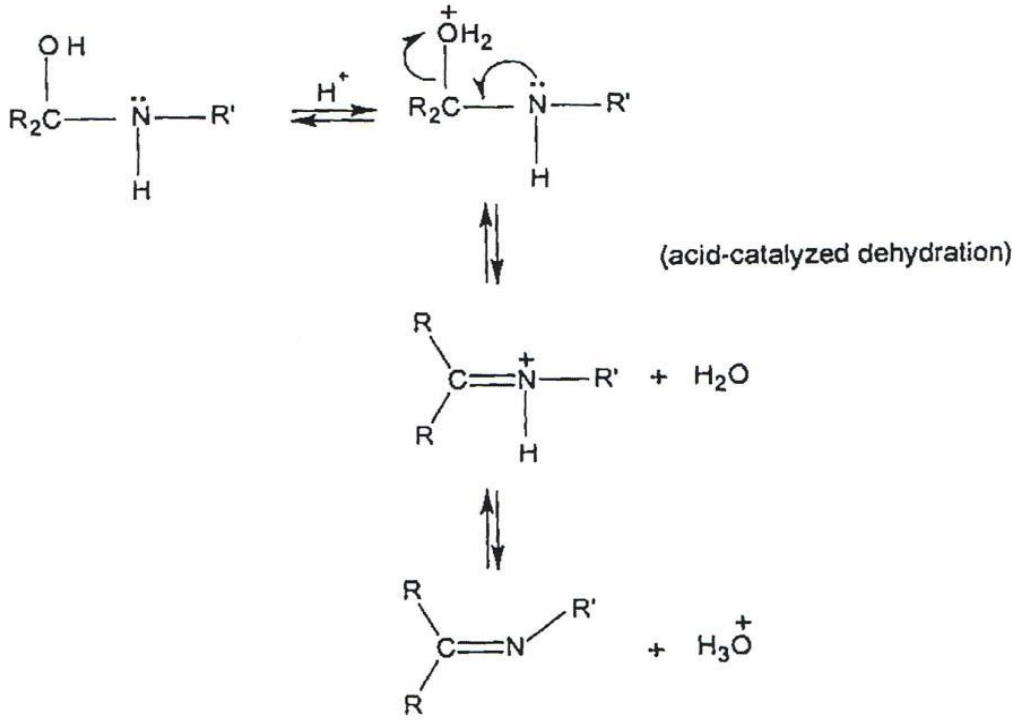


Aldehyde or ketone Primary amine Carbinolamine

N-substituted imine Water

The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base.

The mechanism of Schiff base formation is another variation on the theme of nucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine. In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration.



Typically the dehydration of the carbinolamine is the rate-determining step of Schiff base formation and that is why the reaction is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and becomes non-nucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. Therefore, many Schiff bases synthesis are best carried out at mildly acidic p^H.

Chemistry and Biological Importance of Schiff bases.

Schiff bases have a large number of synthetic uses in organic chemistry. Acylation of Schiff bases by acid anhydrides, acid chlorides and acyl cyanides is initiated by attack at the nitrogen atom and leads to net addition of the acylating agent to the carbon-nitrogen double bond. Reactions of this type have been put to good use in natural product synthesis.

Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base. Stereochemical investigation carried out with the aid of molecular model showed that Schiff base formed between methylglyoxal and the amino group of the lysine side chains of proteins can bent back in such a way towards the N atom of peptide groups that a charge transfer can occur between these groups and oxygen atoms of the Schiff bases. In this respect pyridoxal Schiff bases derived from pyridoxal and amino acids have been prepared and studied from the biological point of view. Transition metal complexes of such ligands are important enzyme models. The rapid development of these ligands resulted in an enhance research activity in the field of coordination chemistry leading to very interesting conclusions.

Thin layer chromatography (TLC) is a chromatography technique used to separate non-volatile mixtures.[1] Thin layer chromatography is performed on a sheet of glass, plastic, or aluminium foil, which is coated with a thin layer of adsorbent material, usually silica gel, aluminium oxide, or cellulose. This layer of adsorbent is known as the stationary phase.

After the sample has been applied on the plate, a solvent or solvent mixture (known as the mobile phase) is drawn up the plate via capillary action. Because differentanalytes ascend the TLC plate at different rates, separation is achieved.[2]

Thin layer chromatography can be used to monitor the progress of a reaction, identify compounds present in a given mixture, and determine the purity of a substance. Specific examples of these applications include: analyzing ceramides and fatty acids, detection of pesticides or insecticides in food and water, analyzing the dye composition of fibers

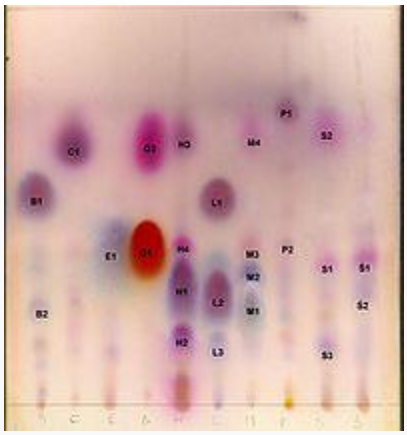
in forensics, assaying the radiochemical purity ofradiopharmaceuticals, or identification of medicinal plants and their constituents [3]

A number of enhancements can be made to the original method to automate the different steps, to increase the resolution achieved with TLC and to allow more accurate quantitative analysis. This method is referred to as HPTLC, or "high performance TLC".

Plate preparation

TLC plates are usually commercially available, with standard particle size ranges to improve reproducibility. They are prepared by mixing the adsorbent, such as silica gel, with a small amount of inert binder like calcium sulfate (gypsum) and water. This mixture is spread as a thick slurry on an unreactive carrier sheet, usually glass, thick aluminum foil, or plastic. The resultant plate is dried and *activated* by heating in an oven for thirty minutes at 110 °C. The thickness of the absorbent layer is typically around 0.1 – 0.25 mm for analytical purposes and around 0.5 – 2.0 mm for preparative TLC.[4]

Technique[edit]



Chromatogram of 10 essential oilscoloured with vanillin reagent.

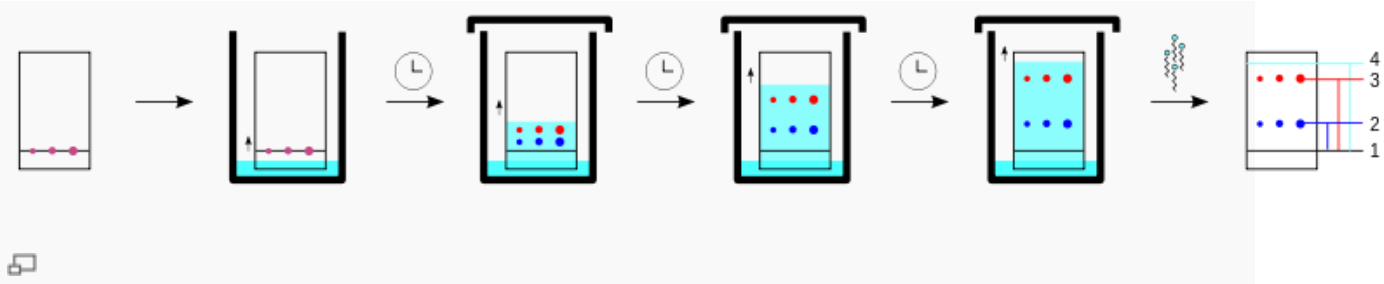
The process is similar to paper chromatography with the advantage of faster runs, better separations, and the choice between different stationary phases. Because of its simplicity and speed TLC is often used for monitoring chemical reactions and for the qualitative analysis of reaction products.

To run a thin layer chromatography, the following procedure is carried out:[5]

- A small spot of solution containing the sample is applied to a plate, about 1.5 centimeters from the bottom edge. The solvent is allowed to completely evaporate off, otherwise a very poor or no separation will be achieved. If a non-volatile solvent was used to apply the sample, the plate needs to be dried in a vacuum chamber.
- A small amount of an appropriate solvent (eluent) is poured into a glass beaker or any other suitable transparent container (separation chamber) to a depth of less than 1 centimeter. A strip of filter paper (aka "wick") is put into the chamber, so that its bottom touches the solvent, and the paper lies on the chamber wall and reaches almost to the top of the container. The container is closed with a cover glass or any other lid and is left for a few minutes to let the solvent vapors ascend the filter paper and saturate the air in the chamber. (Failure to saturate the chamber will result in poor separation and non-reproducible results).
- The TLC plate is then placed in the chamber so that the spot(s) of the sample do not touch the surface of the eluent in the chamber, and the lid is closed. The solvent moves up the plate by capillary action, meets the sample mixture and carries it up the plate (elutes the sample). The plate should be removed from the chamber before the solvent front reaches the top of the stationary phase (continuation of the elution will give a misleading result) and dried.

Separation Process and Principle[edit]

Different compounds in the sample mixture travel at different rates due to the differences in their attraction to the stationary phase, and because of differences in solubility in the solvent.[6] By changing the solvent, or perhaps using a mixture, the separation of components (measured by the R_f value) can be adjusted. Also, the separation achieved with a TLC plate can be used to estimate the separation of a flash chromatography column.[7]



Development of a TLC plate, a purple spot separates into a red and blue spot.

Separation of compounds is based on the competition of the solute and the mobile phase for binding places on the stationary phase. For instance, if normal phase silica gel is used as the stationary phase it can be considered polar. Given two compounds which differ in polarity, the more polar compound has a stronger interaction with the silica and is therefore more capable to dispel the mobile phase from the binding places. Consequently, the less polar compound moves higher up the plate (resulting in a higher Rf value).[6] If the mobile phase is changed to a more polar solvent or mixture of solvents, it is more capable of dispelling solutes from the silica binding places and all compounds on the TLC plate will move higher up the plate. It is commonly said that "strong" solvents (eluents) push the analyzed compounds up the plate, while "weak" eluents barely move them. The order of strength/weakness depends on the coating (stationary phase) of the TLC plate. For silica gel coated TLC plates, the eluent strength increases in the following order: Perfluoroalkane (weakest), Hexane, Pentane, Carbon tetrachloride, Benzene/Toluene,Dichloromethane, Diethyl ether, Ethylacetate, Acetonitrile, Acetone, 2-Propanol/n-Butanol, Water, Methanol, Triethylamine, Acetic acid, Formic acid (strongest). For C18 coated plates the order is reverse. Practically this means that if you use a mixture of ethyl acetate and hexane as the mobile phase, adding more ethyl acetate results in higher Rf values for all compounds on the TLC plate. *Changing the polarity of the mobile phase will normally not result in reversed order of running of the compounds on the TLC plate.* An eluotropic series can be used as a guide in selecting a mobile phase. If a reversed order of running of the compounds is desired, an apolar stationary phase should be used, such as C18-functionalized silica.

Analysis[edit]

As the chemicals being separated may be colorless, several methods exist to visualize the spots:

- fluorescent analytes like quinine may be detected under blacklight (366 nm)
- Often a small amount of a fluorescent compound, usually manganese-activated zinc silicate, is added to the adsorbent that allows the visualization of spots under UV-C light (254 nm). The adsorbent layer will thus fluoresce light green by itself, but spots of analyte quench this fluorescence.
- Iodine vapors are a general unspecific color reagent

- Specific color reagents exist into which the TLC plate is dipped or which are sprayed onto the plate.[8] [9] [10]
  - Potassium permanganate - oxidation
  - Bromine
- In the case of lipids, the chromatogram may be transferred to a PVDF membrane and then subjected to further analysis, for example mass spectrometry, a technique known as Far-Eastern blotting.

Once visible, the R_f value, or retardation factor, of each spot can be determined by dividing the distance the product traveled by the distance the solvent front traveled using the initial spotting site as reference. These values depend on the solvent used and the type of TLC plate and are not physical constants.

Applications[edit]

In organic chemistry, reactions are qualitatively monitored with TLC. Spots sampled with a capillary tube are placed on the plate: a spot of starting material, a spot from the reaction mixture, and a cross-spot with both. A small (3 by 7 cm) TLC plate takes a couple of minutes to run. The analysis is qualitative, and it will show if the starting material has disappeared, i.e. the reaction is complete, if any product has appeared, and how many products are generated (although this might be underestimated due to co-elution). Unfortunately, TLCs from low-temperature reactions may give misleading results, because the sample is warmed to room temperature in the capillary, which can alter the reaction—the warmed sample analyzed by TLC is not the same as what is in the low-temperature flask. One such reaction is the DIBALH reduction of ester to aldehyde.

UTRAVIOLET AND VISIBLE (UV-VIS) ABSORPTION SPECTROSCOPY

Instruments for measuring the absorption of UV or Visible radiation are made up of the following components

1. Sources (UV and Visible)
2. Wavelength selector (monochromator)
3. Sample containers

4. Detector
5. Single processor and readout

Each of these components will be considered in turn.

Sources of UV radiation

It is important that the power of the radiation source does not change abruptly over its wavelength range.

The electrical excitation of deuterium or hydrogen at low pressure produces a continuous UV spectrum. The mechanism for this involves formation of an excited molecular species, which breaks up to give two atomic species and an ultraviolet photon. This can be shown as;

$$D_2 + \text{electrical energy} \rightarrow D_2^* \rightarrow D' + D'' + h\nu$$

Both deuterium and hydrogen lamps emit radiation in the range 160-375nm. Quartz windows must be used in these lamps, and quartz cuvettes must be used, because glass absorbs radiation of wavelengths less than 350nm.

Sources of visible radiation

The tungsten filament lamp is commonly employed as a source of visible light. This type of lamp is used in the wavelength range of 350-2500 nm. The energy emitted by a tungsten filament lamp is proportional to the fourth power of the operating voltage. This means that for the energy output to be stable, the voltage to the lamp must be very stable indeed. Electronic voltage regulators or constant-voltage transformers are used to ensure this stability.

Tungsten/halogen lamps contain a small amount of iodine in quartz "envelop" which also contains the tungsten filament. The iodine reacts with gaseous tungsten, formed by sublimation, producing the volatile compound WI_2. When molecules of WI_2 hit the filament they decompose, redepositing tungsten back on the filament. The lifetime of a tungsten/halogen lamp is approximately double that of an ordinary tungsten filament lamp. Tungsten /halogen lamps are very efficient, and their output extends well into the ultra-violet. They are used in many modern spectrophotometers.

Wavelength selector (monochromator)

All monochromators contain the following component parts;

An entrance slit

A collimating lens

A dispersing device (usually a prism or a grating)

A focusing lens

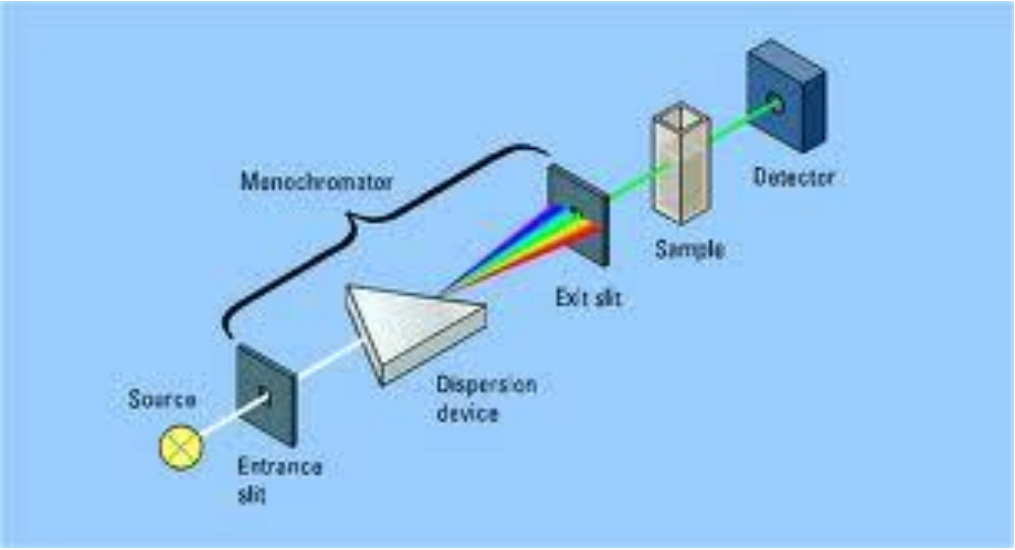
An exit slit

Polychromatic radiation (radiation of more than one wavelength) enters the monochromator through the entrance slit. The beam is collimated, and then strikes the dispersing element at an angle. The beam is split into its component wavelengths by the grating or prism. By moving the dispersing element or the exit slit, radiation of only a particular wavelength leaves the monochromator through the exit slit.

Cuvettes

The containers for the sample and reference solution must be transparent to the radiation which will pass through them. Quartz or fused silica cuvettes are required for spectroscopy in the UV region. These cells are also transparent in the visible region. Silicate glasses can be used for the manufacture of cuvettes for use between 350 and 2000nm.

Schematic diagram of a double-beam UV-Vis. Spectrometer



Detectors

The photomultiplier tube is commonly used detector in UV-Vis spectroscopy. It consists of a photo emissive cathode (a cathode which emits electrons when struck by photons of radiation), several dynodes (which emit several electrons for each electron striking them) and an anode.

A photon of radiation entering the tube strikes the cathode, causing the emission of several electrons. These electrons are accelerated towards the first dynode (which is 90v more positive than the cathode). The electrons strike the first dynode, causing the emission of several electrons for each incident electron. These electrons are then accelerated towards the second dynode, to produce more electrons which are accelerated towards dynode three and so on. Eventually, the electrons are collected at the anode. By this time, each original photon has produced $10^6 – 10^7$ electrons. The resulting current is amplified and measured.

Photomultipliers are very sensitive to UV and Visible radiation. They have fast response times. Intense light damages photomultipliers; they are limited to measuring low power radiation.

The linear photodiode array is an example of a multichannel photon detector. These detectors are capable of measuring all elements of a beam of dispersed radiation simultaneously.

A linear photodiode array comprises many small silicon photodiodes formed on a single silicon chip. There can be between 64to4096 sensor elements on a chip, the most common being 1024 photodiodes. For each diode, there is also a storage capacitor and a switch. The individual diode-capacitor circuits can be sequentially scanned.

In use, the photodiode array is positioned at the focal plane of the monochromator (after the dispersing element) such that the spectrum falls on the diode array. They are useful for recording UV-Vis. Absorption spectra of sample that are rapidly passing through a sample flow cell, such as in an HPLC detector.

Selection rule for UV spectroscopy

The selection Rules governing transitions between electronic energy levels of transition metal complexes are:

1.Δs=0 The spin Rule

2. Δ1=+/-1The Orbital Rule (Laporte)

The first rule says that allowed transitions must involve the promotion of electrons without a change in their spin.

The second rule says that if the molecule has a center of symmetry, transitions within a given set of p or d orbitals (i.e. those which only involve distributions of electrons within a given subshell) are forbidden.

Relaxation of the Rules can occur through:

a) Spin-orbit coupling- this gives rise to week spin forbidden bands
b) Vibronic coupling- an octahedral complex may have allowed vibrations where the molecule is asymmetric.

Absorption of light at that moment is then possible.

c) π –acceptor and π-donor ligands can mix with the d-orbitals so transitions are no longer purely d-d.

Color Region	Wavelength (nm)
Violet	380-435
Blue	435-500
Cyan	500-520
Green	520-565
Yellow	565-590
Orange	590-625
Red	625-740

Application of Ultraviolet and Visible spectroscopy

A few functional groups (Chromophores) may be detected by the ultra violet and visible (electronic) spectroscopy, but it is especially useful for detecting the presence and elucidating the nature of conjugated system including aromatic rings. In the application of the electronic spectroscopy for structural analysis, only the region above 200 nm is really useful and the region below 200 nm is hardly useful for this purpose.

INSTRUMENTATION FOR STUDYING INFRA-RED SPECTRA

The essential features of an infrared spectrometer are source of infrared light, a monochromator and detector. Light from the source is passed through a sample, splits into its individual frequencies in the monochromator, and the relative intensities of frequencies are measured in the detector.

a) INFRA-RED SOURCE:

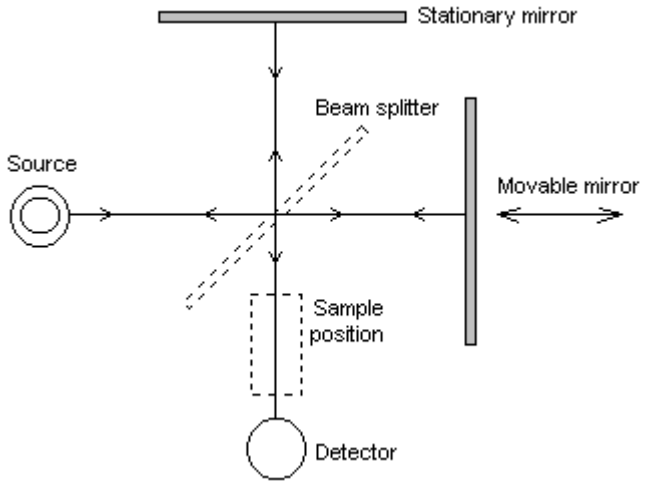
Common sources are electrically heated rods of ‘Nernst glower; or ‘globar’. Since the infrared output from these source varies in intensity over the required frequency range

compensating variable slit is pro open add close in unison with the scanning over the individual frequencies.

b) MONOCHROMATOR:

Both prisms and grating are used. The most common prism material is NaCl. Since NaCl is only transparent down to 625cm^{-1}, other alkali metal halides must be used for low frequency work. In general gratings give better resolution at high frequencies than do prisms, and NaCl suffers from the optics must be protected from condensation of moisture, usually maintaining them at about 20^{0}C above ambient temperature.

The Michelson interferometer



Radiation leaves the source and is split. Half is reflect

c) DETECTORS:

Most modern instruments use thermopile detectors. These work on the thermocouple principle that if two dissimilar metal wires are head to tail, then a different in between head and tail causes a current to flow in the wires. In the infrared spectrometer this current is proportional to the intensity of radiation falling on the thermopile.

Application of vibration spectroscopy

The force constant which is a measure of stiffness of a chemical bond, in a molecule can be evaluated. The moment of inertia can be deduced from the rotational structure of the vibrational band. The molecular shape can sometimes be deduced from the molecular shape can sometimes be deduced from the number of absorption bands observed in the vibrational spectrum of the molecule.

The vibrational spectrum is used in identifying a compound by matching its infrared spectrum to that of known samples is identical, the compounds are also identical. It is also used to study the structure of molecules and structure elucidation.

The infrared spectrum of compound is essentially the superposition of absorption bands of specific functional groups and total of skeletal vibrations. No two compounds expect the optical enantiomorphism give the infrared spectrum.

In the near infrared region which extend from 1250 to 4000cm^{-1} are found may absorption bands and combination adds often associated with H atoms. Ear infrared spectrometry is a valuable tool analyzing aromatic amines, water in other sample etc. Many useful correlations have been found in the mid-infrared region 4000-65cm^{-1}. This region is further divided into "group frequency" region 4000-1300cm^{-1} and the "finger print" region, 1300-65cm^{-1}. The presence of absorption in the assigned ranges for the various functional groups can be used as an evidence for the presence of such group in the molecule. Further the presence of inter intra-molecular hydrogen bonding and cis-trans isomers can be ascertained.

The absorption pattern in the finger region is complex and is originating from the interaction vibrational modes. Absorption in this region is unique for every molecular species.

The far-infrared region 650-10cm^{-1} containing bending vibrations of carbon, nitrogen, oxygen and fluorine bonded with atoms heavier than 19, and in addition bending motion in cyclic system. In the study of conformation of a molecule as a whole, it is seen that the different conformers differ in their far-infrared bands. Also far infrared region is well suited for the study of metal coordination compounds and organometallic compounds. Infrared spectroscopy can also be used for quantitative analyses sample.

INSTRUMENTATION FOR NMR SPECTRA

The NMR sample is prepared in a thin-walled glass tube - a NMR tube.

When placed in a magnetic field, NMR active nuclei (such as ^{1}H) absorb electromagnetic

Bruker 300 MHz. Nuclear Magnetic Resonance (NMR) spectrometer

In NMR, transitions from the more stable alignment, A, (with the field) to the less stable alignment, B, (against the field) occurs when the nucleus absorbs electromagnetic energy that is exactly equal to the energy separation between the states (ΔE). This amount of energy is

usually found in the radiofrequency range. The condition for absorption of energy is called the condition of resonance. It can be calculated as the following:

$$\Delta E=\frac{\gamma h}{2\pi}H = h\nu$$

h = Planck's constant; H= the strength of the applied magnetic field, H_o, at the nucleus; γ=the gyro magnetic ratio (a constant that is characteristic of a particular nucleus); ν=the frequency of the electromagnetic energy absorbed that causes the change in spin states

There are three factures of NMR spectra that we will focus on: the number and size of signals, the chemical shift, and spin-spin coupling.

Number and Size of signals

Let's consider how the NMR spectrometer can distinguish between hydrogen nuclei and produce multiple signals. Magnetically equivalent hydrogen nuclei produce one signal. These hydrogen nuclei experience the same local environment. For example, in a molecule such as diethyl ether, there are two sets of magnetically equivalent hydrogen. The hydrogen labeled are six magnetically equivalent methyl hydrogen, while the hydrogen labeled b are four magnetically equivalent methylene hydrogens. Notice that the methyl (a) hydrogen are all located adjacent to a carbon containing two hydrogen atoms. Additionally, the methylene (b) hydrogenare all located adjacent to an oxygen atom and a carbon atom containing three hydrogen atoms.

Antibacterial study

Antibacterial agents are of two types

i) Bacteriostatic

ii) Bacteriocidal

Antibacterial agents which inhibit the cell growth are called bacteriostatic

Ex Sulpha drugs

Antibacterial agents which actively kill the bacterial cells are called bacteriocidal

Ex Penicillin

Bacteria are of two types

i) Gram Positive

ii) Gram Negative

Bacteria that retain the dark blue or violet color of the crystal violet-iodine complex, when stained by the Gram technique are known as Gram positive bacteria. Bacteria that do not retain the color of the crystal violet-iodine complex when subjected to the Gram technique, but acquire the color of the dye (red dye) that is used to counter stain the cells are called as Gram negative bacteria Antibacterial activity is effective mainly against Gram positive and Gram negative

Ex For Gram positive

i) Bacillus subtilis

ii) Staphylococcus aureus

For Gram negative

i) Escherichia coli

Bacillus subtilis

Bacillus subtilis are sporogenous, rod shaped bacteria. The genus Bacillus consists of Bacilli forming heat resistant spores. They are gram positive but tend to be decolorized easily so as to appear Gram Variable, or even frankly gram negative. Bacilli are ubiquitous in nature including both free living and pathogenic species. Two species are considered medically significant

a) B. anthracis which cause anthrax and

b) B. cereus which cause food borne illness

Staphylococcus epidermidis

Staphylococci are gram positive cocci that occur in grape like clusters. They are unambiquitous and from the commencement cause of localized suppurative lesions in human beings. Their ability to develop resistance to penicillin and other antibiotics enhances their importance as a human pathogen, especially in hospital environment. Although, S. Epidermidis is usually non pathogenic, it is an important cause of infection in patients whose immune system is compromised, or who have in dwelling catheters.

Streptococcus Viridians

It is a miscellany of streptococci, normally resident in the mouth and upper respiratory tract and typically producing greening (alphalysis) on blood agar. Some of them may be nonlytic. They cannot be categorized under the lance field of antigenic groups. However, based on sugar fermentation, cell wall composition and production of dextrans and levans they have been classified into many species of Str. Mutans, Str Salivaius, Str Sanguis

Central nervous system

Central nervous system depressants slow normal brain functions in higher doses, some CNS depressants can become general anaesthetics

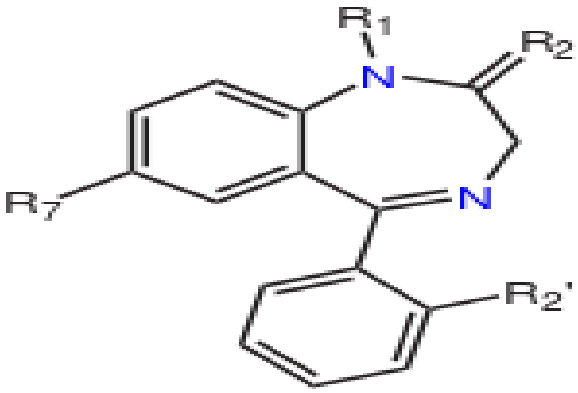
CNS depressant is used for the treatment of anxiety, panic, sleep disorders, acute stress reactions and muscle spasms, includes drugs such as valium, Librium and Xanax. Most CNS depressants act on the brain by affecting the neurotransmitter gamma aminobutyric acid (GABA). GABA unique ways, it is through their ability to increase GABA activity that they produce a drowsy or calming effect that is beneficial to that suffering room anxiety or sleep disorders. These drugs are also particulary dangerous when mixed with other medications or alcohol; overdose can cause breathing problems and lead to death. Although the newer sleep medications such as ambient, lunesta and sonasta---appear to have reduced dependence and abuse liabilities.

Over the counter medications such as certain cough suppressants containing dextromethrophan(DXM) are also abused for their psychoactive effects producing hallucinations and dissociative sensations. However, overdose of DXM can also produce confusion, disorientation, motor impairment, blurred vision and nausea, rapid or irregular heartbeat, high blood pressure and loss of consciousness. Transquilizers and sedatives are examples are examples of CNS depressants.

Barbiturates such as mephobarbital (Mebaral) and pentobarbital sodium (Nembutal) are used to treat anxiety tension and sleep disorders.

Benzodiazepines

The various benzodiazepines drugs such as diazepam, chlordiazepoxide HCl (Librium) and alprozolam (Xanax), which can be prescribed to treat anxiety, acute stress reactions and panic attacks. Benzodiazepines that have a more sedating effect such as estazolam can be prescribed for short term treatment of sleep disorders



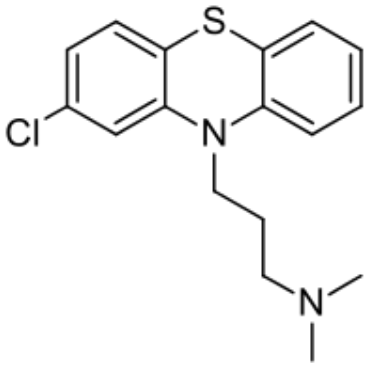
The core structure of benzodiazepines. "R" labels denote common locations of side chains, which give different benzodiazepines their unique properties.

There are many CNS depressants and most on the brain similarly they affect neurotransmitter gamma-amino butyric acid(GABA). Neurotransmitters are brain chemicals that facilitate communication between brain cells. GABA works by decreasing brain activity. Although different classes of CNS depressants work in unique ways ultimately it is their ability to increase GABA activity that produces a drowsy or calming effect. Despite these beneficial effects for people suffering from anxiety or sleep disorders, barbiturates and benzodiazepines can be addictive and should be used only as prescribed. CNS depressants should not be combined with any medication or substance that causes sleepiness, including prescription pain medicines, certain over the counter cold and allergy medications or alcohol if combined they can slow breathing or slow both the heart and respiration, which can be fatal

Chlorpromazine

Chlorpromazine is the oldest antipsychotic drug. The molecular structure is 3-(2-chlorophenothiazin-10-yl)-N,N-dimethylpropan-1-amine. Chlorpromazine was the first drug developed with specific antipsychotic action. Its use has been described as the single biggest advance in psychiatric treatment, dramatically improving the prognosis of patients in psychiatric hospitals world-wide. It was the prototype for the phenothiazine class which later grew to comprise several other agents. Chlorpromazine works on a variety of receptors in the central nervous system producing anticholinergic,antidopaminergic,antihistaminic and antiadrenergic effects. Its anticholinergic properties cause constipation, sedation,hypotension and relieve nausea. Its also has anxiolytic (anxiety relieving) properties. Its antidopaminergic properties can cause extrapyrimidal symptoms such as akathisa(restlessness), dystonia and Parkinosonism.

Chlorpromazine inhibits clathrin-mediated endocytosis. It is often administered in acute settings as syrup which has a faster onset of action than tablets



Structure of Chlorpramazine

Pharmacodynamics and central effects

Chlorpromazine is a very effective antagonist of D_2 dopamine receptors and similar receptors such as D_3 and D_5. Unlike most other drugs of this genre, it also has a high affinity for D_1 receptors. Blocking these receptors cause diminished neurotransmitter binding in the forebrain, resulting in many different effects. Dopamine, unable to bind with a receptor, cause a feedback loop that causes dopaminergic neurons to release more dopamine. Therefore, upon first taking the drug patients will experience an increase in activity of dopaminergic neural activity.

Eventually, dopamine production of the neurons will drop substantially and dopamine will be removed from the synaptic left. At that point, neural activity decreases greatly, the continual blockade or receptors only compounds this effect. Chlorpromazine acts as an antagonist on different postsynaptic receptors.

Dopamine receptors (Subtypes D_1,D_2,D_3 and D_4) which account for its different antipsynoptic properties on productive and unproductive symptoms; in the mesolimbic dopamine system accounts for the antipsychotic effect whereas the blockade in the nigrostraiatal system produces the extra pyramidal effects.

Serotonin receptors (5-HT_1 and 5-HT_2) with anxiolytic, and antiaggresive properties as well as an attenuation of extrapyrimidal side effects, but also leading to weight gain, fall in blood pressure, sedation and ejaculation difficulties

Histamine receptors (H_1 receptors accounting the sedation,antiemetic effect, vertigo, fall in blood pressure and weight gain)

Alpha1 and alpha 2 – Adrenergic receptors (antisympathomimetic properties, lowering of blood pressure, reflex tachycardia,vertigo,sedation,hypersalivation,sexual dysfunction

M_1 and M_2 muscarinic acetylcholine receptors (causing anticholinergic symptoms such as dry mouth, blurred vision, constipation, tachycardia side effects)

Peripheral effects

Chlorpromazine is an antagonist to H1 receptors (antiallergic effects). H_2 receptors (forming of gastric juice and 5-HT receptors (antiallergic/gastrointestinal actions) Chlorpromazine is often referred to as a "dirty drugs" , where as the atypical antipsychotic amisulpride, for example, acts only on central D2 and D3 receptors and is therefore a "Clean drug".

Analgesic

Drug that relieves pain without blocking the conduction of nerve impulses

Analgesics are classified by the mechanism of their pain relieving act on receptor in brain to inhibit pain impulses on which inhibit the systhesis of prostaglandins

The antipyretic agents also have mild analgesic activity.

Amongst the most common group of compounds used as antipyretic, analgesics are salicylates,aniline and aminophenol analogues, pyrazolones and quinoline derivatives. Though these heterogeneous groups of compounds are analgesics, they have no addictive properties. Their analgesic use is limited to mild aches and pains like headache and backache.

Analgesic is an ill defined unpleasant sensation usually evolved by external or internal noxious

Analgesics are classified into two

Opiod analgesics

Opiod analgesics- The word opiates refers to the products obtained from the opium poppy. The term opiod is used to denote all naturally occurring, semi synthetic and synthetic drugs which have a morphine like action via relief from pain and depression of them (Such as morphine) induce sleep

Non Opioid analgesic

Non-opioid analgesics which do not interact with opioid receptors and relieve pain without depression of the CNS (ex salicylates and related compounds). Painful reaction in experiment animals can be produced by applying noxious (unpleasant) stimuli such as.

I Thermal (radiant heat as a source of pain)

II Chemical (irritant such as acetic acid and bradykinin) and

III Physical pressure (tail compression)

In the laboratory commonly used procedures are Tail-flicking (tail-withdrawal from the radiant heat) method using analgesiometer and hot plate method etc

Mechanism of action of analgesic drugs

Though these drugs have different chemical structure, they produce qualitatively similar analgesic effects. According to the current unify concept of NSAID action during inflammatory pain and fever. Arachidonic acid (AA) is liberated from phospholipids fraction of the cell membrane. AA is then converted via,cyclo oxygenase (Cox-I and Cox-2) pathway to prostaglandin (PGs).

The steps are

1) Oxidation of AA to the hydroxyl endoperoxide and
2) Its subsequent reduction transformed into the primary prostaglandin PGE_2,PGF_2,PGD_2,PGI_2 and TXA_2

Though Cox-1 and Cox-2 are structurally very similar there are clear biochemical differences between them. Even then both use the same.

CHAPTER II

REVIEW OF LITERATURE

REVIEW OF LITERATURE

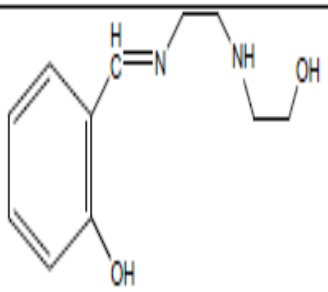
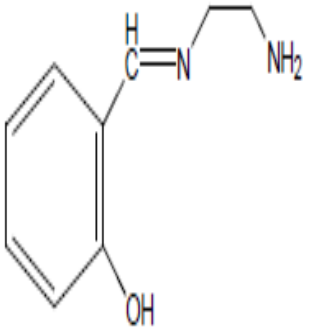
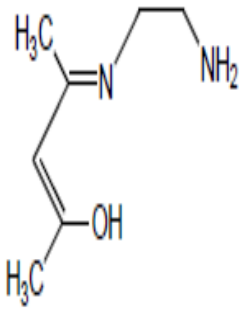
Review on of mono and polynuclear metal complexes of mono - condensed imino-Schiff bases:

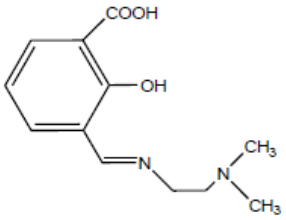
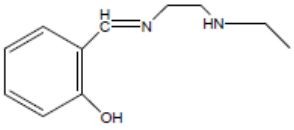
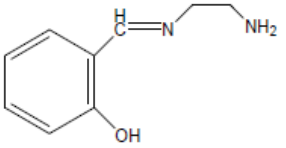
The Schiff bases derived from the mono-condensation of diamines with carbonyl compounds (salicylaldehyde, o-hydroxyacetophenone, acetylacetone or benzoylacetone) are a group of mono-negative NNO donor ligands which readily react with transition metal ions (especially Cu(II)). These ligands are readily available and versatile. Depending on the nature of the starting materials (primary amines and carbonyl precursors), they exhibit various denticities and functionalities. Depending on the number, the nature and the relative position of the donor atoms

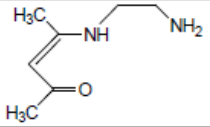
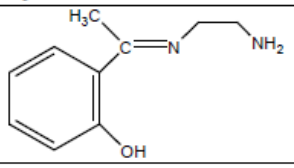
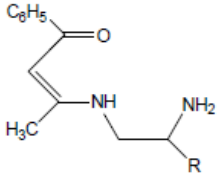
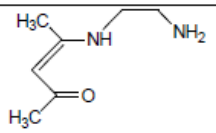
of a Schiff base, the ligand allows a good control over the stereochemistry of the metallic centers in homo and hetero polynuclear complexes . All these advantages make Schiff bases very good ligands in the effort to synthesize metal complexes having relevance to bioinorganic chemistry, catalysis, encapsulation, transport and separation processes. The review deals with di- and polynuclear complexes of mono- condensed imino-Schiff base ligands .

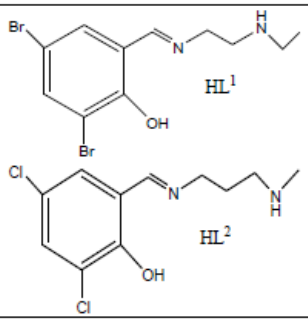
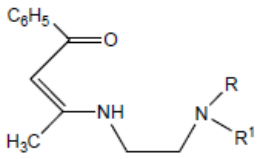
There are very few reports available regarding with the metal complexes of mono-condensed imino-Schiff bases derived from N-methylethylenediamine/N-propylethylenediamine with salicylaldehyde/o-hydroxyacetophenone. Moreover the nuclease activity of these complexes was not reported so far in the literature.

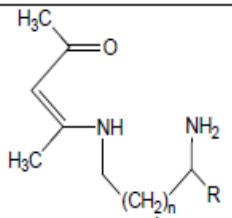
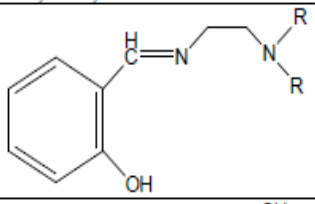
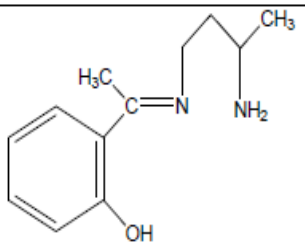
Mono and polynuclear metal complexes with imino-schiff bases

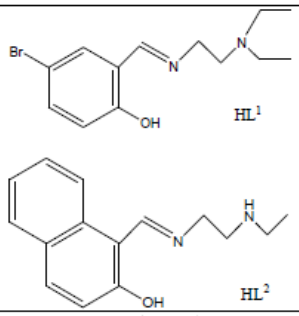
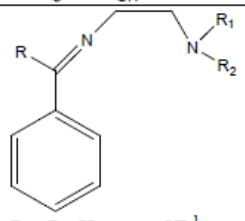
S.No (A)	Name of the ligand (B)	Structure of the ligand (C)	Metal nuclearity (D)	Geometry around the metal (E)	General formula of the complex (F)	Ref (G)
1	N-salicylidene-N'-(2-hydroxyethyl ethylene-diamine) (shen)		Dinuclear Cu(II)	Distorted Square-based pyramid (X-ray Structure)	[[Cu(shen)]$_2$(tp)] tp= dianion of terepthalic acid	5
2	N-(2-aminoethyl)salicylal dimine (SEH)		Di and Trinuclear Cu(II)	Square planar	[SECuImCuSE](ClO$_4$) [(SECu)$_3$OH](ClO$_4$)$_2$.H$_2$O	6
3	7-amino-4-metthyl-5-aza-3-hepten-2-one (AEH)		Di and Trinuclear Cu(II)	Square Planar (di) Square pyramidal (tri) (X-ray Structure)	[AECuOAC]$_2$ *[(AECu)$_3$OH](ClO$_4$)$_2$	7, *8

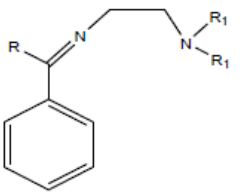
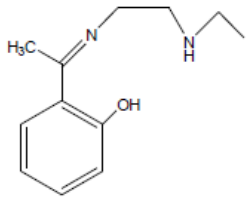
A	B	C	D	E	F	G
4	3-{N-[2-(dimethylamino)ethyl] iminomethyl}-salicylicacid (H_2L)		Di and tetranuclear Zn(II)	(di)-Square pyramidal, (tertra)-two Zn(II) centers Square pyramidal, two Zn(II) centers distorted octahedral (X-ray Structure)	$[Zn_2(HL)_2(H_2O)_2]$-$(NO_3)_2.2H_2O$ $[Zn_2(HL)_2(CH_3CO_2)_2]6H_2O$ $[Zn_4(L)_4]$. $6.5H_2O$	9
5	N-ethyl-N'-salicylidene-1-2-diaminoethane (HL)		Tetranuclear Cu(II)	Square planar (X-ray Structure)	$\{[Cu_3(L)_3(\mu_3\text{-}C_2O_4)]$-$[Cu(L)(H_2O)](ClO_4)_2\}$. 0.5(H2O). 0.5(CH3OH)	10
6	2-[(2-amino-ethylimino)-methyl]-phenol (SE)		Trinuclear Cu(II)	Square pyramidal (X-ray Structure)	$[Cu_3(\mu_3\text{-}OH)(SE)](ClO_4)_2$. $0.5\ H_2O$	11

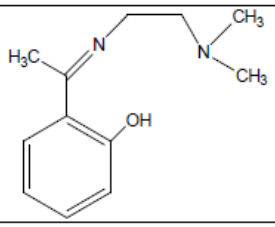
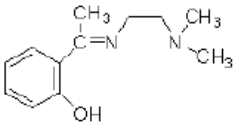
A	B	C	D	E	F	G
7	7-amino-4-metthyl-5-aza-3-hepten-2-one (AE)		Trinuclear Cu(II)	Square pyramidal (X-ray Structure)	$[Cu_3(\mu_3\text{-}OH)(AE)](ClO_4)_2$. $1.5\ H_2O$	11
8	1-(N-*ortho*-hydroxyaceto phenonimine)-2-aminoethane (L)		Dinuclear (Cu)	Square pyramidal (X-ray Structure)	$[Cu_2L_2(\mu_2\text{-}1,1\text{-}N_3)_2]$. H2O. CH3OH	12
9	6-amino-3-methyl-1-phenyl-4-azahex-2-en-1-one (HL^1) (R=H) 6-amino-3,6-dimethyl-1-phenyl-4-azahex-2-en-1-one (HL^2) (R=CH_3)		Trinuclear Cu(II)	Square pyramidal (X-ray Structure)	$[(CuL^1)_3(\mu_3\text{-}OH)](ClO_4)_2$ $[(CuL^2)_3(\mu_3\text{-}OH)](ClO_4)_2$ $0.75H_2O$	13
10	7-amino-4-metthyl-5-aza-3-hepten-2-one (HAMAH)		Dinuclear Cu(II)	Square planar (X-ray Structure)	$[\{Cu(AMAH)\}_2$ $(\mu\text{-}4,4'\text{-}bipy)](BF_4)_2$	14

A	B	C	D	E	F	G
11	2,4-dibromo-6-[(2-ethyl aminoethylimino)methyl] Phenol(HL^1) 2,4-dichloro-6-[3-methyl aminopropylimino)methyl] phenol (HL^2)		Dinuclear Ni(II) with HL^1 & two dinuclear Ni(II) units with HL^2 in same molecule	Octahedral (X-ray structure)	$[Ni_2(L^1)_2(MeCN)_2(\mu_{1,1}\text{-}N_3)_2]\cdot MeOH$ $[Ni_2(L^2)_2(MeOH)_2(\mu_{1,1}\text{-}N_3)_2][Ni_2(L_2)_2(OH_2)_2(\mu_{1,1}\text{-}N_3)_2]\cdot MeOH$	15
12	6- aminomethyl-3-methyl-1-phenyl-4-azahex-2-en-1-one (HL^1) 6- aminoethyl-3-methyl-1-phenyl-4-azahex-2-en-1-one (HL^2) 6- aminodimethyl-3-methyl-1-phenyl-4-aza-hex-2-en-1-one (HL^3)	 R=H, R^1=CH_3 (HL^1) R=H, R^1=C_2H_5 (HL^2) R, R^1=CH_3 (HL^3)	Trinuclear Cu(II)	Distorted square based pyramid (X-ray structure)	$[(CuL^1)_3(\mu_3\text{-}OH)]\,[ClO_4]_2\cdot 3H_2O$ $[(CuL^2)_3(\mu_3\text{-}OH)]\,[ClO_4]_2\cdot H_2O$ $[(CuL^3)_3(\mu_3\text{-}OH)]\,[ClO_4]_2\cdot 7H_2O$	16

A	B	C	D	E	F	G
13	8-amino-4-methyl-5-azaoct-3-en-2-one (HL^1) 7-amino-4-methyl-5-azaoct-3-en-2-one (HL^2) 7-amino-4-methyl-5-azahept-3-en-2-one (HL^3)	 n=1, R=H, HL^1 n=0, R=CH_3, HL^2 n=0, R=H, HL^3	Trinuclear Cu(II)	Distorted square-pyramidal (X-ray structure)	$[(CuL^1)_3(\mu_3\text{-}OH)](NO_3)_2$ $[(CuL^2)_3(\mu_3\text{-}OH)](I)_2.H_2O$ $[(CuL^3)_3(\mu_3\text{-}OH)](I)_2$ $[(CuL^1)_3(\mu_3\text{-}OH)][Cu^1I_3]$	17
14	N-[2-(N,N-dimethyl-amino)-ethyl]-salicylamine (HL)		Trinuclear Zn(II)	Distorted square-pyramidal (X-ray structure)	$[(Zn_3L_3)OH](ClO_4)_2.$ $0.25H_2O$	4
15	1-(N-*ortho*-hydroxyaceto phenonimine)-3-aminobutane (HL)	 R=CH_3, HL	Dinuclear Co(III)	Distorted octahedral (X-ray structure)	$[Co_2(\mu\text{–}N_3)_2(L)_2(N_3)_2]$	18

A	B	C	D	E	F	G
16	4-bromo-2-[(2-diethylamino ethylimino)methyl]phenol (HL^1) 1-[(2-ethylaminoethylimino)-methyl]-napthalen-2-ol (HL^2)		Dinuclear Cu(II)	Square pyramidal (X-ray structure)	$[(CuL^1)_2(\mu_{1,1}\text{-}N_3)_2]$ $[(CuL^2)_2(\mu_{1,1}\text{-}N_3)_2]$	19
17	2-[(2-amino-ethylimino)-methyl]-phenol (HL^1) 2-[(2-methylamino-ehtylimino) -methyl]-phenol (HL^2) 2-[(2-dimethylamino-ehtylimino)-ethyl]-phenol (HL^3)	 $R= R_1= R_2=H$ HL^1 $R=R_1=H, R_2=CH_3$ HL^2 $R=R_1=R_2=CH_3$ HL^3	Trinuclear Cu(II)	Square pyramidal (X-ray structure)	$[(CuL^1)_3(\mu_3\text{-}OH)]\ (ClO_4)_2 \cdot 3.75H2O$ $[(CuL_2)_0(\mu_3\text{-}OH)](ClO_4)_2$ $[(CuL_3)_3(\mu_3\text{-}OH)]\ (BF_4)_2 \cdot 0.5CH_3CN$	20

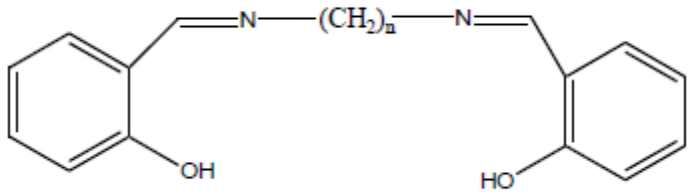
A	B	C	D	E	F	G
18	2-[1-(2-dimethylamino-ethylimino)-ethyl]-phenol (HL^1) 2-[(1-2-dimethylamino-ethylimino)-methyl]-phenol (HL^2)	 $R=R_1=CH_3$ HL^1 $R=H, R_1=CH_3$ HL^2	Dinuclear Cu(II)	Square pyramidal (X-ray structure)	$[Cu_2(\mu\text{-}H_2O)(L^1)_2(H_2O)_2]\ (BF_4)_2.2H2O$ $[Cu_2(\mu\text{-}H_2O)(L^2)_2(H_2O)_2]\ (BF_4)_2.2H2O$	21
19	1-(N-ortho-hydroxyacetophen imine)-2-(N-ethyl)amino-ethane) (HL)		Polynuclear Cu(II)	Distorted Square pyramidal (X-ray structure)	$[CuL(\mu_{1,1}\text{-}N_3)]_n$	22

A	B	C	D	E	F	G
20	2-[(1-2-dimethylamino-ethylimino)-methyl]-phenol (HL^1)		Di and polynuclear	Square pyramidal (X-ray structure)	$[CuL(N_3)]_2$ $[Cu_7L_2(N_3)_{12}]_n$ $[Cu_2L(dmen)(N_3)_3]_n$	23
21	2-[1-(2-dimethylamino-ethylimino)-ethyl]-phenol		Mono & tri nuclear	Distorted square pyramidal (x-ray structure)	$[CuL(H_2O)(NO_3)]$ $[(CuL)_3(\mu_3\text{-}OH)]\ (ClO_4)_2.H_2O$	24

Review on transition metal complexes with tetradentate Schiff base ligands containing polymethylene diamines of varying chain length:

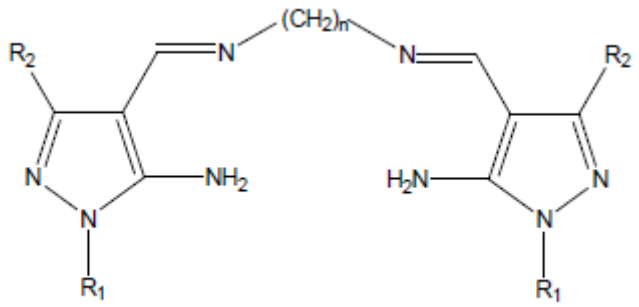
Transition metal complexes containing salen type of ligands derived from o-hydroxy aromatic carbonyl compound and various primary diamines have been the subject of a number of investigation.

Lawrence C. Nathan et al have reported the x-ray structures of N,N'-polymethylene-bis(salicyldiminato) copper(II) Schiff base complexes with polymethylene backbones ranging from two to eight carbons. The complexes were found to have square planar and distorted tetrahedral structure. Structure of the ligand is shown in present work copper(II) and nickel(II) Schiff base complexes derived from polymethylene diamine backbones containing six to eight carbon atoms and salicylaldehyde/o-hydroxyacetophenone.



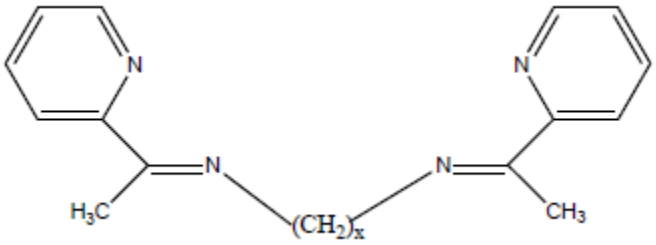
Structure of N, N'-polymethylene-bis (salicyldimine)

Two series of copper (II) and Nickel (II) complexes containing deprotanated tetradentate N, N'-bis (5-aminopyrazol-4-yl-methylene) polymethylene diamine ligand with varying length (n = 2-4) of the brigde $-HC=N(CH_2)_nN=CH-$ have been prepared and investigated by A.L. Nivorozhkin *et al* . The complex was found to have distorted square planar structure.



N, N'-bis (5-aminopyrazol-4-yl-methylene) polymethylenediamine

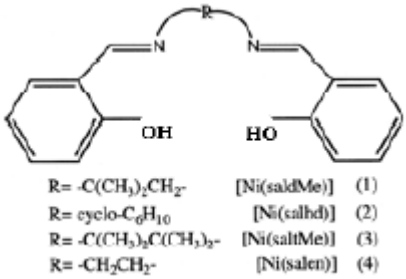
Suparna Banerjee *et al* have investigated the unusual trigonal prismatic and severely distorted octahedral coordination for cadmium (II) complexes derived from tetradentate pyridyl di-Schiff base ligands, N, N'-bis (1-pyridin-2-yl-ethylidine)-propane 1,3- diamine or N, N'-bis (1-pyridin-2-yl-ethylidine)-ethane 1,2-diamine.



R.N. Prasad *et al* have reported a large number of macrocyclic transition metal complexes derived from α-diketones and polyamines. Randhir Singh *et al* reported macrocyclic complexes of copper(II), nickel(II) and cobalt(II) derived from α and β- diketones and 2,6-diaminopyridine.

Sulekh Chandra *et al* have reported a series of macrocyclic tetradentate ligands derived from α and β- diketones and 1,3-propanediamine/1,3-phenylenediamine.

I.C Santos *et al* have investigated the oxidative chemistry of three nickel(II) complexes with Schiff base ligands derived from salicylaldehyde and diamines with different steric demands, N,N'-2-methylpropane-2,3-diyl-bis(salicylaldimine) and N,N'-2-methylbutane-2,3-diyl-bis(salicylaldimine).

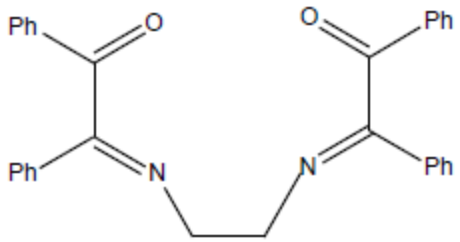


N, N'-2-methylbutane-2, 3-diyl-bis (salicylaldimine)

In both the compounds the coordination geometry around the nickel atom is roughly square planar, with the ligands bound through two nitrogen atoms and two oxygen atoms in a *cis* configuration, but with the four N_2O_2 atoms distorted in a tetrahedral fashion.

Josie Hunter *et al* have reported N-only bridging thiocyanate, homo and hetero binuclear complexes derived from 2,6-diacetylpyridine and 1,5-diaminopentane through transmetallation process.

M. Radhakrishna Reddy *et al* have reported cobalt (II) complexes of Schiff base ligands derived from benzil and various diamines.



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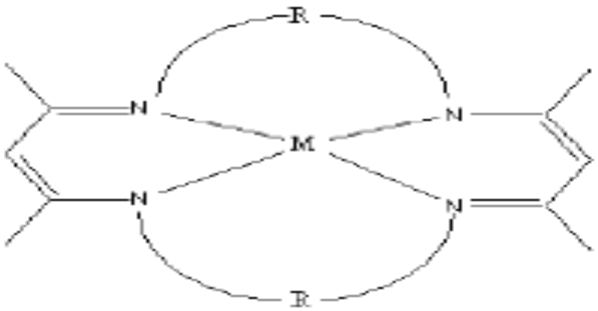
Structure of bis(benzil)ethylenediamine

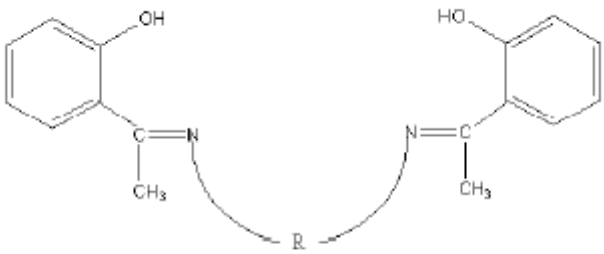
K.H.Reddy *et al* have synthesized a series of macrocyclic divalent metal complexes of acetylacetone buckled with different diamines by template method. It gives the structure of macrocyclic metal complex of acetylacetone buckled with different diamines.



R= 1,2-C_2H_4 / 1,3- C_6H_4 /3,4-CH_3 C_6H_3 / C_2H_4 / 1,2-C_3H_6

Structure of macrocyclic metal complex of acetylacetone buckled with various diamines

T.D. Thangadurai *et al* have reported several hexacoordinated ruthenium (III) complexes derived from o-hydroxyacetophenone and different diamines. The general structure of Schiff base ligands used in this study is given in.



R= -$(CH_2)_2$- /-(CH(CH_3)-CH_2-)-/-$(CH_2)_4$-/-(C_6H_4)-

Structure of Schiff base

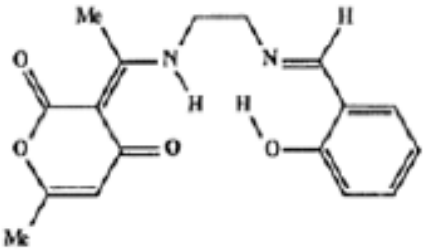
There are no reports regarding with acetato bridged dinuclear metal complexes of Schiff base ligands derived from polymethylene diamines viz., 1,6-diaminohexane, 1,7-diaminoheptane, 1,8-diaminooctane and salicylaldehyde/o-hydroxyacetophenone.

A brief review on mononuclear metal complexes of unsymmetrical Schiff bases:

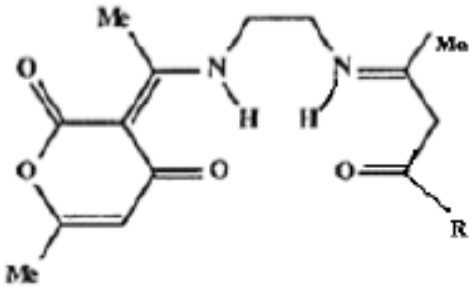
Over the past two decades, extensive research has been carried out on symmetrical bis-Schiff base ligands and their transition metal complexes, which can be prepared by usual condensation of one mole of diamine and two moles of β-diketone or an aromatic o-hydroxy carbonyl compound . But there are only a few reports regarding with synthesis of unsymmetrical Schiff bases derived from equimolar condensation of a diamine and two different aldehydes ketones which is more difficult to obtain during the recent years, there has been a remarkable interest in the design, synthesis and characterization of transition metal complexes of unsymmetrical Schiff base ligands from the fact that the central metal ions in natural systems are in unsymmetrical organic moities. Hence transition metal complexes synthesized from unsymmetrical Schiff bases serve as models of relevance to bio-inorganic chemistry such as metalloproteins and metalloenzymes in which transition metal ions are found usually in a distorted environment. Unsymmetrical Schiff base complexes have shown a wide spectrum of applications such as biochemical, analytical, industrial and antimicrobial agents.

Sau-Fun Tan *et al* reported unsymmetrical bis-Schiff base ligands by partial displacement of the symmetrical bis-Schiff bases of ethylenediamine and salicylaldehyde/ o-hydroxyacetophenone/ acetylacetone/ benzoylacetone which have led to the formation and

isolation of unsymmetrical Schiff base ligands. Nickel(II) and copper(II) complexes of these ligands have been prepared and characterized.

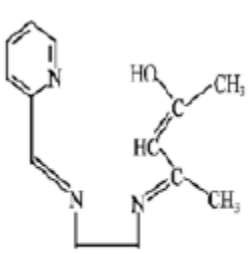


(dha,sal)en

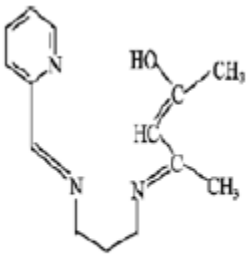


(acac,dha)en

Mau Sinha Ray *et al* have reported the synthesis, characterization and x-ray crystal structure of mononuclear copper(II) complexes with unsymmetrical quadridentate Schiff base ligands derived from the 1:1:1 condensation of 2,4-pentanedione, pyridine-2-carboxaldehyde and 1,2-ethanediamine or 1,3-ethanediamine. They also reported the evidence for copper(II) catalyzed rearrangement of unsymmetrical to symmetrical complex.



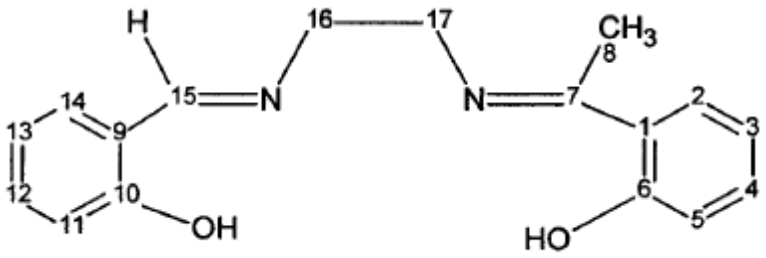
HL^1



HL^2

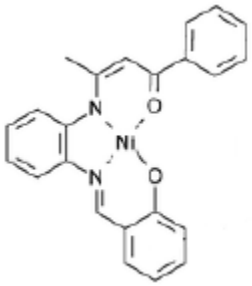
Apurba Biswas *et al* have prepared two reduced Schiff base ligands viz., 4-{2-[(Pyridin-2-yl-methyl)-amino]-ethylimino}-pentan-2-one and 4-{2-[(Pyridin-2-yl-ethyl)-amino]-ethylimino}-pentan-2-one by the reduction of the corresponding tetradentate unsymmetrical Schiff bases derived from 1:1:1 condensation of 1,2-diaminoethane, acetylacetone and pyridine-2-carboxaldehyde/2-acetylpyridine. Four mononuclear complexes of copper(II) and Nickel(II) with these two reduced Schiff base ligands have been synthesized and structurally characterized by x-ray crystallography.

A.K. Maldhure *et al* have reported the synthesis, characterization and antimicrobial activity of nickel (II), cobalt(II), manganese(II), copper(II), iron(III) and chromium(III) complexes of Schiff base ligand N-(Salicyldene)-N'-(o-hydroxyacetophenone)-ethylenediamine



N-(Salicyldene)-N'-(o-hydroxyacetophenone)-ethylenediamine

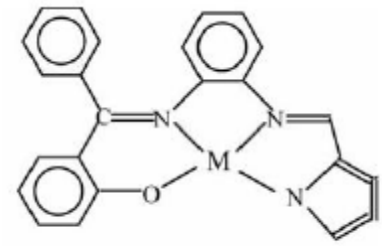
Geon-Joong Kim *et al* have reported the synthesis and catalytic application of unsymmetrical chiral salen complexes of manganese(III), titanium(IV), cobalt(II) and cobalt(III). Tarek M.A.Ismail have reported mononuclear Fe(III) complexes of unsymmetrical Schiff bases containing quinoline derivatives. Xiu R.Bu *et al* have reported eight vanadyl complexes utilizing unsymmetrical bis-Schiff base ligands prepared from ethylenediamine, acetylacetone and a salicylaldehyde derivative. D.Pawlica *et al* have developed an efficient stepwise template approach that leads to a novel nickel(II) complex of an unsymmetrical 1:1:1 Schiff base derived from o-phenylenediamine, benzoylacetone and salicylaldehyde .



:

Structure of nickel complexes

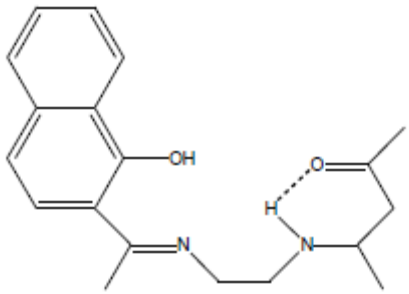
M. Lashanizadegan *et al* have synthesized unsymmetrical Schiff base ligands from o-hydroxyacetophenone, o-phenylenediamine and 2-hydroxy-1-naphthaldehyde and their zinc(II), cobalt(II) and copper(II) metal complexes. E.-P. Luo *et al* have synthesized copper(II), cobalt(II) and mercury(II) metal chelates of unsymmetrical tetradentate Schiff base, o-hydroxybenzophenone-1,2 diaminobenzene-pyrrole-2-carbaldehyde



M = Cu (II), Co (II), Hg (II)

General structure of metal complexes

Davar M. Boghaei *et al* have synthesized and characterized copper(II), nickel(II) and palladium(II) complexes from unsymmetrical Schiff base 1'-hydroxy-2'-acetonaphthoneacetylacetoneethylenediamine (Hhan)(Hacac)en



1'-hydroxy-2'-acetonaphthoneacetylacetoneethylenediamine

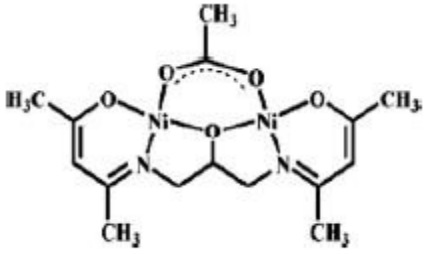
There are no reports available regarding the synthesis of copper(II) and nickel(II) complexes of unsymmetrical Schiff bases derived from salicylaldehyde/ o-hydroxyacetophenone, acetylacetone and 1,2-ethanediamine/ 1,3-propanediamine and their DNA binding and cleavage activities.

A brief review on metal complexes of quinquedentate (N_2O_3) Schiff base ligands:

Schiff base ligands which are able to form binuclear transition metal complexes have been of interest for many years, partly because of the relation between structures and magnetic exchange effects in homo- and hetero-binuclear metal complexes and partly because of the use of such complexes to mimic aspects of bimetallic biosites in various proteins and enzymes. The design of dinucleating ligands, with an additional donor atom that can bridge two metals in a more or less fixed geometry has rapidly developed in recent years. Part of the interest stems from the fact that the corresponding complexes are often studied as enzyme mimics.

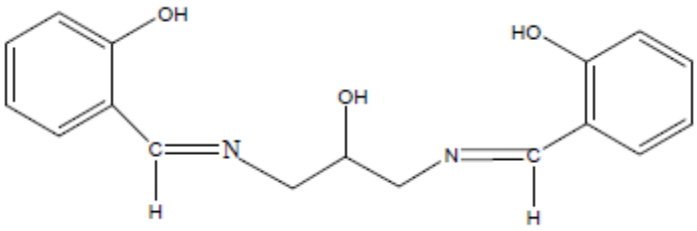
Qi-Long Zhang *et al* have reported x-ray structure of dinuclear nickel (II) complexes of the triply deprotanated pentadentate Schiff base, N,N-(2-hydroxypropane-1,3-diyl) bis

(acetylacetoneimine) (apacaH$_3$). The complex has a binuclear structure of type [Ni$_2$(apaca)OAc] in which each metal centre was bound to a deprotanated enolic oxygen and an imine nitrogen from an acetylacetoneimine 'arm' of "apaca". The nickel centres are bridged by both alkoxide oxygen derived from the 2-hydroxypropane unit in apaca and acetato group (. Each metal centre has a distorted square planar geometry with the overall configuration being non-planar.



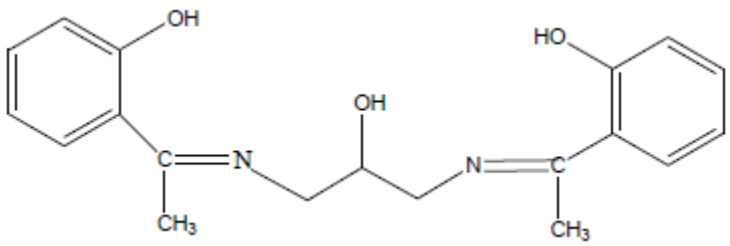
Structure of [Ni$_2$ (apaca)OAc]

Molybdenum (VI) complexes have been prepared with quinquedentate (N_2O_3) ligands derived from Schiff base condensation using 1,3-diamino-2-hydroxypropane by James H. Cameron *et al* . Thompson N. Doman *et al* have reported the synthesis and crystal structure of a mononuclear copper(II) complex of 1,3-bis(N-methylimidazolimine)propan-2-ol. The complex was found to have a distorted square pyramidal geometry.Masahiro Mikuriya *et al* have reported tetranuclear zinc(II) complex with 1,3 bis-(Salicylideneamino)-2-propanol (H$_3$salpro)



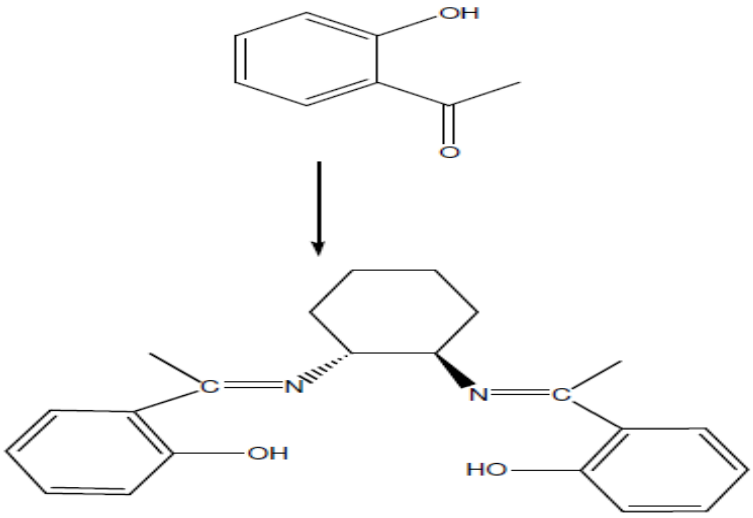
Structure of H$_3$salpro

A Novel μ1,1-azido-, μ2-alkoxo-, and μ2-phenoxo-bridged tetranuclear copper(II) complex was reported by Subhra basak *et al* synthesized from a symmetrical quinquedentate N_2O_3-donor Schiff base ligand H3L N,N'-(2-hydroxypropane-1,3-diyl) bis(2-hydroxyacetophenimine)

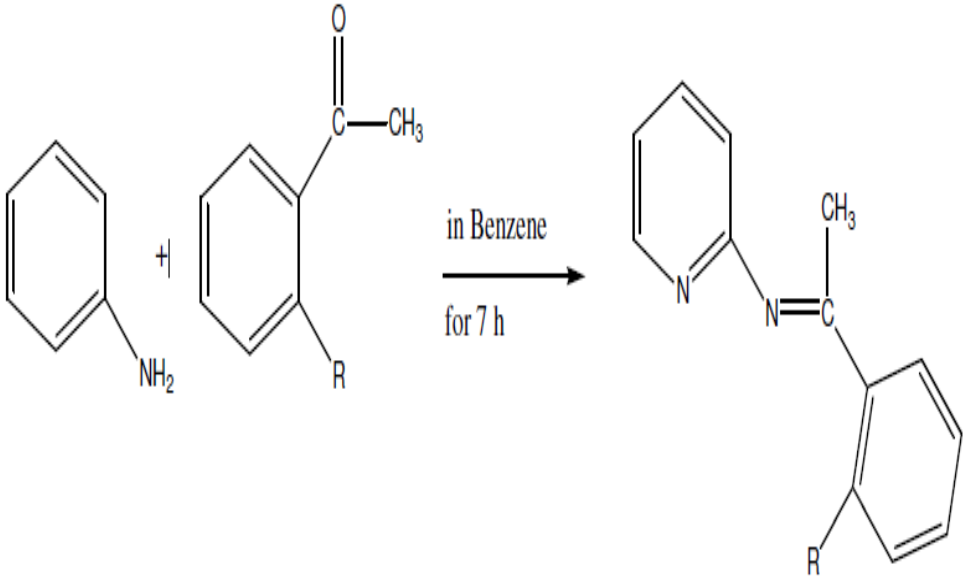


Structure of N,N'-(2-hydroxypropane-1,3-diyl) bis(2-hydroxyacetophenimine)

Gao and Zheng have reported the synthesis of optically active Schiff base ligand derived from condensation of 2-hydroxyacetophenone and 1,2- diaminocyclohexane



Gudasi *et al* [31] have reported the synthesis, characterization and biological studies of dioxouranium(II) and thorium(IV) complexes of Schiff base derived from 2-amino pyridine and acetophenones.



Schiff bases and their first row transition metal complexes such as Co(II), Ni(II), Cu(II), etc., were reported to exhibit fungicidal, bactericidal, antiviral and antitubarcular activity. In specially, Cu(II) complexes with diverse drugs have been the subject of a large number of research studies presumably due to the biological role of Cu(II) and its synergetic activity with the drug. The antifungal and antibacterial properties of a range of Cu (II) complexes have been evaluated against several pathogenic fungi and bacteria. For many years it has been believed a trace of Cu(II) destroys the microbe, however, recent mechanisms becomes activated oxygen in the surface of metal Cu kills the microbe because Cu(II) activity is weak. For the past two decades, there has been tremendous interest in studies pertaining to interaction of transition metal complexes with nucleic acid. These studies are relevant for the development of new reagents for biotechnology and medicine. Researchers have shown substantial interest in the rational design of novel transition metal complexes, which bind and cleave duplex DNA with high sequence and structure selectivity.

In developing new DNA-interacting transition metal based coordination compounds, it has been realized that multi-mode binding would provide advantages in terms of administration, lowering of toxicity etc.. Among the two modes of binding with DNA residues, i.e., intercalating and covalent binding, the former requires planar type structures while the latter needs coordination complexes with potential coordination sites .

Copper(II) complexes are also attractive since Cu(II) is known to play a significant role in naturally occurring biological systems as well as a pharmacological agent. Copper is a biologically relevant element and many enzymes that depend on copper for their activity have been identified. The metabolic conversions catalysed by most of these enzymes are oxidative. Because of their biological relevance a large number of copper(II) complexes have been synthesized with different perspectives.

CHAPTER III

SCOPE

Aim and Scope of the present work

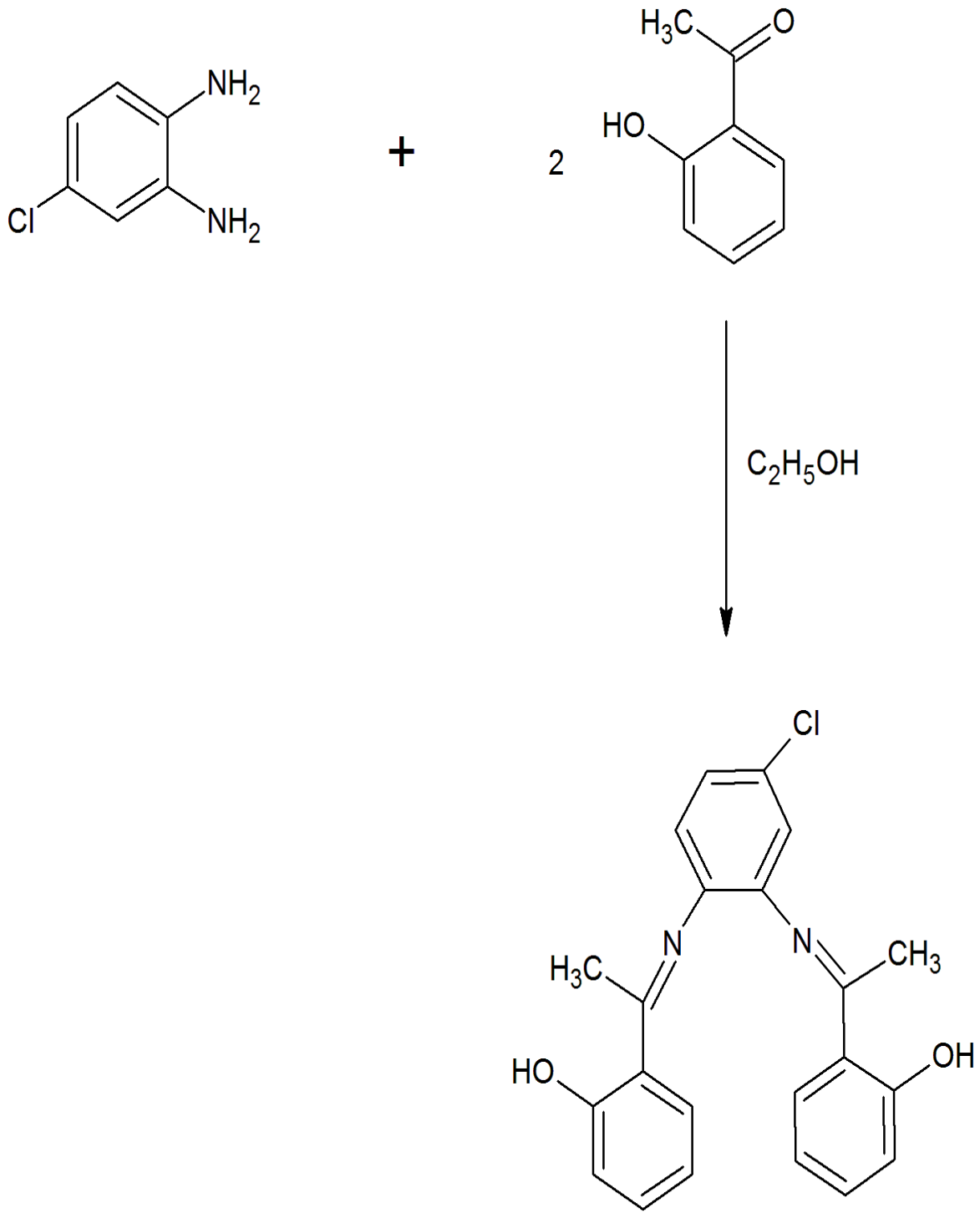
My present work aims,

- To synthesis Schiff base ligand and complex comprising derivatives of 4-Chloro-O-Phenylene diamine and 2-Hydroxy acetophenone
- To determine the structure of the product UV, IR, and ^{1} H NMR spectroscopy are used. It is also confirmed by TLC
- To study the biological activity of synthesized complex.
- To evaluate the CNS activity of synthesized complex and compared with the standard drug chlorpromazine using digital actophotometer
- To determine the analgesic activity of complex using analgesiometer

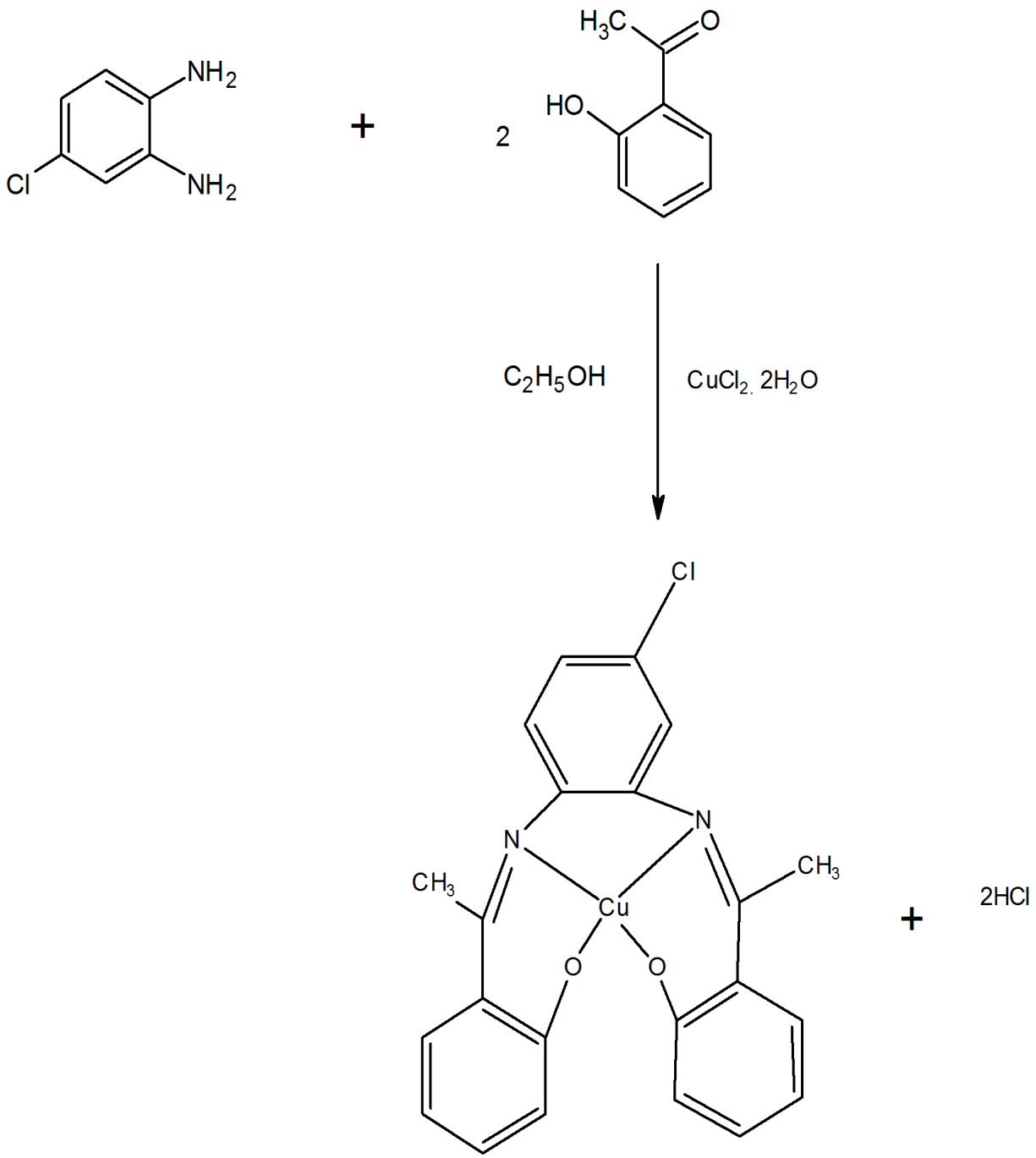
CHAPTER IV

SCHEME

SCHEME I



SCHEME II


NH2
Cl
NH2
+
2
H3C
O
HO
C2H5OH
CuCl2. 2H2O
Cl
N
N
CH3
CH3
Cu
O
O
+
2HCl

CHAPTER V

EXPERIMENTAL SECTION

Experimental

2- Hydroxyacetophenone, 4-Chloro-O-Phenylene diamine ,ethanol,Copper(II) Chloride were purchased from sigma Aldrich. The solvents were analar grade.

EXPRIMENTAL TECHNIQUES

A short account of the analytical methods employed in this work is presented in this chapter. The physical methods adopted for characterization of the compounds are determination of melting point, electrical conductivity measurement, UV-Vis, Infra-red and ^{1}H NMR spectral measurement.

Melting point Determination

Melting point or decomposition temperatures of the compounds were determined with a Toshiwal melting point apparatus

UV spectral measurement

The UV spectra of title compound and its complex were recorded in the conventional region (200-800nm) using DMSO as solvent. The UV spectral measurements were done in the BL 198 Biospectrophotometer. The UV spectral study helps to decide the **absorption (λ_{max}) of Schiff base ligand and complex**

Infrared spectral measurement

The infra-red spectra of the compounds were recorded in the conventional region (400-4000cm^{-1}) as KBr pellets. The infra-red spectral measurements were done using FT-IR-Shimadzu spectrometer. The IR spectral study helps to decide the mode of coordination of the ligand to the metal.

NMR spectral measurement

The NMR spectroscopy for the Schiff base ligand is recorded in BRUKER (300MHz) instrument using DMSO as solvent.

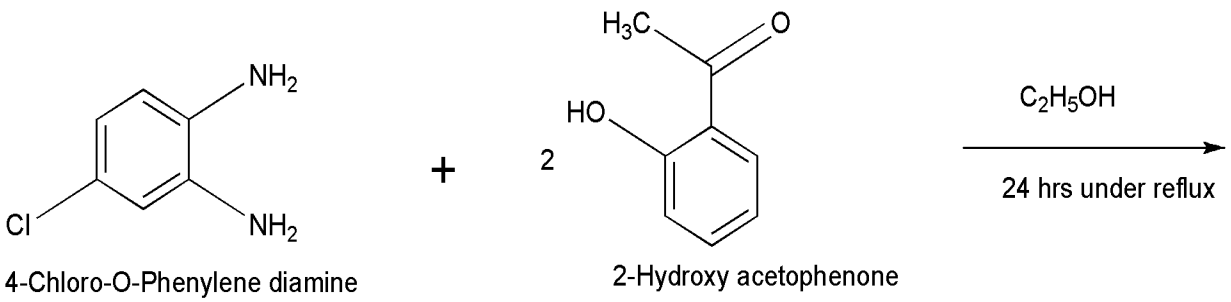
Synthesis of 2-[*N*-(4-chloro-2-{[1-(2-hydroxyphenyl)ethylidene]amino}phenyl)ethanimidoyl]phenol and its complexes

2-Hydroxy acetophenone (0.002 mole) dissolved in ethanol (10 ml). 4-Chloro-O-Phenylene diamine (0.001 mole). dissolved in ethanol(5 ml). The mixture was refluxed for 24 hrs. The Product as solid mass started appearing after 24 h. The Precipitate was filtered and washed with

water, ethanol,acetone and diethyl ether. The brown product obtained were recrystallized from tetrahydrofuran(THF) and methanol

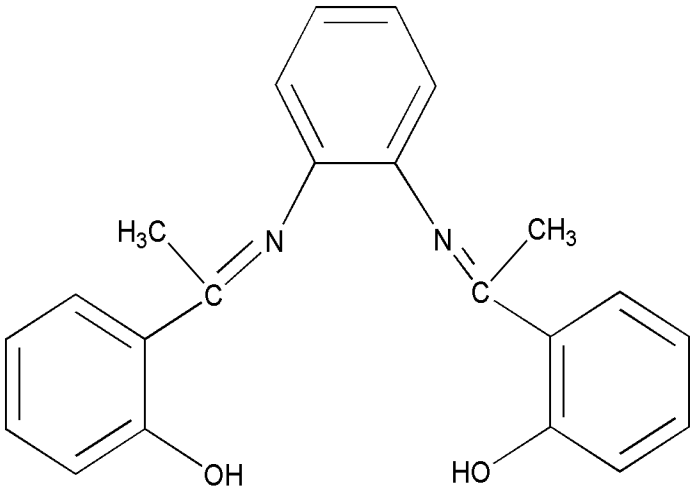
The Yield of the product is 80%

Melting point – 212 ^{o}C



4-Chloro-O-Phenylene diamine

2-Hydroxy acetophenone



2-[*N*-(4-chloro-2-{[1-(2-hydroxyphenyl)ethylidene]amino}phenyl)ethanimidoyl]phenol

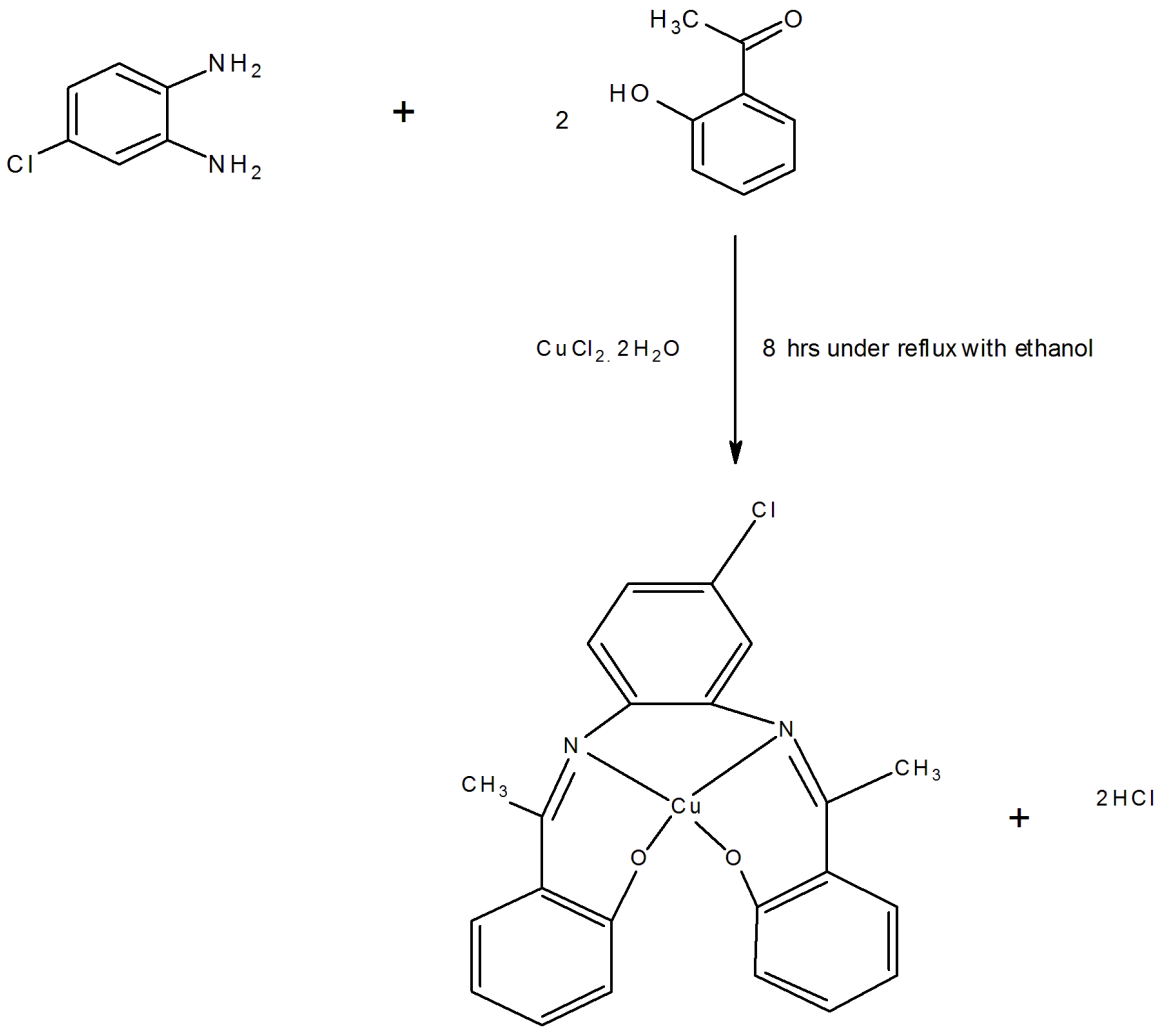
Synthesis of Schiff base Cu(II) Complex

2-hydroxy acetophenone (0.002 mole) dissolved in ethanol (10 ml). 4-Chloro-O-Phenylene diamine (0.001 mole) dissolved in ethanol (5 ml) and Copper (II) Chloride(0.002 mole) dissolved in ethanol (10 ml) . The mixture was refluxed for 8 hrs. The Product as solid mass

started appearing after 8 h. The Precipitate was filtered and washed with water, ethanol,acetone and diethyl ether. The brown products obtained were recrystallized from tetrahydrofuran (THF) and methanol.

The yield of the product is 68%

Melting point – 282 ^{o}C



Confirmation of Schiff base Complex By TLC Analysis

TLC Analysis

The presence of Schiff base complex is analyzed by using TLC method

Preperation of TLC plates

The square glass plate is cleanly washed with chromic acid followed by water. It is dried in hot air oven at $110^{O}C$

Preperation of Stationary Phase

28 g of silica gel (TLC) is mixed with 100 ml of double distilled water. It is allowed to settle for one and half hour.

Spraying of silica gel

The glass plate is coated with silica gel by sprayer. The thickness of silica gel is 0.25 mm. Now the silica gel coated glass plate is kept in hot air oven at 110 ^{O}C for one and half hour. Then it is cooled at room temperature for an hour

Spot

The sample is dissolved in the mixture of cyclohexane and ethyl acetate (8:2). The Spot is made on the glass plate using the capillary tube(0.2 mm) and the plate is dried in hot air oven.

SOLVENT DEVELOPMENT

Mobile phase

Cyclohexane and ethyl acetate(8:2)

The glass plate is developed using cyclohexane and ethyl acetate(8:2) as solvent in solvent chamber by keeping the glass plate at 60^{O} angle.

After development of chromatographic, it is dried in hot air oven at 110 O C for half an hour. Finally the distance travelled by solvent and sample is measured from this Rf Value is calculated

$$R_F = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by solvent}}$$

Experimental procedure for antibacterial activity

For studying the antibacterial activity of the newly synthesized Schiff base complex the following chemicals were used

Peptone : Nice chemicals Private limited

Beef Extract : Merck Limited

Sodium Chloride : Reachem Laboratory Chemicals Private Ltd

Agar-Agar Type I : Himedia Laboratories

Incubator : In lab Equipments Private Ltd.

Laminar air flow Chamber

Preparation of Nutrient Agar medium

Exactly 1 g of peptone, 0.5g of beef extract, 0.5g of sodium chloride were weighed and transferred into a conical flask. This was dissolved in 100 ml of double distilled water. After dissolving it, the P^H was adjusted to neutral P^H, i, e., in between 7 to 7.2. After that around 2% Agar was added and the agar was melted by keeping it in a hot plate or microwave oven. After that, it was closely packed and sterilized in an autoclave.

Disc Diffusion method

Sterilized nutrient agar medium was poured into Sterilized Petri plates. The Petri plates were allowed to stand for some time, until the agar medium gets same time, until the agar medium gets solidified, the bacterial cultures. After that the bacterial culture medium was lawned on the surface of the medium using a sterilized cotton swab. The newly synthesized compound was loaded on sterilized discs in different concentrations. These discs were carefully placed on the surface of the medium. The whole processes were carried out in laminar air flow chamber in order to avoid contamination of the culture. The Petri plates were incubated for 16-18 hrs at 37^oC in inverted position. After that the Zone of inhibiton was measured as minimum inhibitory concentration(MIC) in mm. The antibacterial activity of the compound against gram positive bacteria like bacillus subtilis,Staphylococcus epidermidis and Streptococcus viridians were studied by the disc diffusion method.

Experimental procedure for CNS activity

Materials:

The following materials were used for the CNS depressant activity of schiff base metal complexes.

1. Actophotometer – besto
2. Mice – albino mice (20 -35g)
3. Syringe(1 ml) glass van tubercillin BCG (Borosilicate glass)

Preperation of test drug

40 mg of test compound was taken and it was dissolved by using 10 ml of water and 10 mg of CMC (Carboxy methyl cellulose). Mixed well using mortar and pestle. This was administered through orally using 1 ml syringe in each mouse. The doses were depended upon the body weight of the animals.

Procedure:

- First the animal were weighed, marked and divided into two groups, each containing four mice.
- The mice were placed individually in the activity gauge or actophotometer for 10 minutes
- Then the basal activity score of all the animals were noted.
- The two products were given to each group orally
- After one hour, the activity score for the two groups were noted for 10 minutes (i.e. after the drug treatment)
- The differences in the activity before and after treatment were measured
- Finally the percentage of CNS depressant activity was calculated.

Percentage of change on activity of the compound was calculated by

$$[A-B]/A \times 100$$

Where,

A = The reaction time after the saline administration

B = The reaction time after the drug administration

Experimental procedure for analgesic activity

Materials:

The following materials were used for the analgesic activity of Schiff base complex

1. Analgesiometer - Besto
2. Mice - Albino mice(15-35 g)
3. Syringe 1 ml - Glass Van Tuberculin – BCG
   Borosilicate glass
4. Sodium Chloride - Reachem laboratory chemicals Pvt Ltd

Preparation of test drug

30 mg of compound was taken and it was dissolved by using 10 ml of water and 10 mg of CMC (Carboxy Methyl Cellulose). Mix well using mortar and pestle. This was taken for the test drug.

Preperation of normal saline

About 0.030g of sodium chloride was taken and dissolved in 10 ml distilled water. From this 0.25 ml was injected through Intraperitonial using 1 ml syringe in each mice. This is the control group received the 0.25 ml normal saline. The mice were weighed, marked and divided into control and test group. Five animals were taken in an each group the control group received 0.25 ml normal saline I.P. using 1 ml.

Procedure

The mice were weighed, marked and divided into control and test group. First each mouse in the control and test group were placed one by one on the analgesiometer at 1 Ampere current for heating the coil of the analgesiometer. The basal reaction time was by placing tip of the tail on the radiant heat source. The end point was the tail withdrawal from the heat (flickering response). Basal reaction time for each mouse was noted at a gap of 5 minutes to confirm normal behavior of the animal. Next the control group received 0.05 ml normal saline orally using 1ml syringe and test group received 30 mg/10 ml aqueous solution of the drug. The mice were allowed to stand some time for the drug distribution. After the drug and saline treatment

reaction time were noted at a gap of 15,30,60,90 and 120 seconds. Values of test compared with normal group.

The increased % in reaction time at each interval was calculated by

(A-B)/A X 100

A = Before drug treatment

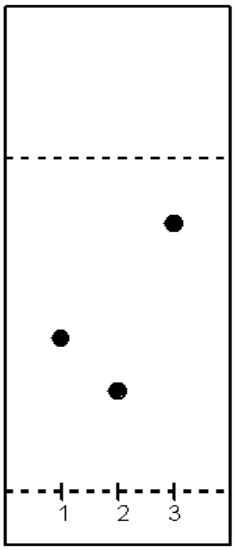
B = After drug treatment

CHAPTER VI

RESULT AND DISCUSSION

By following the synthesis pathways described in experimental section for each steps products were synthesized. The synthesized compounds were first subjected to TLC to confirm the completion of the reaction it was done with suitable solvent systems. Then the structures of the products formed were confirmed by UV, IR and ^{1}H NMR spectral data.

TLC:



1. 4-Chloro- O- Phenylene diamine

2. 2-Hydroxy acetophenone

3. Product

Cyclohexane: Ethyl acetate

8: 2

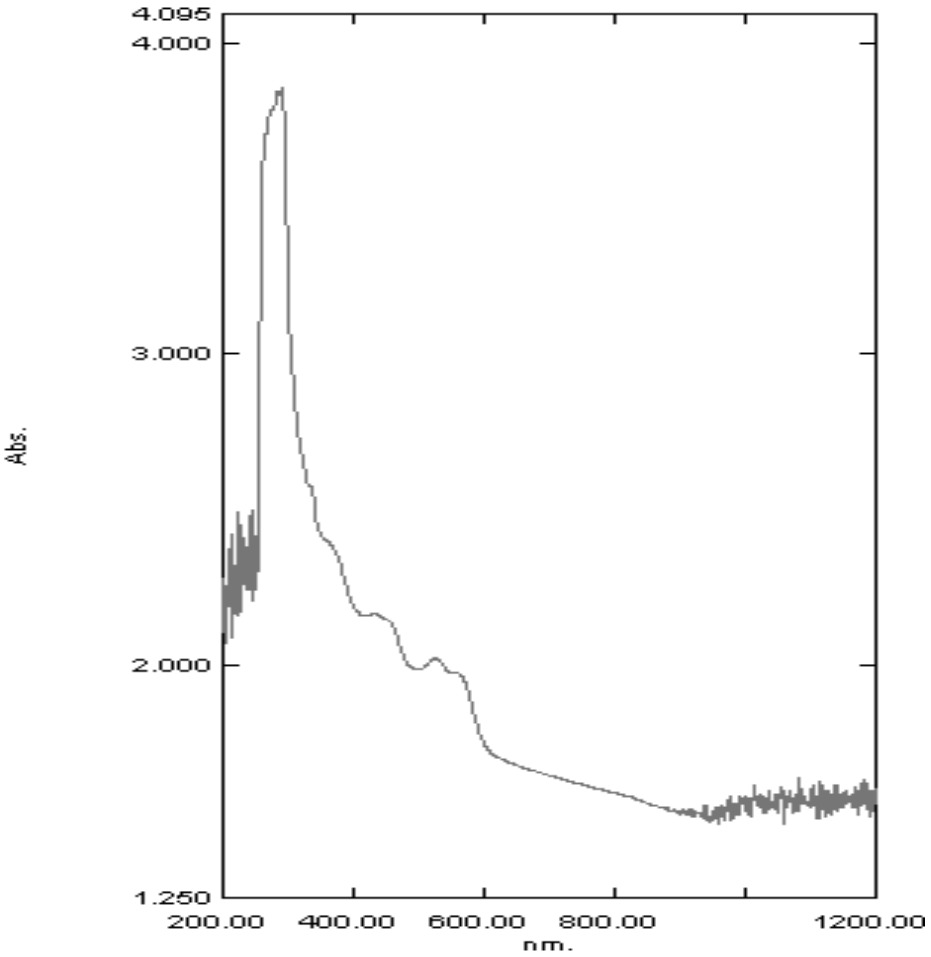
R_f Value = Distance travelled by solute / Distance travelled by solvent

UV SPECTRUM ANALYSIS

UV SPECTRAL INTERPRETATION

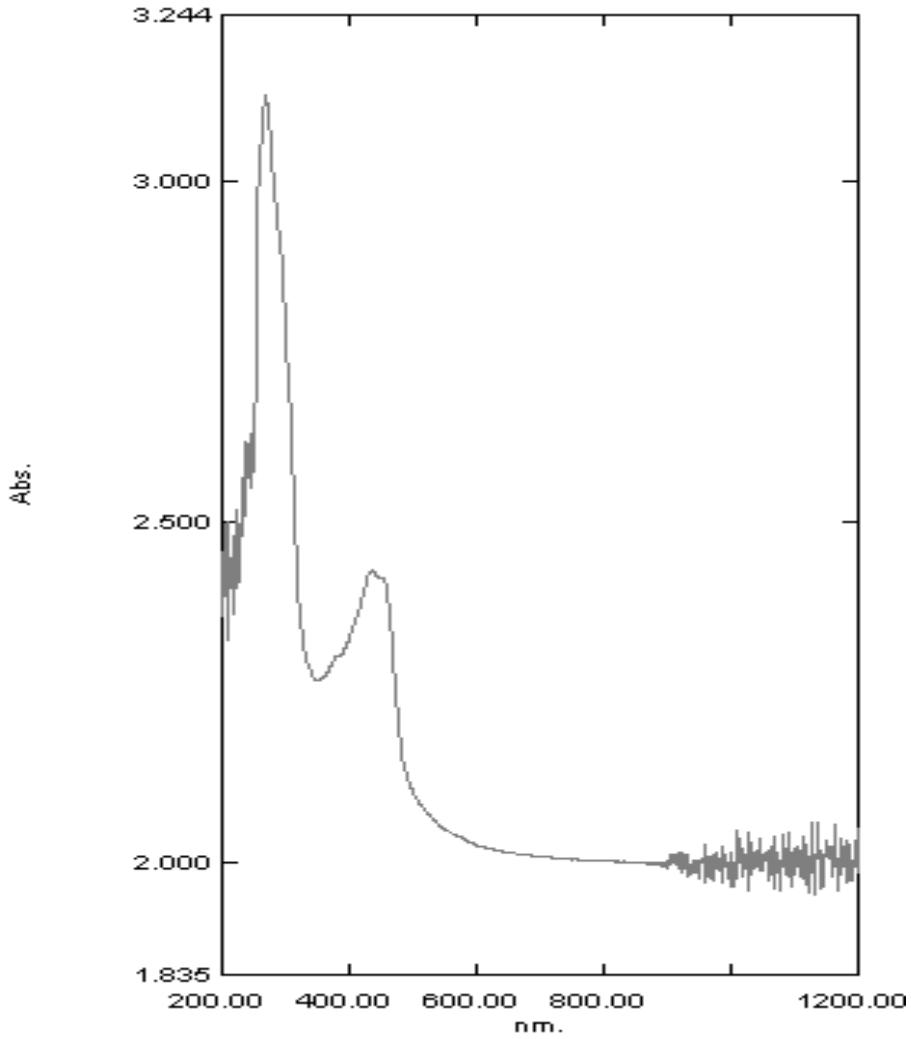
UV Spectrum of ligand

UV-visible spectra of ligand and Cu(II) complex were recorded in DMSO. The corresponding UV visible spectra are shown in the following figure. λ_{max} for ligand and its Copper (II) complex are 300 nm and 480 nm respectively. It confirms complex formation.



Wavelength = 300 nm

UV Spectrum of Complex

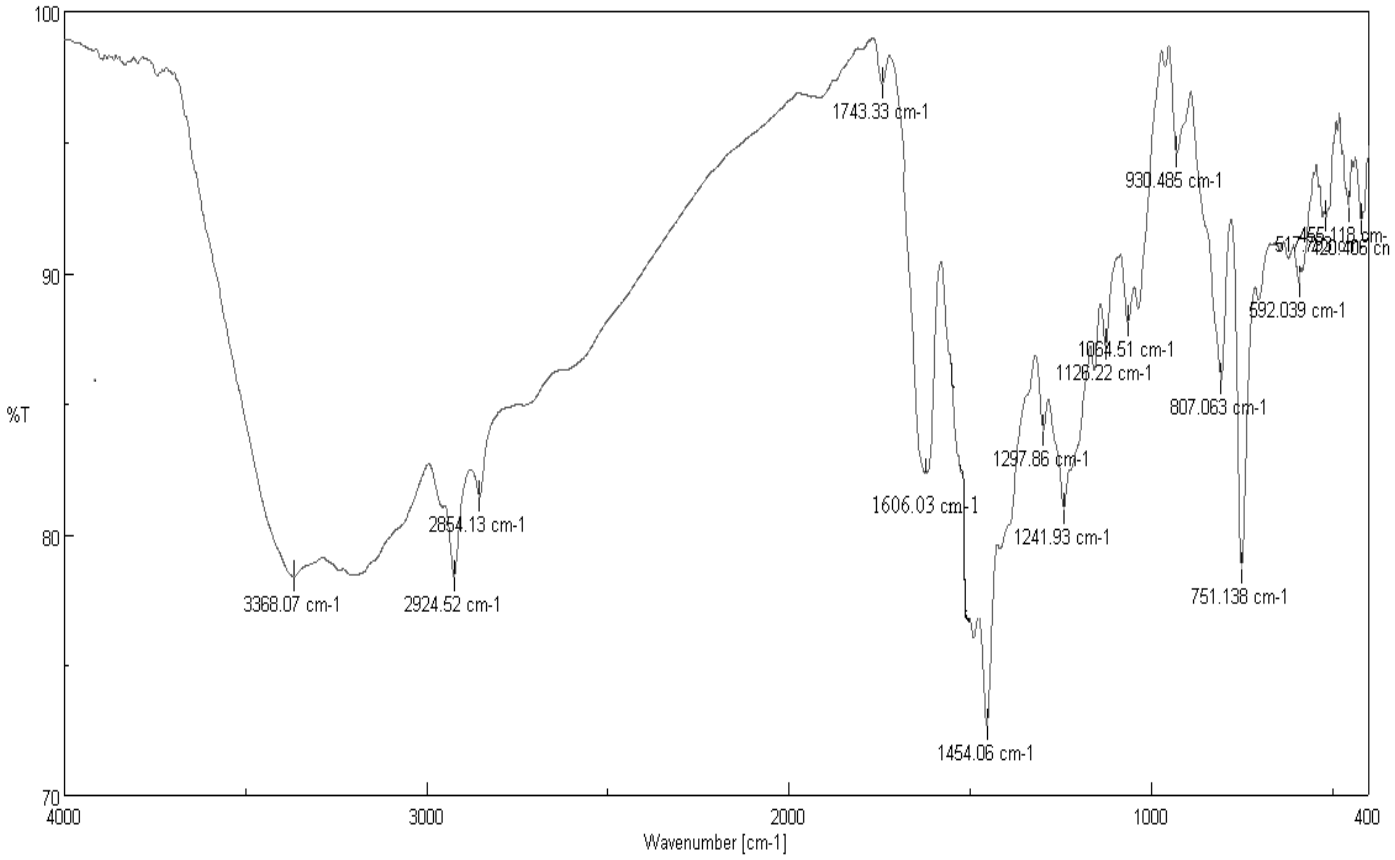


Wavelength = 480 nm

IR SPECTRAL INTERPRETATION

Infrared absorption spectra ligand and complex is recorded with potassium bromide (pelletization). The corresponding spectra are shown in figure

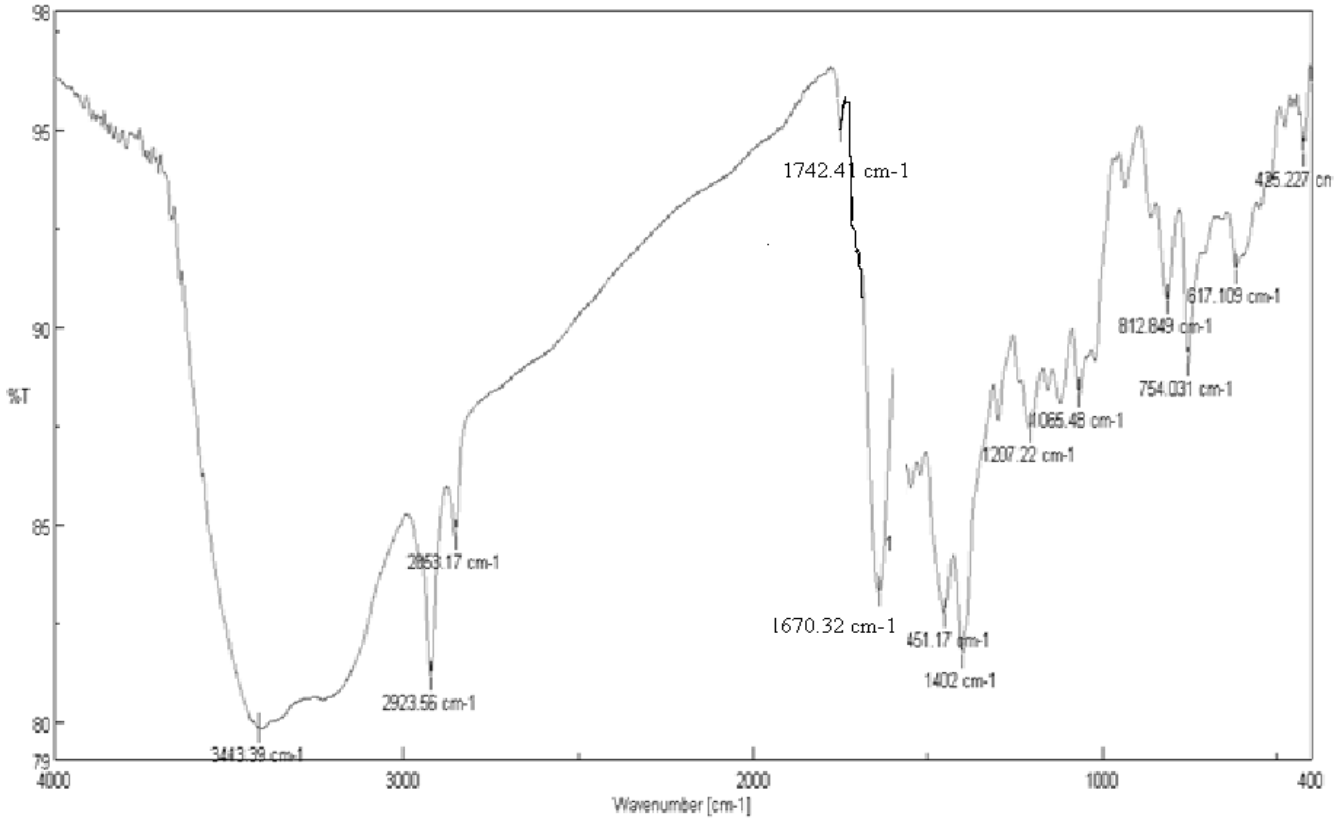
FT-IR Spectrum of ligand



COMPOUND	ν(C-H)	ν(C-C)	ν(C-N-C)	ν(C=C)	ν(C –Cl)	ν(C =N)
Ligand	2854.13	1241.93	1454.06	1559.66	1743.33	1606.03

Stretching at 3368, 2924cm^{-1} shows the presence of two OH group
Stretching at 1297, 1241cm^{-1} shows the presence of two C=N group
Stretching at 1559 cm^{-1} shows the presence of C=C group
Stretching at 2854 cm^{-1} shows the presence of C-H group
Stretching at 1743 cm^{-1} shows the presence of C-Cl group
Stretching at 1454 cm^{-1} shows the presence of C-N-C group
Stretching at 1241 cm^{-1} shows the presence of C-C group

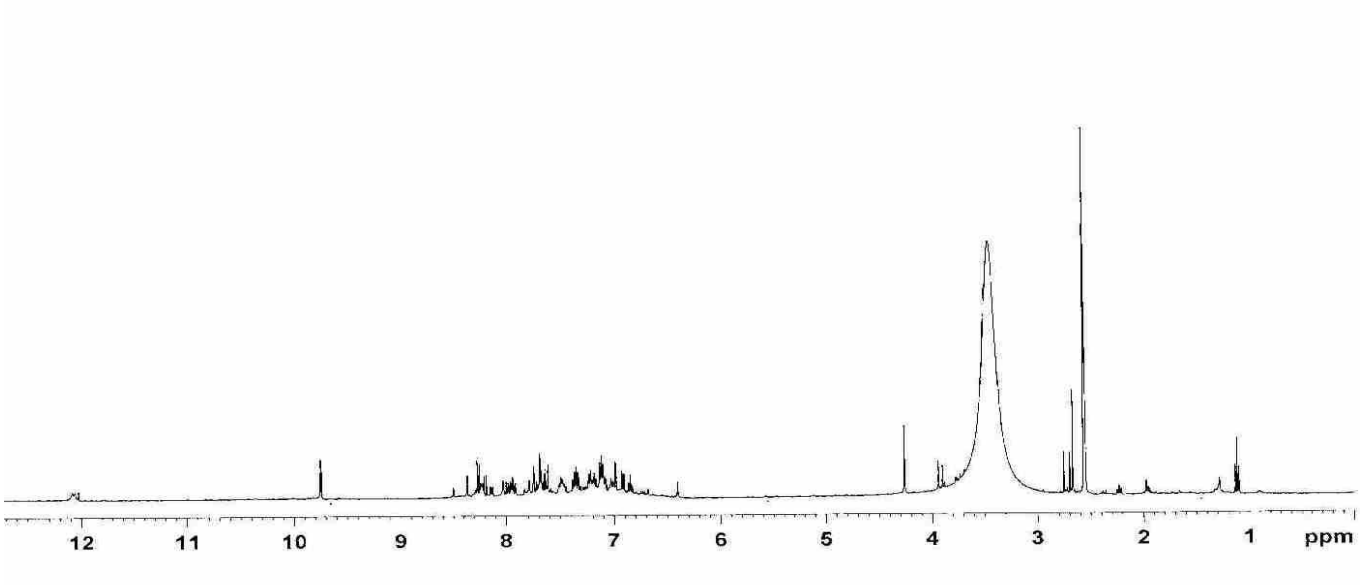
FT-IR spectrum of Complex

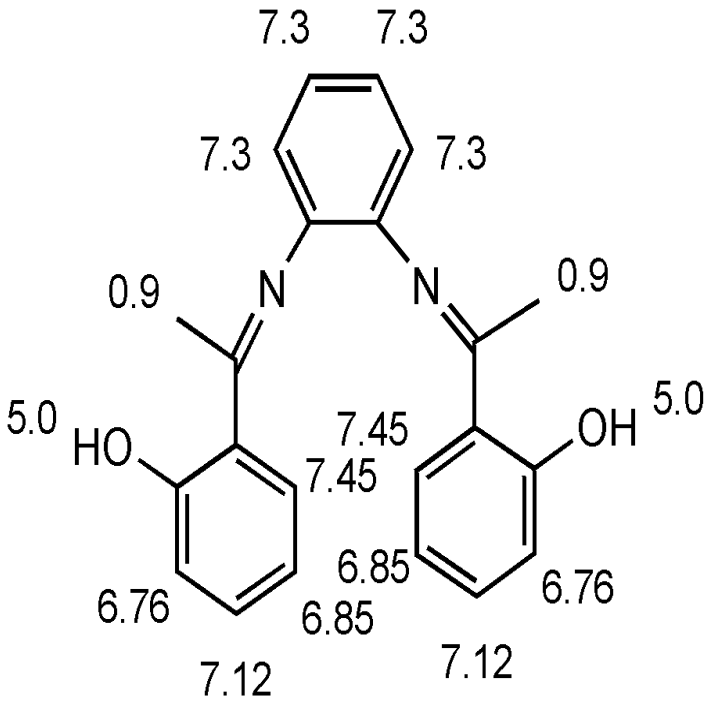


COMPOUND	ν(C-H)	ν(C-C)	ν(C-N-C)	ν(C=C)	ν(C –Cl)	ν(C –N)
Complex	2853.17	1207.22	1402	1606.41	1742.37	1670.32

Stretching at 1207, 1066 cm^{-1} shows the presence of two C=N group
Stretching at 1742 cm^{-1} shows the presence of C-Cl group
Stretching at 1606 cm^{-1} shows the presence of C=C group
Stretching at 2853 cm^{-1} shows the presence of C-H group
Stretching at 3413 cm^{-1} shows the presence of C-C group
Stretching at 1402 cm^{-1} shows the presence of C-N-C group

^{1}H NMR of Schiff base ligand

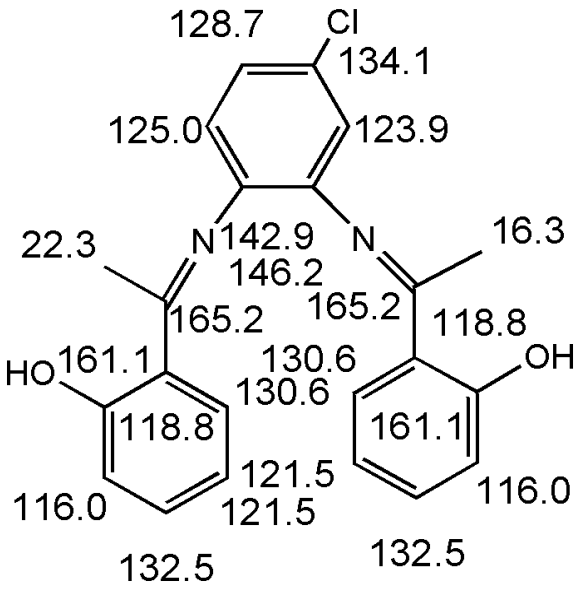




NMR SPECTRAL INTERPRETATION

- ^{1}H-NMR spectroscopy for the ligand is recorded in BRUKER (300MHz) instrument using DMSO as solvent.
- The aromatic protons obtained in the region of 6.76-7.45 ppm
- A doublet at υ=1.1 ppm may be due to the presence of –CH_3 group.
- A doublet at υ= 3.8 and υ= 4.4 ppm may be due to unreacted OH group associated with ligand(Due to hydrogen bonding the value is lowered).

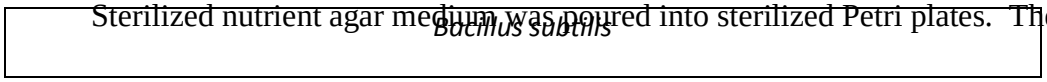
^{13}C NMR of Schiff base Ligand



Antibacterial activity of Schiff base Cu(II) Complex

Antibacterial studies against Gram positive *Bacillus subtilis,*

***Streptococcus viridians* and *Staphylococcus epidermidis* by disc diffusion method**



Sterilized nutrient agar medium was poured into sterilized Petri plates. The Petri plates were allo

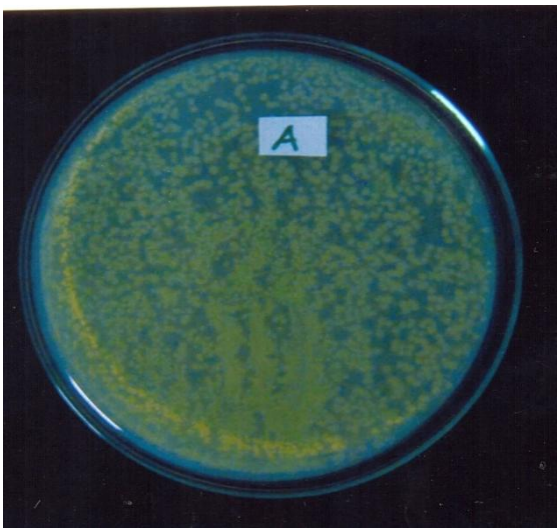
After that the bacterial culture medium was lawned on the surface of the medium using a steriliz

incubated for 16-18 hrs at 37^0C in inverted position. After that the zone of inhibition was measured in mm. The maximum zone of inhibition of 17mm was observed with *Bacillus subtilis* for the concentration of 3000µg. The maximum zone of inhibition of 21mm was observed with *Streptococcus viridians* for the concentration of 3000µg. The maximum zone of inhibition of 19mm was observed with *Staphylococcus epidermidis* for the concentration of 3000µg represented in Table

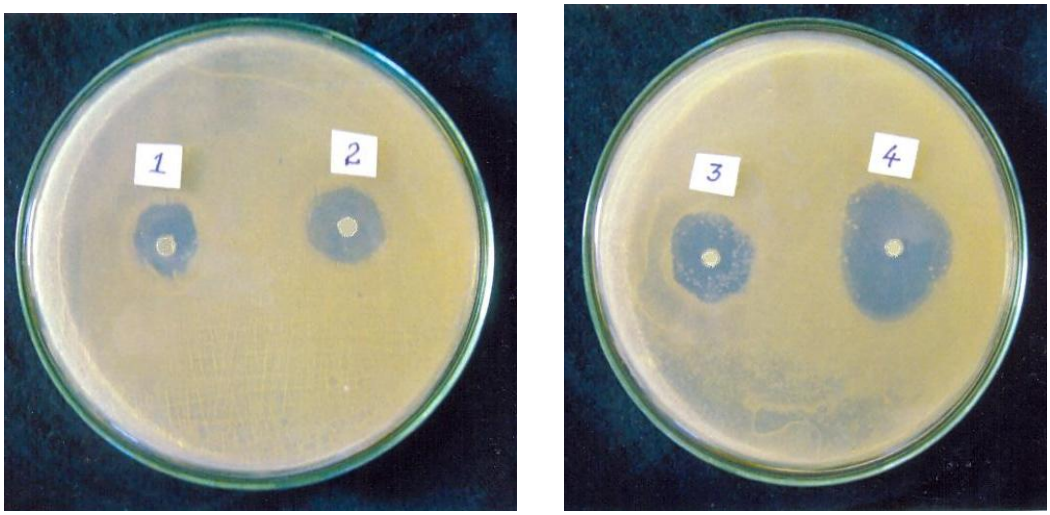
Table

Amount in µg.	Marked as	Zone of inhibition in Mm
500	1	12
1000	2	15
2000	3	16
3000	4	17
Streptococcus viridians		
500	5	15
1000	6	18
2000	7	20
3000	8	21
Staphylococcus epidermidis		
500	9	11
1000	10	14
2000	11	16
3000	12	19

Antibacterial activity of Schiff base Cu (II) Complex against Gram +ve bacteria *Bacillus subtilis*

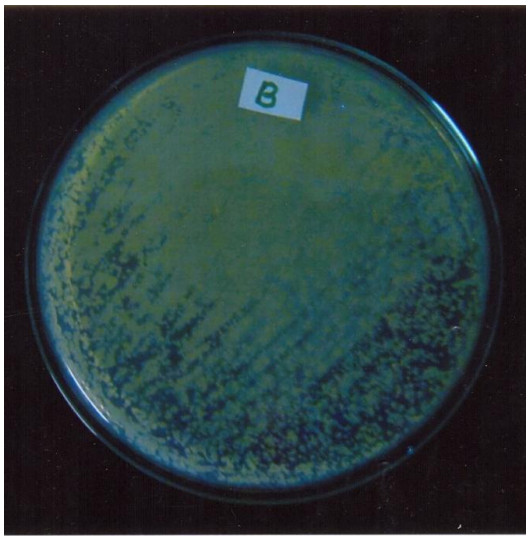


Control

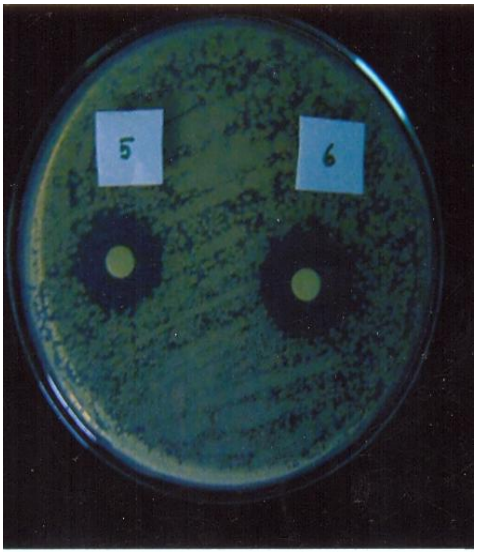


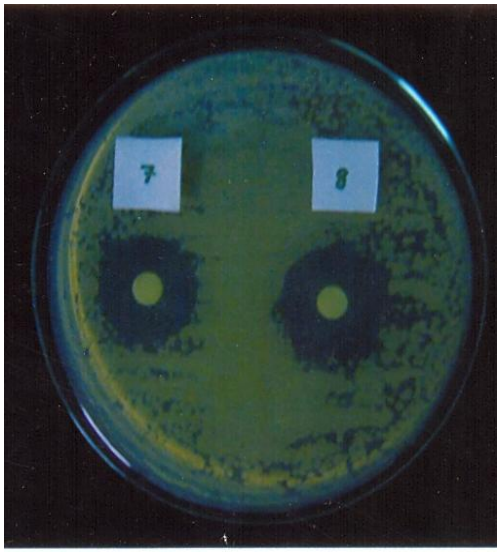
Zone of inhibition for different concentrations

Antibacterial activity of Schiff base Cu(II) Complex against Gram +ve bacteria *Streptococcus viridians*



Control

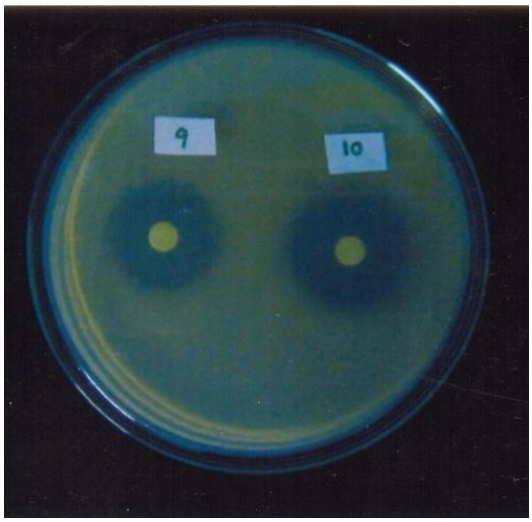


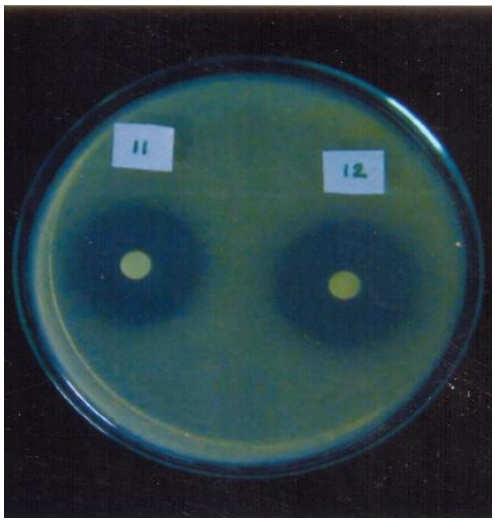


Zone of inhibition for different concentrations

Antibacterial activity of Schiff base Cu(II) Complex against Gram +ve bacteria *Staphylococcus epidermidis*

Control





Zone of inhibition for different Concentrations

CNS depressant activity

Of

Schiff base Cu (II) Complex

CNS STUDY

The CNS activity was studied using albino mice through oral route using canula insertion via mouth. The scores from the digital actophotometer were tabulated before and after drug administration. The mean % score for a group was plotted as chart likewise the tables and chart for dose of drug (30 mg/10 ml) were drawn.

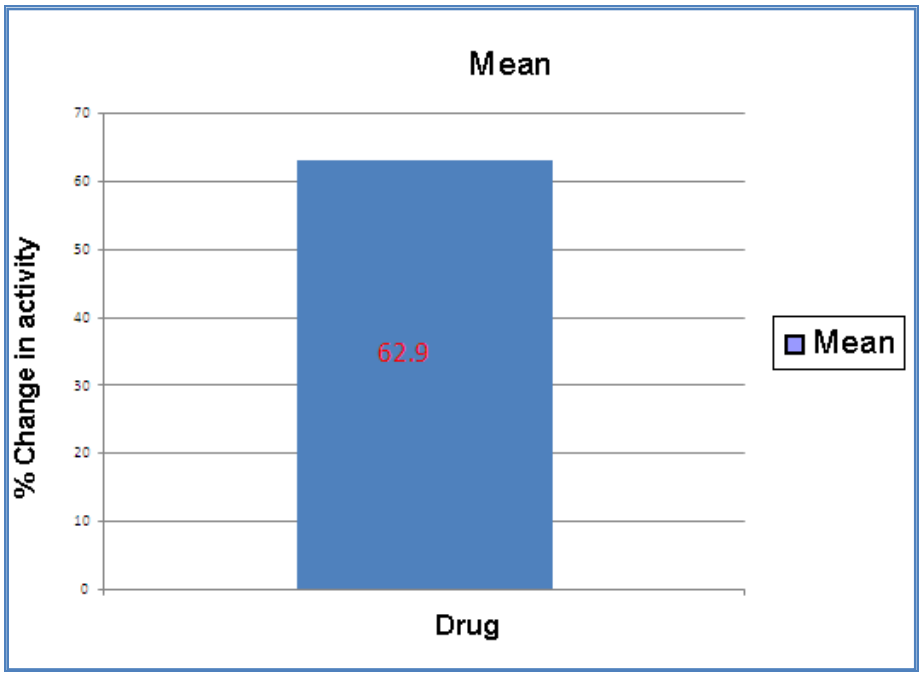
Then from the mean values and chart the dose dependence of the synthesized compound was studied and it shows positive result. All the above facts can be observed using the following table and chart.

CNS study of Chlorpromazine

Animals body weight(g)	Drug	Dose mg/kg	Actophotometer activity in 10 min		
			Before treatment	After treatment	% Change in activity

36.18	Chlorpromazine	30 mg/10 ml	190	30	84.21
34.28			240	198	17.5
35.10			232	48	79.31
35.93			172	70	59.30
36.55			210	54	74.28
				Mean	62.9

CNS activity of Chlorpromazine

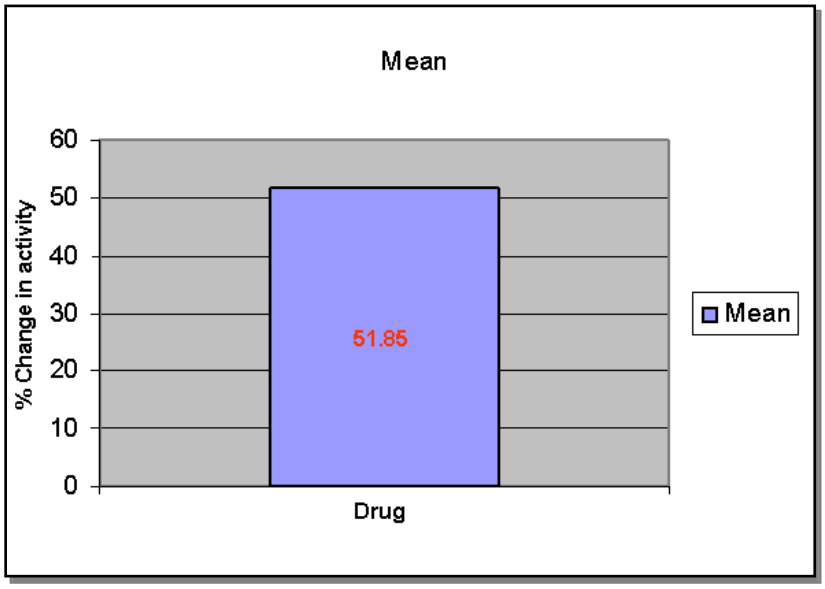


CNS study of Schiff base Cu (II) Complex

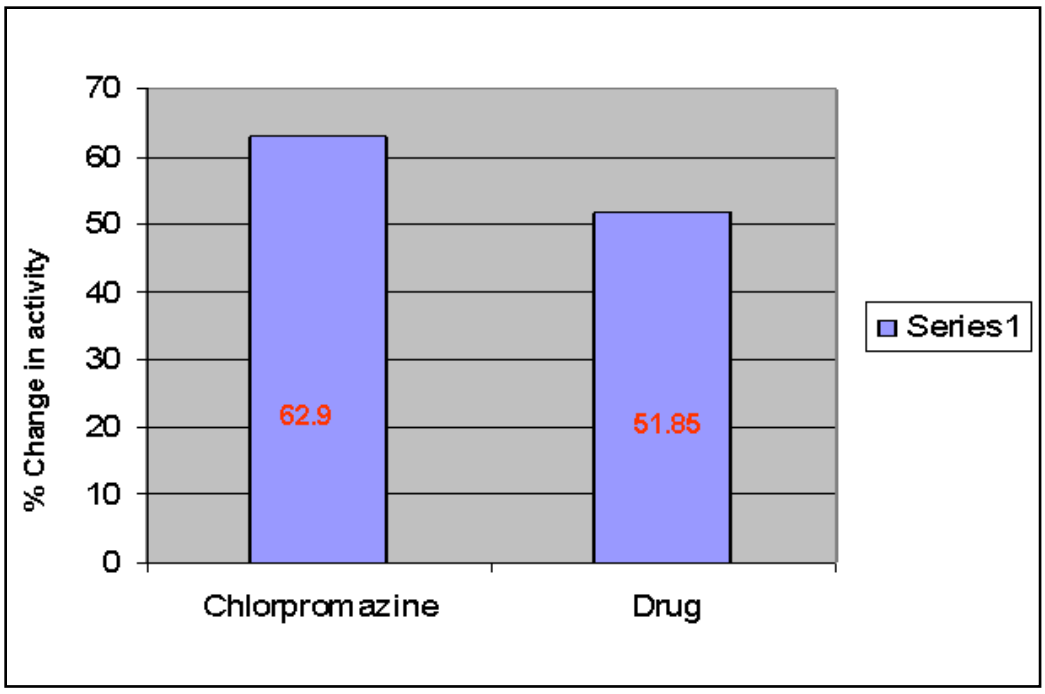
Animals body weight(g)	Drug	Dose mg/kg	Actophtometer activity in 10 min		
			Before treatment	After treatment	% Change in activity

36.18	Schiff base Derivative	30 mg/10 ml	170	60	64.70
34.28			225	201	10.66
35.10			214	53	75.23
35.93			164	90	45.12
36.55			203	74	63.54
				Mean	51.85

CNS activity of Schiff base Cu (II) Complex



Comparison of Chlorpromazine with Schiff base derivative (30mg/10ml)



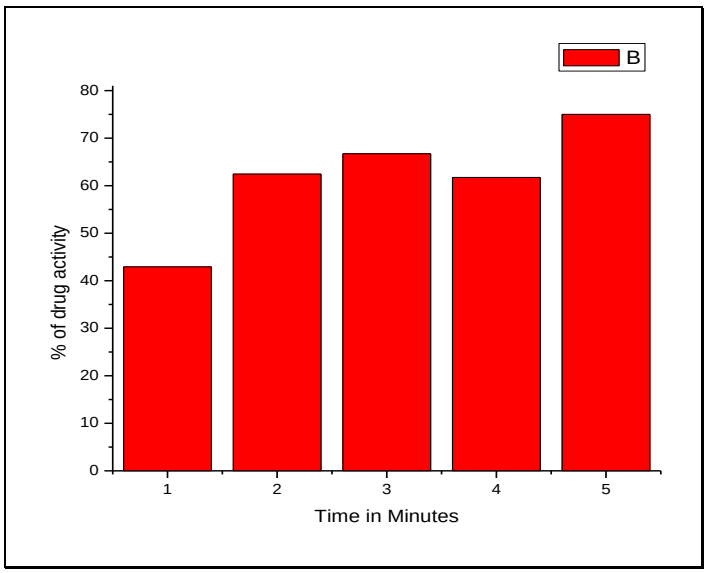
ANALGESIC ACTIVITY:

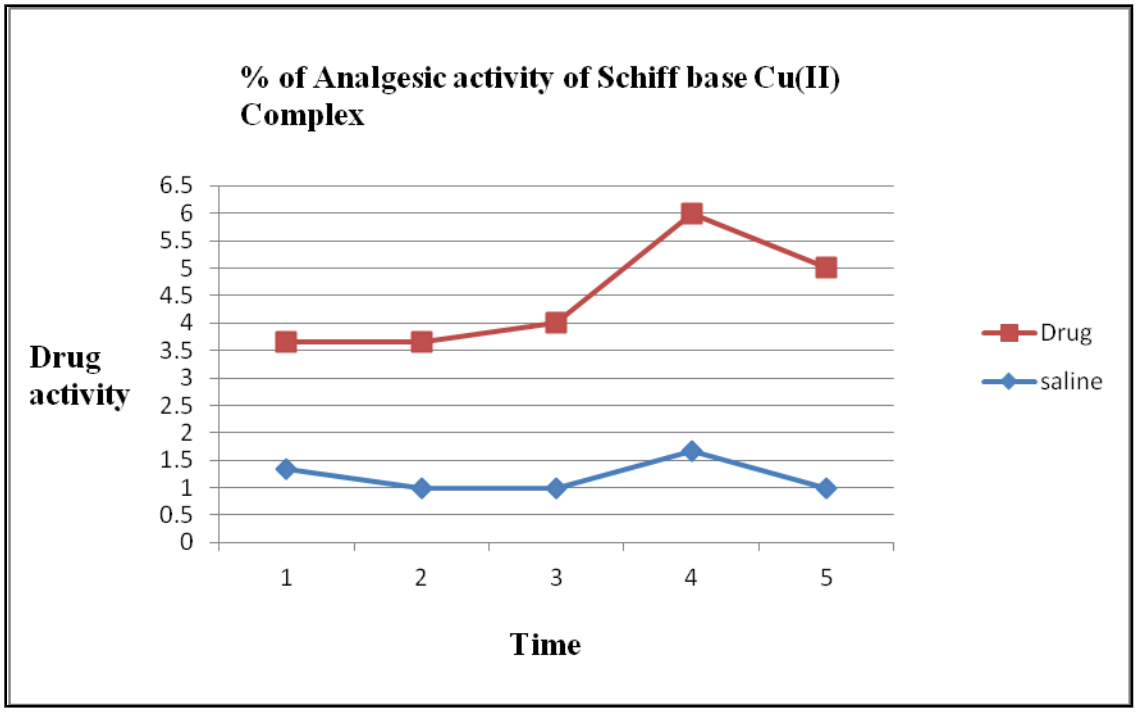
The doses of Schiff base Cu (II) Complex are prepared with a concentration of 20mg/ 10ml. The doses were given depending upon the body weight of the animal.

Analgesic activity of Schiff base Cu(II) Complex

Animal body weight(g)	Drug and dose	Basal reading (Seconds)					Reaction time after treatment (Seconds)				
		1	2	3	4	5	15	30	60	90	120
34.83	**Control 1ml saline**	1	1	2	1	1	2	1	1	1	1
31.45		1	1	1	2	1	1	1	1	2	1
30.19		1	1	1	1	1	1	1	1	2	1
	Mean	1.00	1.00	1.33	1.33	1.00	1.33	1.00	1.00	1.66	1.00
29.18	**Test drug (20 mg in 10 ml)**	1	2	2	1	2	2	2	3	4	4
25.16		1	2	1	1	1	2	3	3	5	4
27.56		1	1	1	1	1	3	3	3	4	4
	Mean	1.00	1.66	1.33	1.00	1.33	2.33	2.66	3.00	4.33	4.00
		% of analgesic activity					42.9	62.4	66.7	61.7	75.0

% of Analgesic activity of Schiff base Cu (II) Complex


B
% of drug activity
0
10
20
30
40
50
60
70
80
1
2
3
4
5
Time in Minutes


% of Analgesic activity of Schiff base Cu(II) Complex
Drug activity
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
1
2
3
4
5
Time
Drug
saline

CHAPTER VII

Summary and Conclusion

SUMMARY

4-Chloro-O-Phenylene diamine and its Copper (II) complex have been prepared by the Schiff base formation. The synthesized compound was confirmed from UV, IR & NMR spectrum. The O-Phenylene diamine and its Copper (II) complex found to have remarkable antimicrobial activity due to the presence of nitrogen group.

The antimicrobial activities of three bactericidal organisms *Bacillus subtilis*, *Streptococcus viridians* and *Staphylococcus epidermidis* on the test compounds 4-Chloro-O-Phenylene diamine and its Copper (II) complex were screened by employing the Disc Diffusion method. A concentration gradient (500, 1000, 2000 and 3000μg) of each compound was put into study. From the study, it is observed that its shows a maximum zone of inbition.

Chapter I is the introduction which deals with the introduction of Schiff base and its complex, Ultraviolet and visible spectroscopy, infrared, NMR spectroscopy of the complexes, biological importance of Schiff base complexes and its applications.

Chapter II describes the literature review about O-phenylene diamine and 2-hydroxy acetophenone, nature of ligand, structure of ligand, nuclearity and its geomentry

Chapter III describes the scope of the present work, synthesis, antimicrobial study, CNS and analgesic study

Chapter IV describes the scheme of the present work which deals with the synthesis of the ligand and its complex

Chapter V describes the experimental section which consists of chemicals required, materials required and synthesis of ligand and its complex comprising derivatives of 4-Chloro-O-Phenylene diamine and 2-hydroxy acetophenone, experimental procedure for antibacterial activity, CNS study and analgesic study

Chapter VI describes the confirmation of synthesized ligand and its complex by TLC, UV, FT-IR, NMR spectroscopy, antimicrobial studies by disc diffusion method, CNS studies using digital actophotometer, analgesic studies using analgesiometer and its graph. The antibacterial studies against Gram positive *Bacillus subtilis, Streptococcus viridians* and *Staphylococcus epidermidis* were determined by disc diffusion method and maximum zone of inhibition was calculated

CONCLUSION

2-hyroxy acetophenone and 4 – chloro – o-phenylene diamine were refluxed in ethanol and the product is 2-[*N*-(4-chloro-2-{[1-(2-hydroxyphenyl)ethylidene]amino}phenyl)ethanimidoyl]phenol and

its complexes were prepared. The product was confirmed by TLC, IR, ^{1}H NMR and UV Studies. The product was subjected to antibacterial activity and it shows a good antibacterial activity. The Schiff base complex was subjected to Central nervous system activity using digital actophotometer it shows a depressant activity when compared to standard drug chlorpromazine. It also subjected to analgesic activity using .analgesiometer the complex shows a good analgesic activity

CHAPTER VIII

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