Synthesis and Characterization of Some Metal Complexes of Tetracycline, Theophylline and Cimetidine

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Research Article

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Posted Date: December 18th, 2025

DOI: https://doi.org/10.21203/rs.3.rs-8205245/v1

Additional Declarations: No competing interests reported.

SYNTHESIS AND CHARACTERIZATION OF SOME METAL COMPLEXES OF TETRACYCLINE, THEOPHYLLINE AND CIMETIDINE

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ABSTRACT

Metal complexes of Tetracycline, Cimetidine, and Theophylline were prepared by the direct reaction of the respective ligands with metal salts namely copper (I) bromide, cobalt carbonate, and vanadyl sulfate. This thesis contains detailed reports on synthesis and characterization of copper, cobalt and vanadium complexes of tetracycline, theophylline and cimetidine. The complexes were synthesized by direct mixing of the metal salt dissolved in water (solvent) and corresponding ligands dissolved also in water (solvent). The complexes were characterized by Ultraviolet spectrophotometer (UV-Vis), FTIR spectrometer and solubility. Metal complex with formula of $M\text{-}L_x$ [where L = Ligands (Tetracycline, Cimetidine, and Theophylline) and M = metal ion (Co, VO and Cu^I, x = coordination number of the ligands to the central atom (M)] were obtained. Some ligands gave crystalline complexes as it bonds to the central metal (cobalt) and others were powdery as it bonds to the central metal (vanadium & copper).

Keywords: Tetracycline, Theophylline, Cimetidine, Cobalt, Vanadium, Copper, Coordination complex, UV-Vis and FTIR spectrometer.

INTRODUCTION

1. 1 BACKGROUND

Coordination chemistry is the foundation of modern inorganic and bioinorganic chemistry, both of which have contributed immensely to the development of the chemical industry and medicine. The knowledge of coordination chemistry has provided insight into the mode of actions (kinetics and mechanisms) of biological molecules in living systems. Important biological molecules such as vitamin B12, chlorophyll, haemoglobin and myoglobin are coordination compounds of cobalt, magnesium and iron. The comprehensive understanding of the mode of actions of these complex molecules has been made possible through the knowledge of coordination chemistry. From this

background, the knowledge of coordination chemistry is inevitable to chemists if not all scientists (Geoffrey, 2010).

1.2 WERNER'S CONTRIBUTIONS TO COORDINATION CHEMISTRY

Alfred Werner (1866-1919) was the first Swiss Chemist to receive the Nobel Prize in Chemistry due to his contribution to coordination chemistry. He prepared, characterized and studied both physical and chemical properties of some coordination compounds by simple experimental techniques such as precipitation. From his findings, he made the following conclusions:

i. Central metal atom or ion in a complex possesses two kinds of valencies named primary and secondary valencies
ii. The primary valency is ionisable and can be satisfied by anions only. It can be considered as the oxidation state of the central metal.
iii. The secondary valency is not ionisable and can be satisfied by both molecules and anions. It gives rise to the coordination number.
iv. The spatial arrangement of the anions and molecules satisfying the secondary valency determines the shape of the complex.

The complex species is enclosed in square bracket while the anions satisfying only the primary valency lie outside the coordination sphere (square bracket). Note that anions in the coordination sphere satisfied both primary and secondary valencies but the molecules only satisfy secondary valency. From Werner's postulates geometries have been assigned to complexes based on the number of the secondary valencies (Miessler and Tarr, 2010).

1.3 DRUG

A drug is any substance that causes a change in an organism's physiology or psychology when consumed (Random House, *2007).* Drugs are typically distinguished from food and substances that provide nutritional support. Consumption of drugs can be via inhalation, injection, and smoking. Aspirin is a pharmaceutical drug often used to treat pain, fever, and inflammation. Ingestion, absorption via a patch on the skin, or dissolution under the tongue. In pharmacology, a drug is a chemical substance, typically of known structure, which, when administered to a living organism, produces a biological effect (Rang *et al.,* 2011*).* A pharmaceutical drug, also called a medication or medicine, is a chemical substance used to treat, cure, prevent, or diagnose a disease or to promote wellbeing (Random House, 2007*).* Traditionally drugs were obtained through extraction from medicinal plants, but more recently also by organic synthesis (Atanasov et al., 2015*).* Pharmaceutical drugs may be used for a limited duration, or on a regular basis for chronic disorders (American Heritage Science Dictionary, 2007*).* Pharmaceutical drugs are often classified into drug classes groups of related drugs that have similar chemical structures, the same mechanism of action (binding to the same biological target), a related mode of action, and that are used to treat the same disease (Mahoney and Evans,2008; WHO,2003*).* The Anatomical Therapeutic Chemical Classification System (ATC), the most widely used drug classification system, assigns drugs a unique ATC code, which is an alphanumeric code that assigns it to specific drug classes within the ATC system. Another major classification system is the Bio-pharmaceutics Classification System. This classifies drugs according to their solubility and permeability or absorption properties (Bergström *et al.,* 2014).

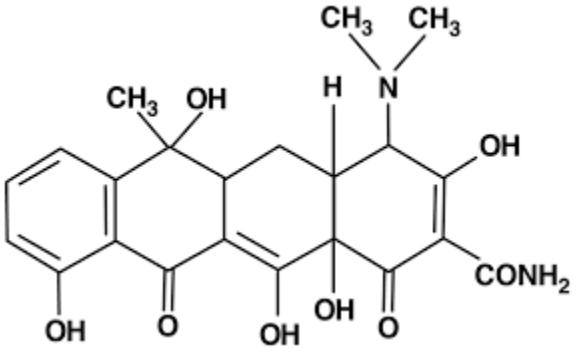


Fig 1.1 Structure of Tetracycline

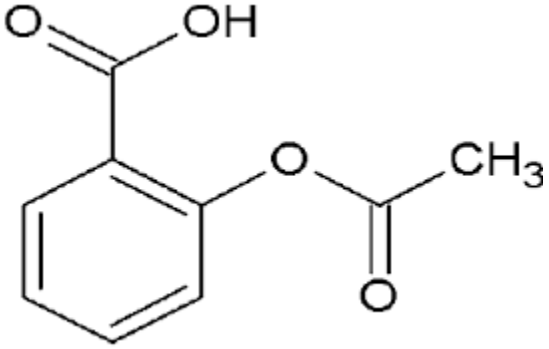


Fig.1.2 Structure of Aspirin

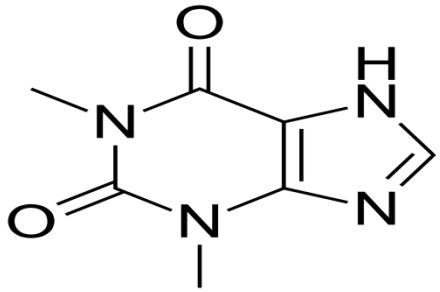
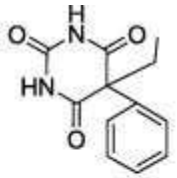
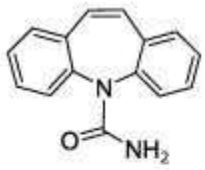


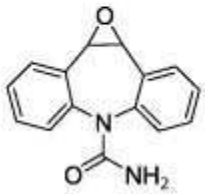
Fig 1.3 Structure of Theophylline



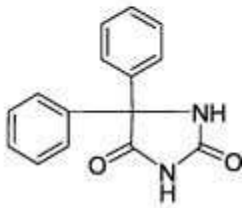
Phenobarbital



Carbamazepine



Carbamazepine 10,11 epoxide



Phenytoin

Fig 1.4 Structure of some other API'S

1.4 COORDINATION COMPOUNDS (METAL COMPLEXES)

Coordination compounds are formed by the reaction between Lewis acids and Lewis bases. By Definition, Lewis acids are electron pair acceptors while Lewis bases are electron pair donors. Thus a Lewis acid must have empty suitable orbitals to accommodate the donated electron pairs. The presence of empty suitable orbitals in transition metals (e.g. Cu, Co, Fe etc) and some compounds (BF_3, $BeCl_2$ with empty p-orbital) and ions (H^+) of main block elements makes them to act as Lewis acids.

A molecule can function as a Lewis base provided it has heteroatom(s) with lone pair(s) on them. Examples of such molecules are H_2O, NH_3, CO etc, anions such as halides (F^-, Cl^-, Br^-), cyanide (CN^-) are also Lewis bases (Cox, 2004; Housecroft and Sharpe, 2005). The chemical interaction between a Lewis acid and a Lewis base leads to coordinate bond formation hence the product of the interaction is called coordination compound. By definition, coordination compound is compound formed when a central metal atom or ion is surrounded (coordinated) to a number of anions or molecules in such a way that the number of the coordinated anions or molecules exceeds the normal covalency of the central atom or ion. The compound is also referred to as complex because on ionization, it exists as an independent species without dissociation, unlike normal or double salt which dissociates on ionization. Complexes are enclosed in square brackets to distinguish them from other types of salts (Cotton and Wilkinson, 1972).

1.4.1 Metal Ions Role in Biological Systems

Some metals are essentials. Others are considered toxic. When it comes to transition metals, the story is not different from that of the main group metals. Some have no known biological effects, such as Scandium in its +2 and +3 oxidation states in its various isotopic forms. Some are hypoallergenic such as Titanium (Ti), while others are essential to all forms of life such as iron and copper. For example, iron ($Fe^{2+/3+}$), by far, is the most important metal ion not only within the first transition series, but also within the entire periodic table. Without iron, there will be no life. On the other hand, Chromium (III) or (Cr^{3+}) may have a role to play in glucose metabolism. On the other hand, the toxic effect of Cr (VI) or (Cr^{6+}) is undeniable which prompted researches to search for specific Cr^{6+} chelators. Cr^{6+} also is considered to be mutagenic and/or carcinogenic (Lippard and Berg; Cowan, 1997 and Tietz, 1994). The rest of the first transition metal series are: V, Mn, Co, Ni, and Cu. Cu^{2+} are an essential trace metal ion involved in many metalloproteins including: ceruloplasmin, cytochrome oxidase, superoxide dismutase, dopamine-β-hydroxylase, ascorbate oxidase, lysyl oxidase, and tyrosinase (Lippard and Berg, 1994; Cowan, 1997 and Tietz, 1994).

1.4.2 Metal Complexes in Medicinal Chemistry

Medicinal inorganic chemistry is a fairly recent offshoot of bio-inorganic chemistry, itself a science still with much to learn. It is at the interface between medicine and inorganic chemistry, and includes metal-based drugs, metal sequestering or mobilizing agents, metal-containing diagnostic aids, and the medicinal recruitment of endogenous metal ions. The number of moderately comprehensive reviews of the topic can still be counted on the fingers of one hand **(**Sadler, 1991; Abrams amd Murrer, 1993; Farrell, 2002; Thompson and Orvig, 2003). However,

this field is growing exponentially **(**Orvig and Abrams, 1999). Rapid growth stems from some spectacular successes, most notably cisplatin for treatment of testicular cancer, gadolinium complexes in magnetic resonance imaging (MRI), and the rise of nuclear medicine, for both therapy and diagnosis. The use of metals in medical practice is certainly not in and of itself anything new. The lure of precious metals, such as gold and silver, attracted ancient Chinese, Egyptian, Greek and Indian healers to use them in cures of various sorts. Copper and iron have also been used since antiquity in metal-based therapies. There has always been a curious connection between the discovery of a new precious element and its quick movement into the medicinal armamentarium. Today, therapeutic applications of inorganic chemistry in medicine are varied, encompassing many aspects of the introduction of metal ions into the body (or their intentional removal) for therapeutic or diagnostic effect **(**Sadler, 1991). Cisplatin can be considered the archetypal inorganic drug, as it contains not one atom of carbon **(**Rosenberg *et al*., 1969). Nonetheless, most metal-based pharmaceuticals today are constructed with carbon-based ligands.

1.4.3 Metal Complexes as Drugs and Chemotherapeutic Agents

The medicinal uses and applications of metals and metal complexes are of increasing clinical and Commercial importance. Monographs and major reviews, as well as dedicated volumes, testify to the growing importance of the discipline (Farrell, 1989; Farrell, 1999; Orvig and Abrams, 1999; Guo, *et al.*, 1999; Keppler, 1993; Clarke, 1989; Clarke and saddler, 1999; Fricker, 1994; Berthon, 1995 and Roat, 2002). Relevant reviews are to be found throughout annual series, for example Metal Ions in Biological Systems and Coordination Chemistry Reviews (Sigel and Sigel, 1995). The field of inorganic chemistry in medicine may usefully be divided into two main categories: firstly, ligands as drugs which target metal ions in some form, whether free or protein-bound; and secondly, metal-based drugs and imaging agents where the central metal ion is usually the key feature of the mechanism of action (Reynolds, 1996). This latter class may also be conveniently expanded to include those radio nuclides used in radioimmunology imaging and radioimmunology therapy. A list of clinically used chelating agents may be found in most pharmacopoeia (Andersen, 1999), while new chelating agents continue to be sought (Liu and Hider, 2002; Andersen, 1999). The use of chelating agents in the treatment of Wilson's disease is a good example of how medical problems due to free metal ion (Cu^{2+}) toxicity may be ameliorated by chelating agents (Sarkar, 1999) The extensive work on matrix metalloproteinases likewise represents a case study in design of small organic ligands as drugs to inactivate a metal enzyme (Parks *et al.*, 1998 and Whittaker *et al., 1999).* Over expression of these zinc-containing enzymes is associated with several diseases including arthritis and cancer, so inhibition of the zinc active site is a reasonable drug development strategy. Indeed, enzymatic zinc is an attractive target because of the diversity of its structural and catalytic roles in enzymes (Vallee and Auld, 1993; and Rein *et al*, 1998). An important distinction to be made is between drugs as chemotherapeutic agents, whose function is to kill cells, and drugs acting by a pharmacodynamic mechanism whose action must be essentially reversible and/or short lived (Albert, 1979).

1.5 DESIGN OF LIGANDS FOR METAL-BASED PHARMACEUTICALS

The importance of ligands in modifying the biological effects of metal-based drugs cannot be overestimated (Thompson and Orvig, 2003). Ligands can modify the oral/systemic bioavailability of metal ions, can assist in targeting specific tissues or enzymes; can deliver, protect, or sequester a particular metal ion, depending on the requirements, for therapy or diagnosis. Ligands can also ensure protection of tissues from toxic metal ions or, in a contrasting strategy, enhance uptake of

pharmacologically beneficial metal ions. Ligands can, of course, also serve in the traditional coordination chemistry capacities of modifying reactivity and/or substitutional inertness **(**Liu and Edwards, 2001.

1.5.1 Synergistic Ligands for Enhanced Functionality

Another type of ligand functionality can be achieved by utilizing ligands that are pharmaceutically active, thus incorporating multi-functionality within a single molecule. Examples include ketoconazole and clotrimazole as ligands for Cu(II), Ru(II) and Au(I) for more effective anti-malarial compounds, (compared to non-metal containing analogues) and anti-trypanosome therapeutics (Navarro *et al.,* 2001*).* Other examples in development include vanadium-based thiazolidinedione compounds for diabetes therapy and gold-based curcumin compounds as anti-arthritics (Sharma *et al.*, 1987). Appreciation is growing for the roles of the ligands in metal based therapeutic compounds, as distinct from those in metal based diagnostic agents. Specifically, in diagnostic agents based on metal ions which may be toxic when unprotected, substitutional inertness can be a valuable property (Xu *et al, 2001; and* Aime *et al.*, 2000). For therapeutic agents, on the other hand, bio-molecular rearrangement can be expected, and even be considered an advantage. In both cases, portions of the ligand may be designed to serve as targeting agents, either towards a particular tissue, or an enzyme. In diagnostic agents, the whole molecule can usually be expected to remain intact, from administration through to excretion. Not so in metal-based therapeutics, some of which would not even function if they remained intact indefinitely (Louie and Meade, 1999).

1.5.2 Oxidation State as a Critical Factor in Bioavailability of Metal-Based Drugs

Besides ligands choice, another critical factor in design of a metallopharmaceutical is oxidation state. The oxidation state of the metal ion can be decisive in regulating the immediate in-vivo response to metal-based pharmaceutical agents, often making the difference between a beneficial and a toxic response at the same administered dose of a metal ion, and also directing towards the metabolic pathways by which the compound will be integrated. The oxidation state of the metal ion also dictates particular coordination geometries, hence limiting appropriate binding for different ligands set. By optimizing choice of ligands and oxidation state, investigators can build in control of kinetic and thermodynamic properties of metallopharmaceuticals for specific therapeutic needs (Reedijk, 2003).

1.6 IMORTANCE OF TRANSITION METAL COMPLEXES

Metals have an esteemed place in medicinal chemistry. Transition metals represent the d block element which includes groups 3-12 on the periodic table. Their d shells are in process of filling. This property of transition metals resulted in the foundation of coordination complexes. Metal complex or coordination compound is a structure consisting of a central metal atom, bonded to a surrounding array of molecules or anions. Sophus Jorgensen in Denmark synthesized metal conjugates for the first time in the mid 1870's. In 1893 the major breakthrough in this field occurred when Alfred Werner investigated a series of compounds, which contained cobalt, chlorine and ammonia.

1.6.1 TRANSITION METAL COMPLEXES AS ANTICANCER AGENTS

1.6.1.1 Platinum Based Anticancer Drugs

Platinum (II) complexes has been used as anti cancer drugs since long, among them cisplatin has proven to be a highly effective chemotherapeutic agent for treating various types of cancers (Jamieson and Lippard, 1999). Cisplatin moves into the cell through diffusion and active transport. Inside the cell it causes platination of DNA, which involves interstrand and intrastrand cross-linking as well as formation of adducts, usually through guanine, as it is the most electron rich site and hence, easily oxidized. Formation of cisplatin DNA adducts causes distortion and results in inhibition of DNA replication (Lee *et al.,* 2002). Cisplatin DNA adducts also serve as binding site for cellular proteins such as repair enzymes, histones, transcription factors (Louie 1999; Volkter 1999; Cohen et al., 2001; He *et al.,* 2000; Wong *et al.*, 2002). Beside the effectiveness of cisplatin against cancer, it has encountered many side effects.

Drugs like cisplatin does not specifically affect cancer cells but it also effect the rapidly dividing cells of certain normal tissues, such as those found in hair follicles, bone marrow, and the lining of the gastrointestinal tract. Inside the cell it interacts with a number of other negatively charged bio molecules besides DNA such as proteins, sulphur-containing compounds like metallothioneins and glutathiones that sequester heavy metals like Pt and remove it from the cell. Pt (II) and Pt (IV) complexes are photo reactive. Irradiation of cis-platin modified DNA with UV light can induce cross-links with the protein HMG, which can inhibits RNA transcription (Bartkowiak *et al.*, 2009; Qutob, *et al.*, 2004; McKay , *et al.,* 2001).

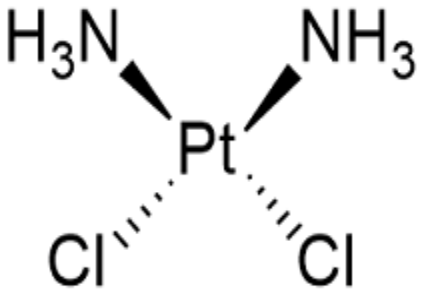


Fig 1.5 Cisplatin

1.6.1.2 Non-Platinum Anticancer Agents

Platinum is not the only transition metal used in the treatment of cancer, various other transition metals have been used in anticancer drugs (Chen et al., 2009). Titanium complexes such as Titanocene dichloride had been recognized as active anticancer drug against breast and gastrointestinal carcinomas. Gold complexes also show anti-cancer activity, these complexes act through a different mechanism as compared to cisplatin (Au et al., 2008). The target site of Au complexes is mitochondria not DNA. Certain gold complexes with aromatic bipyridyl ligands have shown cytotoxicity against cancer cells (Marcon et al., 2002). The 2-[(dimethylamino) methyl] phenyl gold (III) complex has also proven to be anti tumor agent against human cancers (Messori et al., 2000). Gold nanoparticles when used in combination with radio therapy or chemotherapy enhance DNA damage and make the treatment target specific (Zheng et al., 2009). Lanthanum has also been used to treat various forms of cancer (Kapoor, 2009). Ansari et al. in 2009 studied some complexes of Mn (III) induce tumor selective apoptosis of human cells.

1.6.2 Transition Metal Complexes as Anti -Infective Agents

Transition metals like silver have been used for years as anti microbial agents. Silver has low toxicity as compared to other transition metals. Silver nitrate is still given to the infants to prevent the development of opthalmia neonatorum. One of the most commonly used compounds of silver is silver (I) sulfazine; it is used to treat severe burns to prevent them from bacterial infections (Clarke et al. 1975). Chlorohexidine- Silver Sulfadiazine is an anti infective metal complex against catheter infections in-vivo (Bassetti et al., 2001). Organometallic complexes of Pt, Rh, Ir, Pd, and Os with active organic molecules have been reported to exhibit trypanocidal activity (Lorisean et al., 1992). An increasing amount of data showing the beneficial use of zinc (Zn) in treating diarrhea continues to emerge from epidemiological and clinical trials. Nitrogen containing macrocyclic complexes of Manganese (II) have shown anti microbial activity. An octahedral geometry for these complexes has been confirmed by spectroscopic analysis. Many manganese complexes have been screened against a number of pathogenic fungi and bacteria to evaluate their growth and potential Metal complexes of Pt (II) and Ru (II) with o-vanillin- (4- methyl thiosemicarbazone), and o-vinillin- (4-phenyl thiosemicarbazone) have been prepared, characterized by chemical methods and studied for antibacterial, antifungal, and antiamoebidal activity and have been proven more efficient anti infective agents (Offing et al., 1996).

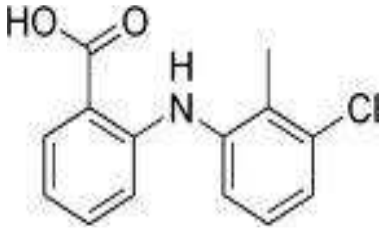


Fig 1.6 Tolfenamic acid.

1.6.3 Transition Metal Complexes as Anti-Inflammatory Agents and Free Radical Quenchers

Transition metals have also been used as anti-inflammatory and anti-arthritic agents (Aras *et al.,* 2009). Several inject able transition gold complexes like sodium aurothiomalate, aurothioglucose and sodium aurothiopropanol are used clinically in the treatment of severe cases of rheumatoid arthritis. Gold and silver nanoparticles conjugated with heparin derivative possess antiangiogenesis properties (Kemp *et al*., 2009). Silver nanoparticles are used in the development of an antimicrobial gel formulation for topical use (Jain *et al.,* 2009). Gold has been used in the treatment of peripheral psoriatic arthropathy (Nash and Clegg, 2005).

1.5.4 Transition Metals as Anti-Diabetic Agents

More than 2 - 8% of world's population is suffering from diabetes (Wild et al., 2004). It is a condition in which body do not produce a hormone called insulin which is necessary for the absorption of glucose in cells (Rother, 2007). Scientists are looking for alternative approaches for the treatment of diabetes (Nahas et al., 2009). Control of the glucose level in the blood plasma has been achieved by administration of vanadium and zinc in form of inorganic salts.

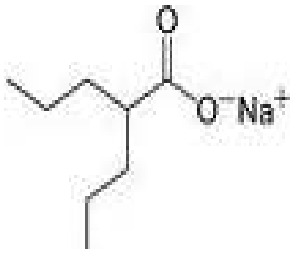


Fig 1.7 Sodium Valproate.

It has been shown that elements are poorly absorbed in their inorganic forms and required high doses, which have been associated with undesirable side effects. Vanadium complexes with organic ligands have proved to be less toxic, with improved solubility and lipophilicity. There are a number of vanadium complexes that have been developed, all of which have insulin-mimetic properties. The molecular mechanism responsible for the insulin-like effects of vanadium compounds have been shown to involve the activation of several key components of insulin-signaling pathways. It is interesting that the vanadium effect on these signaling systems is independent of insulin receptor protein tyrosine kinase activity, but it is associated with enhanced tyrosine phosphorylation of insulin receptor substrate (Mehdi *et al*., 2006). Chromium supplementation significantly improved glycemia among patients with diabetes but do not show any significant effect on glucose metabolism in healthy individuals (Balk *et al*., 2007). Higher zinc intake has also been associated with a slightly lower risk of type 2 diabetes in women (Sun *et al.,* 2009).

1.6.5 Transition Metal as Neurological Drugs

Transition metal complexes are also used in the treatment of neurological disorders (Hashimoto *et al*., 2003). One example of this is lithium. Lithium has been used to cure many neurological disorders like Huntington's chorea, tardive, dyskinesia, spasmodic torticollis, Tourette's syndrome, L-dopa induced hyperkinesias, Parkinsonism, organic brain disorders, drug induced delusional disorders, migraine and cluster headache, periodic hypersomnolence, epilepsy, meniere's disease and periodic hypokalemic paralysis. The mechanism of action involves Li inhibiting the scavenging pathway for capturing inositol in the retrosynthesis of polyphosphoinositides in the brain (Camins, 2009). Valproate treatment in combination with lithium delays disease onset, reduces neurological deficits and prolongs survival in an amyotrophic lateral sclerosis mouse model (Feng, 2008). Other transition metals like zinc are involved as a transmitter in the neuronal signaling pathways. Neuronal Zn (II) serves as an important, highly regulated signaling component responsible for the initiation of a neuro-protective pathway (Aras, 2009).

1.7 JUSTIFICATION

A large amount of information is available on the synthesis and characterization of metal complexes derived from copper, cobalt, vanadium and biological important ligands that established improvements in biological properties of parent ligands upon coordination to metal ions e.g. theophyline, tetracycline e.t.c. The synthesis of these compounds has always been achieved through non-benign routes. Therefore, the synthesis of copper, cobalt and vanadium

complexes of tetracycline, theophyline and cimetidine using environmentally friendly is of paramount interest in order to exploit their coordination chemistry and biological activity.

1.8 BROAD OBJECTIVE

The aim of this research work is to synthesize new metal complexes by the reaction of Cu(I)Br, $VOSO_4$ and $CoCO_3$ with tetracycline, theophyline and cimetidine and also to characterize the resulting complexes.

1.9 SPECIFIC OBJECTIVES OF THE RESEARCH

- To synthesize and obtain the metal complexes in solid state using the ligands mentioned above.
- To characterize the obtained metal complexes using UV-Visible, FT-IR spectrophotometry.
- To study the complexation of Tetracycline, Theophylline, and Cimetidine with copper bromide, cobalt carbonate and vanadium sulphate

CHAPTER TWO
LITERATURE REVIEW

2.1`FUNCTIONS AND STRUCTURAL FORMULA OF SOME BIOLOGICALLY RELEVANT LIGANDS

2.1.1 Tetracycline

Tetracycline, sold under the brand name Sumycin among others, is an antibiotic used to treat a number of infections. This includes acne, cholera, brucellosis, plague, malaria, and syphilis (The American Society of Health-System Pharmacists, 2016).

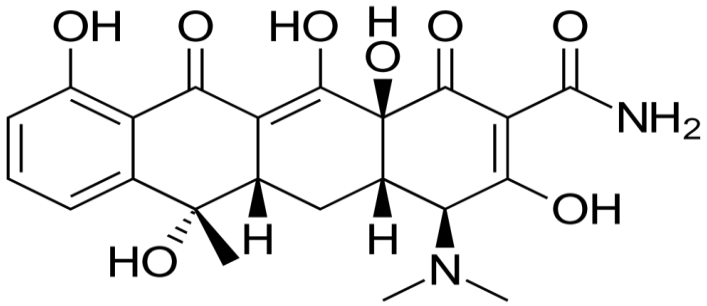


Fig. 2.1 Tetracycline

Formula $C_{22}H_{24}N_2O_8$

Molar mass 444.435 g/mol

Common side effects include vomiting, diarrhea, rash, and loss of appetite. Other side effects include poor tooth development if used by children less than eight years of age, kidney problems, and sun burning easily (The American Society of Health-System Pharmacists, 2016). Use during pregnancy may harm the baby. Tetracycline is in the tetracycline's family of medications. It Molar mass 444.435 g/mol $g \cdot mol^{-1}$ works by blocking the ability of bacteria to make proteins. Tetracycline was patented in 1953 and came into commercial use in 1978 (Fischer *et al*, 2006). It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system and Tetracycline is available as a generic medication (The American Society of Health-System Pharmacists, 2016).

2.1.2 Theophylline

Theophylline, also known as 1,3- dimethylxanthine, is a methylxanthine drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma under a variety of brand names. As a member of the xanthine family, it bears structural and pharmacological similarity to theobromine and caffeine, and is readily found in nature, being present in tea (*Camellia* sinensis) and cocoa (*Theobroma cacao*). A small amount of theophylline is one of the products of caffeine metabolic processing in the liver (*Mandal, 2016).*

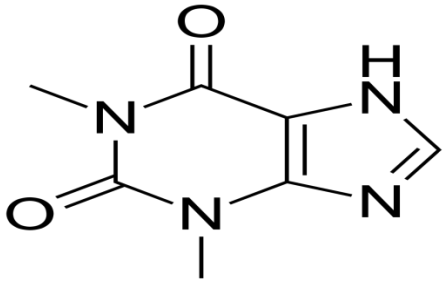


Fig 2.2; Theophyline

Formula $C_7H_8N_4O_2$, Molar mass 180.164 g·mol^{-1}

Medical uses

The main actions of theophylline involve:

- Relaxing bronchial smooth muscle,
- Increasing heart muscle contractility and efficiency (positive inotrope),
- Increasing heart rate (positive chronotropic)
- Increasing blood pressure
- Increasing renal blood flow
- Anti-inflammatory effects
- Central nervous system stimulatory effect mainly on the medullary respiratory center.

The main therapeutic uses of theophylline are aimed at:

- Chronic obstructive pulmonary disease
- Asthma
- Infant apnea
- Blocks the action of adenosine; an inhibitory neurotransmitter that induces sleep, contracts the smooth muscles and relaxes the cardiac muscle (Alboni et al, 2013).

2.1.3 Cimetidine

Cimetidine, sold under the brand name Tagamet among others, is a histamine H_2 receptor antagonist that inhibits stomach acid production (Morton *et al,* 1999*).* It is mainly used in the treatment of heartburn and peptic ulcers (Elks, 2014).

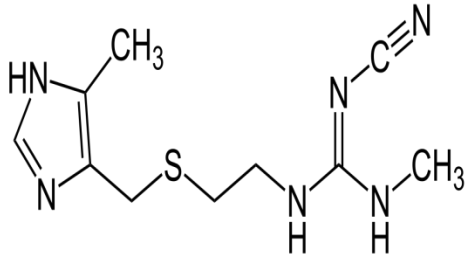


Fig.2.3 Cimetidin

Formula $C_{10}H_{16}N_6S$, Molar mass 252.34 g/mol g·mol^{-1}

2.1.4 Bipyridine

Bipyridines also known as bipyridyls, dipyridyls, and dipyridines, are a family of chemical compounds with the formula $(C_5H_4N)_2$, consisting of two pyridyl (C_5H_4N) rings. Pyridine is an aromatic nitrogen-containing heterocycle that forms complexes with most transition metals. It interacts with metals mainly as a σ- donating Lewis base.

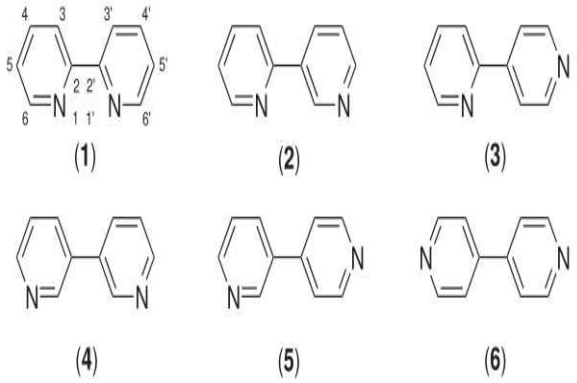


Fig.2.4 Bipyridine

The bipyridines are all colourless solids, which are soluble in organic solvents and slightly soluble in water. 2,2′-Bipyridine (2,2′-bipy) is a chelating ligand that forms complexes with most transition metal ions that are of broad academic interest. Many of these complexes have distinctive optical properties, and some are of interest for analysis. Its complexes are used in studies of electron and energy transfer, supramolecular and materials chemistry, and catalysis. 2,2′-Bipyridine is used in the manufacture of diquat (*Mandal, 2016).*.

2.1.5 Imidazole

Imidazole is an organic compound with the formula $C_3N_2H_4$. It is a white or colourless solid that is soluble in water, producing a mildly alkaline solution. In chemistry, it is an aromatic heterocycle, classified as a diazole, and has nonadjacent nitrogen atoms Chemical formula $C_3H_4N_2$ Molar mass 68.077 g/mol Appearance white or pale yellow solid Density 1.23 g/cm^3, solid Melting point 89 to 91 °C (192 to 196 °F; 362 to 364 K) Boiling point 256 °C (493 °F; 529 K) Solubility in water 633 g/L UV-vis (λmax) 206 nm Structure and properties Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because hydrogen can be bound to one or the other nitrogen atom. Imidazole is a highly polar compound, as evidenced by
its electric dipole moment of 3.67 D (Christen *et al*, 1981). It is highly soluble in water. The compound is classified as aromatic due to the presence of a planar ring containing 6 π- electrons (a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring). Some resonance structures of imidazole are shown below:

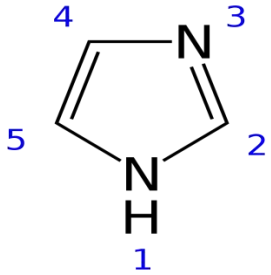


Fig.2.5 Imidazole

2.5.1 Pharmaceutical Derivatives of Imidazole

The substituted imidazole derivatives are valuable in treatment of many systemic fungal infections. Imidazoles belong to the class of azole antifungals, which includes ketoconazole, miconazole, and clotrimazole (Davis *et al*, 2009).

2.1.6 Phenanthroline

Phenanthroline (phen) is a heterocyclic organic compound. It is a white solid that is soluble in organic solvents. It is used as a ligand in coordination chemistry, forming strong complexes with most metal ions.Chemical formula $C_{12}H_8N_2$ Molar mass 180.21 g/mol Appearance colourless crystals Density 1.31 g/cm3, Melting point 117 °C (243 °F 390 K) Solubility in water (moderate),solubility in other solvents, acetone and ethanol. The ferroin analogue $[Ru(phen)_3]^{2+}$ has long been known to be bioactive (Dwyer *et al*, 1982). 1,10-Phenanthroline is an inhibitor of metallopeptidases, with one of the first observed instances reported in carboxypeptidase (Felber *et al.*, 1962). Inhibition of the enzyme occurs by removal and chelation of the metal ion required for catalytic activity, leaving an inactive apoenzyme. 1,10-Phenanthroline targets mainly zinc metallopeptidases, with a much lower affinity for calcium (Salvesen and Nagase, 2001).

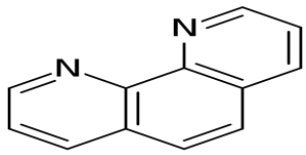


Fig 2.6 1, 10-Phenanthroline

2.2 LITERATURE REVIEW ON METAL-CONTAINING THERAPEUTICS

2.2.1 Vanadium Complexes with Mixed O, S Anionic Ligands Derived From Maltol: Synthesis, Characterization, And Biological Studies

The coordination chemistry of vanadium with sulfur-containing ligands is an emerging field of interest with relevance to several disparate biological systems (Thompson and Orvig, 2001; Rehder, 1999; Chasteen and Kluwer, 1990; and Crans *et al*, 2004). The presence of vanadium-sulfur bonding in the active site of certain nitrogenase enzymes has been well established,5 and vanadium-sulfur coordination also appears to be pivotal to the well-known tyrosine phosphatase inhibition through binding to cysteine at the putative active site (Zhang *et al*, 1997). A third area of interest, vanadium complexes with ligands that supply both sulfur and oxygen donors for candidate therapeutic agents (Sakurai *et al*, 2000; and Nekola *et al*, 2002), is one that dovetailed nicely with our previous explorations in the more general area of vanadium-containing insulin

mimics (Thompson and Orvig, 2004) by oral administration of some vanadium salts (e.g., $VOSO_4$ or sodium vanadate). Numerous studies in experimental animals have shown that tolerable levels of vanadium containing compounds can normalize plasma glucose, lipids, and the thyroid hormone and at least partially counteract the increased oxidative stress that accompanies diabetes mellitus and contributes to secondary complications In previous studies in our laboratories, both vanadium(III) and oxovanadium(IV) complexes with, primarily, oxygen donor ligands have been shown effective, with one compound, bis(ethylmaltolato) oxovanadium(IV), having completed phase I clinical trials (Thompson *et al*, 2003). These compounds should bind to vanadium through the thiocarbonyl sulfur and deprotonated hydroxyl oxygen atoms, thus comprising mixed O,S donor ligands. Two other ligands with mixed O,S donor atoms with the N-R group substituted for the ring oxygen were also synthesized: 3-hydroxy-2-methyl-4-pyridinethione (Hmppt) and 3-hydroxy-1,2-dimethyl-4-pyridinethione (Hdppt). The corresponding oxygen analogues of these compounds (i.e., CdO instead of CdS) are ligands that have been previously synthesized and tested as vanadyl complexes for insulinlike properties (Thompson *et al.*, 2003; and Rehder *et al.*, 2002).The substitution of N-R in the ring provides versatility in terms of varying the R group on the nitrogen and, hence, changing chemical properties such as lipophilicity, solubility, and stability of the vanadium complex.

2.2.2 Vanadium and diabetes

As we approach the 21st century, diabetes research has never been so intense. Along with important improvements in the scientific tools and techniques, deep insights into the complex inter-relationship between insulin action, insulin resistance, lipid and carbohydrate metabolism have been made. Twelve years ago, a very surprising discovery was made in vivo demonstrating that vanadium can enhance and/or mimic the physiological effects of insulin in an experimental model of diabetes (Heyliger *et al.,* 1985). Since this first observation, a great deal of work has been done and recently data demonstrating beneficial effects of vanadium in humans have been published leading to the question, 'could vanadium be a useful adjunct in the treatment of diabetes?'. Key aspects of the findings with this unique trace element in relation to its insulin-mimetic, anti-hyperglycemic and anti-hypertensive effects are reviewed below.

2.2.2.1 In-Vitro Insulin Mimetic Actions of Vanadium

In vitro, the insulin-like effects of vanadium extend to numerous processes involved in carbohydrate, lipid and protein metabolism: (i) carbohydrate metabolism through glucose transport, glucose transport translocation, glycolysis and glycogen synthesis (Nakai *et al*, 1995; Duckworth *et al*, 1988; Schechter 1980 and Karlish ; Tamura *et al, 1984;* Tamura *et al, 1983;* McNeill *et al*, 1995; and Orvig *et al*, 1995); (ii) lipid metabolism primarily by inhibition of lipolysis, and (iii) protein metabolism and mitogenesis (Jackson *et al*, 1988; Morita *et al*, 1995; Maher, 1992; Barnes *et al*, 1995; and Hajjar *et al*, 1987).

2.2.2.2 In-Vivo Insulin Mimetic Actions of Vanadium

The first report of vanadium's insulin mimetic and antidiabetic potential in vivo was published by Heyliger et al, 1985. This study was performed on streptozotocin (STZ) diabetic rats chronically treated with sodium orthovanadate. Normalization of hyperglycemia and improvement of cardiac depressed function were both recorded without an increase in plasma insulin levels in the diabetic rats. This observation demonstrated the ability of vanadium to improve insulin sensitivity. Hyperinsulinemic clamp studies later confirmed a decreased insulin resistance following

vanadium treatment (Bhanot *et al.*, 1994). In 1987, Meyerovitch showed that in addition to lowering plasma glucose levels, chronic sodium metavanadate administration could also enhance basal hexose transport in both liver and muscle (Meyerovitch *et al.*, 1987). Brichard et al. subsequently described a dose-response relationship between vanadate and its glucose lowering effects (Brichard *et al.*, 1988). Since vanadyl sulfate was reported to be 6–10 times less toxic than vanadate (Hudson, 1964) this form of vanadium was extensively investigated for its insulin-like effects. STZ-diabetic animals responded to vanadyl sulfate given in drinking water with corrected plasma glucose, lipids, creatinine and thyroid hormone blood levels. This improvement was accompanied by correction of abnormalities in isolated heart function and glycerol output from adipose tissue (Ramanadham *et al.*, 1989). The use of organic vanadium complexes to increase potency In order to overcome poor absorption of vanadate and vanadyl from the gastrointestinal (GI) tract and GI toxicity, i.e. diarrhea, our laboratory and others have synthesized various organic vanadium compounds which were designed to improve absorption, potency and therapeutic safety. Bis(maltolato)oxovanadium (IV) (BMOV), a maltol/ vanadyl compound, was developed in collaboration with Dr. C. Orvig in the Department of Chemistry at the University of British Columbia, Vancouver, Canada (McNeill *et al.*, 1992). BMOV is an example of a series of compounds specifically designed to be administered orally and absorbed by passive diffusion. It is water soluble, electrically neutral and has a low molecular weight (McNeill *et al.*, 1992; and Yuen *et al.*, 1993). BMOV and vanadyl sulfate have been compared for their effects by both oral administration and intra peritoneal (i.p.) administration using a single dose (Yuen *et al*, 1995). This observation is important regarding some concerns expressed in the literature about vanadium toxicity. Chronic BMOV treatment completely prevented elevations in plasma urea, creatinine, alanine, aminotransferase (ALT) and improved histological abnormalities in the kidney and liver from STZ diabetic rats (Yuen *et al*, 1995).

2.2.2.3 Vanadium Glucose Lowering Effects and Food Restriction

Vanadium compounds have now been extensively demonstrated to normalize the hyperphagia associated with experimental diabetes. In 1994, Malabu et al. stated some concerns claiming that the decrease in plasma glucose levels observed after vanadate administration was entirely attributable to a reduction in food intake (Malabu *et al.*, 1994). In our laboratory, Yuen et al. conducted a detailed study on STZ-diabetic rats to precisely define the respective effects attributable to vanadium alone or to food restriction alone. Two main parameters were used to assess these influences: plasma glucose levels and lipid levels (Yuen *et al.*, 1997). STZ-diabetic rats were treated daily over a 6 week period with BMOV dissolved in drinking water. Pair-fed groups were fed based on the intake of their respective counterparts from the previous day. Decreases in plasma glucose, triglycerides and cholesterol levels in diabetic-treated rats were recorded with no effect on the plasma insulin level. None of these parameters were affected in pair-fed animals. In addition, prevention of cardiac function impairment was observed in STZ-diabetic rats treated with BMOV but not in pair-fed diabetic animals. The experimental design used in Malabu's study may explain the different results since food was given to pair-fed animals only once a day. Our observation is that hyperphagic diabetic animals consume this small amount of food in a very short period of time after provided. The animals are therefore left fasting for a long period of time since blood was not collected until the morning. This factor is crucial since reduction in plasma glucose levels in their study for pair-fed diabetic groups was similar to what we have observed after a prolonged (20 h) period of fasting (Malabu *et al.*, 1994).

2.2.2.4 Vanadium in Bone

Concern has been raised by the fact that vanadium deposits in bone and could be potentially toxic (Mravoca *et al.*, 1993). Indeed studies have shown that chronic vanadium administration to rat results in bone concentrations of vanadium of 10–26 μg/g (Yuen *et al.*, 1993; and Mongold *et al.*, 1990). These concentrations were twice that of the accumulation in kidney and 6–10 times higher than those found in liver. Vanadium treatment did not affect the content of other minerals in the bone (K, Mg, Na, Ca, P) nor did it affect bone crystal size as determined by X-ray diffraction (Yuen *et al*, 1993; and Mongold *et al*, 1990).

2.2.3 Synthesis, Characterization, Antimicrobial and Density Functional Theory Studies of Metal Complexes of 3-Benzoyl-7-Methoxy Coumarin

Coumarin is a phytochemical compound existing in many plants such as Tonka bean, lavender, sweet clover grass, liquorice, strawberries, apricots, cherries, and cinnamon. Recently, coumarin derivatives are used to prepare new drugs with low toxicity and are being used as anticoagulants, antibacterial agents antifungal agents, biological inhibitors, chemotherapeutics and bioanalytical reagents(Mendez and Brown, 1982; Suttie *et al.*, 1990; Bedair *et al.*, 2000; Patonay *et a.l*, 1984; Gnerre *et al.*, 2000; Egan *et al.*, 1997; Budzisz *et al.*, 2004; and Jimenez *et al.,* 2000). Coumarin derivatives are known to have good complexing ability (Marshall *et al.*, 1994). The formation of metal complexes with coumarin plays an important role in the growth of biological activity. Recently, it has been reported that 4-methyl-7-hydroxycoumarin complexes with several metals might be applicable as anticoagulants and spasmolytic agents (Myers *et al.*, 1994; and Kawaii *et al.*, 2001). Ferroquine, a metal complex, can produce reactive oxygen species (ROS), which kill the parasites resistant to chloroquine (Gasser, 2015). Luminescent metal complexes show selective binding affinity with specific DNA conformations (Lin *et al.*, 2015). Considerable effort has now been given to the functionalization of coumarin so that metal-coumarin complexes may be synthesized towards the development of artificial photosynthetic systems, chemical sensors, and molecular level devices (Sathisha *et al.*, 2008).

A solution of 3-benzoyl-7-methoxycoumarin (L1, $C_{17}H_{12}O_4$, 0.560 g, 2 mmol) in 20 ml of methanol was treated with a solution of nickel (II) nitrate (0.290 g, 1 mmol) in methanol. The reaction mixture was stirred on a magnetic stirrer. Bluish green crystalline product formed after 6-7 h was collected by filtration. The solid was washed several times with methanol (50 ml), then with diethyl ether (30 ml) and finally dried in vacuum. The obtained complex (1a) was recrystallized from dry methanol. Molecular formula of 1a, $NiC_{34}H_{24}O_{14}N_2$: molecular weight 743.23, yield: 0.492 g, colour: bluish-green powder. Copper (II) nitrate and zinc (II) nitrate were dissolved in methanol and added to a solution of L1 in methanol in 2:1 mole ratio of ligand to metal, respectively, with stirring. The reaction mixture was heated under reflux for 3-4 h, during this period the precipitation was completed and filtered. Then, the precipitates (1b and 1c) were washed with methanol and dried under vacuum for 3 h. Molecular formula of 1b was Cu $C_{34}H_{24}O_{14}N_2$, molecular weight 748.09, yield, 0.589 g, colour: brown powder; molecular formula of 1c was $ZnC_{34}H_{24}O_{14}N_2$, molecular weight 749.92, yield, 0.596 g, colour: white crystals.

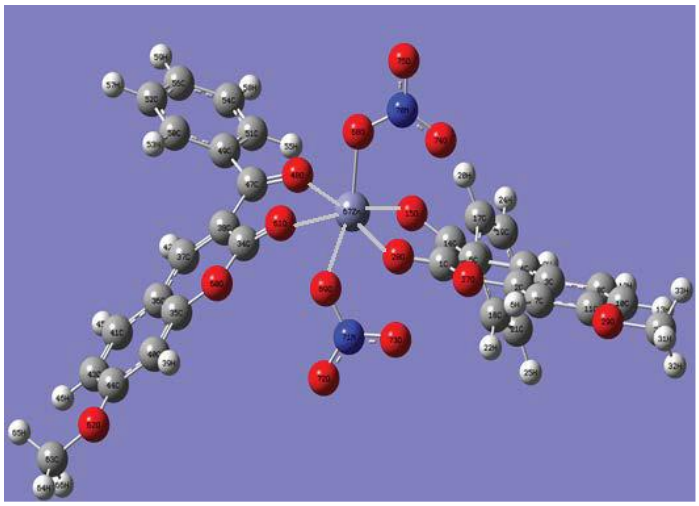


Fig. 2.7: Optimized geometry of the Cu complex 1b at B3LYP

2.2.4 Oxovanadium(Iv) Complexes with Nitrogen Donors: Synthesis, Characterisation, and Biological Activities

Macrocyclic nitrogen donor ligands have received special attention because of their versatile coordination modes and for their biological activities, that is, toxicity against bacterial and fungal growth, anticancerous , and other biochemical properties (Sellappan *et a.l*, 2010; Sengupta *et al.*, 2003; Pujar *et al.*, 1986; and Mishra *et al.,* 1997). Such ligands, for example, porphyrins, salicylates, and sulphosalicylates, are known to play a very important and vital role in the stability of the metal complexes with the factor of having specific cavity size, stereochemical rigidity, flexibility, and ability to coordinate with metal atom. SA/SSA ligands and their complexes are widespread in nature and of considerable relevance in medicinal chemistry and also in industries (Smith *et al.*, 1997; and Martell *et al.*, 1990) (e.g. in the preparation of heterometallic precursors to oxide materials). VO^{2+} complexes have extensive clinical applications. However, there have been no reports on the corresponding organo oxovanadium(IV) salicylates, sulphosalicylates and porphyrins, though these compounds are expected to be biomedical relevant (Saha *et al.*, 2006).
The VO(SA/SSA) precursors were prepared by the reaction of vanadyl sulphate (0.40 g, 2.5 mM)with salicylic acid(SA) (0.34g,2.5mM)/sulphosalicylic acid (SSA) (0.54 g,2.5 mM) and granular zinc (mesh size 20, 0.10g, 1.5mM) in 30mL methanol. The reaction mixture was refluxed for one hour. There fluxing led to the formation of [VO(SA/SSA)] precursor. The complexes of [VO(SA/SSA)L] with pyridines had been prepared by adding the appropriate ligand directly to the solution of this [VO(SA/SSA)] precursor as

VOSO4 + SA +2L $\xrightarrow{\text{Zn, methanol}}$ [VO(SA)(L)2],

Where L=o-aminopyridineandoandm - methylpyridines. The complexes were also synthesized by using bidentate nitrogen donors such as ethylene diamine, 2,2-bipyridyl, and1,10-phenanthroline.Thesaturatedsolutionofligandwas added drop wise to the hot reaction mixture of [VO(SA/SSA)] precursor. The addition of ligands resulted in the precipitation of complex. This reaction mixture obtained was again refluxed for fifteen minutes. The complex was filtered and dried. The colour of complexes was muddy brown and physical state was dry powder.

VOSO4 + SA + L-L Zn, methanol [VO(SA)(L-L)], (2)
Where L-L=ethylenediamineand1, 10-phenanthroline.

Antifungal Studies. In vitro antifungal activity of some of the selected complexes was tested against the pathogen "Sclerotiumrolfsii" by the poisoned food method using Potato Dextrose Agar (PDA) nutrient as the medium. The linear growth of fungus in control and treatment were recorded at different concentrations of the complexes. The media was prepared by dissolving dextrose and agar to the solution of fresh potato starch. The sterilization of media (PDA) was carried out by autoclaving it at 15mm pressure per square inch for 20 minutes in sterile conditions. The test solutions were prepared by dissolving the compounds in DMSO. The test solutions were mixed in the PDA and poured into Petri plates in sterilized conditions inside laminar flow. After solidification, the plates were inoculated with seven-day-old culture of pathogen by placing 2mm bit in the centre of plates. The inoculated plates were incubated at 27°C for 4 days. The linear growth of fungus in control and treatment were recorded at different concentrations of the complexes (Vincent, 1927).

2.2.5 Synthesis and Characterization of Ternary Complexes of Copper (II), Nickel (II), Zinc (II) Cobalt (II)-and Mercury (II) Theophylline with Ethylenediamine

Theophylline is a derivative of purine, consisting of a fused pyrimidine-imidazole ring system with conjugated double bonds and it has biological importance which can be used in anticancer drugs (Shohreh *et al*, 2003; Francesco et al, 2005; Jacek *et al*, 2005; and Kiriaki *et al*, 2007). The purines including theophylline, theobromine and caffeine, constitute an important class of anti-inflammatory agents (Marwaha *et al*, 1995). As it is structurally related to nucleic acids components it has tremendous biological importance (Nafisi *et al*, 2003). Thus it can be used as a drug in pulmonary disease. On the other hand, many metal ions present in small quantities in living organism and play significant roles of extreme biological importance. The metals essential for such diverse intricate functions, beyond certain levels of concentration and in certain chemical forms may bring about adverse effects. Like other purine derivative theophylline has many pharmacologic properties. Since a few metal-theophylline complexes have shown significant antitumor activity (David *et al*, 1999), it is very important to know the coordinating behavior of theophylline with transition metal ions.The antibacterial activity of theophylline is wellknown, especially as this alkaloid is present in tea leaves (Dreosti, 1996).

Mono (ethylenediamine) bis(theophyllinato)copper(II) A. 0.1705g (1.0 mmol) of $CuCl_2.2H_2O$ was dissolved into 5 ml of distilled water and added to an aqueous solution of 15 ml theophylline (0.1802g). The resultant blue colored solution was treated with 7 drops of ethylenediamine and it was allowed to stand at room temperate for crystallization. Deep blue crystals were formed at 24 hours. The crystals was filtered, washed with hot water and dried over silica gel.

Mono (ethylenediamine) bis(theophyllinato)nickel(II) B. Aqueous solutions of $NiCl_2.6H_2O$ (0.2400g in 5 ml water) and theophylline (0.1822g in 15 ml water) were mixed together and 6 drops of ethylenediamine was added to it. Then it was refluxed about 3 hours and it was allowed to stand at room temperate for crystallization. Next day violet colored crystals of $[Ni(C_7H_7N_4O_2)_2(C_2H_8N_2)]$ were found. The crystals were filtered, washed with hot water, dried in air first and then over silica gel.

Mono(ethylenediamine) bis(theophyllinato)Zinc(II) C. In aqueous solutions of $ZnSO4.7H_2O$ (0.2901g in 5 ml water) 2 drops of ethylenediamine was added. This resultant solution is trated with 15 ml aqueous solution of theophylline (0.1822g) and instantly jelly like precipitate was found then it was stored. The powdery crystals were filtered, washed with hot water, dried in air first and then over silica gel.

Mono(ethylenediamine)bis(theophyllinato)Cobalt(II). Monohydrate D. Aqueous solutions of cobalt acetate (0.1769 g in 5 ml water) and theophylline (0.1804 g in 15 ml water) were mixed together and 1 drop of ethylenediamine was added to it. Then light pinkish cloudy state was formed so it was filtered to get a clear solution. The volume of the solution was reduced to get a saturated solution for the crystallization and kept at room temperature. After two days pink crystals of $[Co(C_7H_7N_4O_2)_2(C_2H_8N_2)].H_2O$ were found. The crystals were collected by filtration, washed with hot water, dried in air first and then over silica gel.

Mono(ethylenediamine) bis(theophyllinato)Mercury(II) E. 2 drops of ethylenediamine was added in a beaker to the aqueous solution of mercury acetate (0.319 g in 5 ml of water). Aqueous solution of theophylline (0.1809 g in 15 ml of water) was prepared in another beaker and these two solutions were mixed together then white precipitate of $[Hg(C_7H_7N_4O_2)_2(C_2H_8N_2)]$ was found. The crystals were collected, washed with hot water and dried in air first then over silica gel.

2.2.6 Syntheses, Characterization and Antibacterial Susceptibility Testing of Transition Metal Complexes of Doxycycline

Tetracycline is the first semi-synthetic antibiotic of the naturally produced antibiotic aureomycin (chlorotetracycline), the first tetracycline to be discovered by fermentation of Streptomyces (Conover *et al*, 1953 and Boothe *et al*, 1953). Tetracycline was later obtained by fermentation process and is the most basic structure common to the other tetracyclines (Minieri, *et al*, 1956). The successful semi synthesis of tetracycline led to a wide search for superior structurally modified antibiotics and has provided most of the important antibiotic discoveries made since then (Stephens *et al*, 1958 and Conover, 1971). Among the semi synthetic tetracyclines that are in clinical use are doxycycline, methacycline and minocycline (Martell and Boothe, 1967). Many of these compounds retain or have enhanced antibacterial activity and are active in broad panels of organisms resistant to classical tetracyclines and other antibiotics. Xiao-Yi Xiao and co-workers have also described the design, synthesis, and evaluation of a new generation of tetracycline antibacterial agents (fluorocyclines) which possess potent antibacterial activities against multidrug resistant (MDR) Grampositive and Gram-negative pathogens (Xiao *et al*, 2012 and Clark *et al*, 2011). These efforts are in response to the emergence of antibiotic-resistant bacterial strains and towards the development of tetracycline analogues with improved potencies and pharmacological properties. However, the number of antibiotics that have been discovered and introduced to clinical use are declining due to rapid resistance of pathogens against these antibiotics, regulatory hurdles and because of economic reasons (Sun *et al*, 2008; and Sum and Petersen, 1999). This necessitates an urgent need for new classes of antibacterial agents with new modes of action to overcome the virulence of multidrug-resistant pathogens. A possible approach to achieve this is metal complexation of existing drugs (Heasley, 2011). In view of the aforementioned bacterial resistance, the association of activity and toxicity of tetracyclines to metal coordination, the wide application of metal complexes in biology and the use of metal based compounds as

chemotherapeutics (Machado *et al*, 1995; Haas and Franz, 2009; Goodwin *et al*, 2008 and Shingnapurkar *et al*, 2007).

$[CoDox_2(H_2O)_2]CO_3.5H_2O$ (1) To 1.0265 g (2 mM) of doxycycline hyclate in 100 ml of distilled water was added 0.1205 g (1 mM) of CoCO*3* and the solution was stirred at 80 ºC until effervescence stopped and the solution was filtered hot. The orange filterate was kept in freezer for 48 hours and the precipitated orange powder was filtered and dried in vacuum dessicator. Yield: 400 mg (35%). M.p. 107 oC. UV-Vis (H2O): 274, 349; UV-Vis (MeOH): 547,765. Calculated: C, 47.66; H, 5.51; N, 4.94. Found: C, 47.97; H, 5.15; N, 5.24

$[CoDox_2(H_2O)_2](ClO_4)_3.6H_2O$ (2) 0.5130 g (1mM) of doxycycline hyclate was dissolved in 10 ml of distilled water. The solution was heated to 80 ºC and 0.0600 g (0.5 mM) of CoCO3 was added. Heating was continued until effervescence stopped and the solution was filtered hot. To the orange filterate was added aqueous sodium perchlorate. The precipiated powder was filtered and dried in vacuum dessicator. Yield: 314.2 mg (45%). M.p. 168-171. UV-Vis (CH3CN, nm): 268, 365, 540 sh. UV-Vis (MeOH): 460. Calculated: C, 38.07; H, 4.50; N, 4.04. Found: C, 37.68; H, 3.93; N, 3.71. ESI-MS: $(CoDox_2(H_2O)^{2+}Dox)$=1429.1; $(Co^{+}Dox)$= 502.6; $(Co^{+2}Dox)$= 947.5

$[Cophen_2Dox](ClO_4)_3.2H_2O$ (3) 0.2567 g (0.5 mM) of doxycycline and 0.2626 g (0.5 mM) of [Cophen2Cl2]Cl were refluxed in 20 ml of methanol for 1 hour and the resulting solution was filtered. Saturated aqueous $NaClO_4$ was added to the filterate and the precipitated pink product was filtered and dried in vacuum dessicator. Yield: 330 mg (55%). UV-Vis (CH3CN, nm): 206, 207, 210, 271, 363, 543 sh. Calculated: C, 46.11; H, 3.70; N, 7.01. Found: C, 46.29; H, 3.93; N, 6.77

$[CubpgDox(H_2O)_2](NO_3)_2.3H_2O$ (4) 0.2420 g (1 mM) of $CuNO_3.3H_2O$ and 0.5130 g (1mM) of doxycycline hyclate were stirred at room temperature in 10 ml methanol for 50 minutes after which 0.2940g (1mM) of bipyridine glycouril was added. 10 ml of methanol and 5 ml of water were added and the solution further stirred for 5 hours. The solution was covered with perforated aluminum foil and was allowed to evaporate slowly at ambient conditions. 516.4 mg of green powder was obtained after slow evaporation of the solvent. Yield: 516.4 mg (51%). UV-Vis (H2O, nm): 273, 316, 327, 356, 625. Calculated: C, 42.38; H, 4.74; N, 13.73. Found: C, 42.53; H, 4.24; N, 11.85. ESI-MS: $[Cu^{+}bpg^{+}Dox^{+}H]^{+}$= 801.546 (ESI-MS: 800.8); $[CubpgDox]^{2+}$ = 400.773 (ESI-MS: 401.6).

CHAPTER THREE

MATERIALS AND METHODS

3.1 MATERIALS AND MEASUREMENTS

All chemicals (methanol, ethanol, acetone, acetonitril, dimethylflouride and dimethylsulphide) used in this research were of analytical reagents grade, procured from VWR International Ltd and they were used without further purifications. Tetracycline, Theophylline and Cimetidine where obtained from Pharmaceutical companies in Nigeria. Metal salts ($VOSO_4$, Cu(I)Br, and $CoCO_3$), 1,10-phenanthroline, bipyridine and imidazole were purchased from commercial source in Nigeria.

UV-Vis spectra were recorded on a JascoV-730 Uv-Visible spectrophotometer and Infrared spectra were recorded in a range 4,000–400 cm^{-1} on Shimadzu FT-IR-8400 on samples pressed in KBr pellets at Redeemer University of Nigeria.

Magnetic stirring was carried out using the Tecno-Vetro 20052 Monza magnetic stirrer.

3.2 SYNTHESIS OF COMPLEXES

$[CoTet(H_2O)_4]CO_3$ (1): To 0.444 g (1 mM) of tetracycline in 20 ml of distilled water was added 0.118 g (1 mM) of CoCO3 and the solution was stirred at 60 ^oC until effervescence stopped and the solution was filtered hot. The orange filtrate was kept in a cupboard for 96 hours and the precipitated orange crystals were filtered. The orange powder residue was also dried at ambient temperature. Yield (residue): (0.184 g, 32%). UV-Vis water (H_2O): 269 nm; Uv-Vis dimethylformamide (DMF): 269 nm, 384 nm, 453.9 nm.

$[CoTet(H_2O)_3Im]CO_3$ (2): Im= imidazole To 0.444 g (1 mM) of tetracycline in 20 ml of distilled water was added 0.118 g (1 mM) of CoCO3 and the solution was stirred at 60 ^oC until effervescence stopped, 0.068 g (1 mM) imidazole was added and stirred for 2 hours. The solution was filtered. The yellowish brown filtrate was kept in a cupboard for days and the precipitated brown powder was filtered. Yield: (0.460 g, 68%). UV-Vis ethanol (EtOH): 245 nm, 296 nm, 410 nm; UV-Vis dimethylformamide (DMF): 257 nm, 371 nm, 446 nm.

$[CuTheo_2]Br$ (3): To 0.360 g (2 mM) of Theophylline in 20 ml of ethanol and stirred in a round bottom flask, a colour solution was obtained. 0.143 g (1 mM) of Cu(I)Br was added to the solution and stirred for 2 hours and a greenish yellow solution was obtained. The solution was filtered. And a green colour residue was obtained. Yield: (0.210 g, 49.64%). UV-Vis ethanol (EtOH): 245 nm, 296 nm, UV-Vis dimethylformamide (DMF): 257 nm, 371 nm, 446 nm.

[CuTet]Br (4): To 0.444 g (1 mM) of tetracycline in 20 ml of ethanol (EtOH) was added 0.143 g (1 mM) of Cu(I)Br and the solution was stirred for six hours and a dark brown solution was obtain. The solution was filtered and the filtrate was kept in a cupboard for days and the precipitated dark powder was filtered. Yield: (0.248, 46.94%). UV-Vis ethanol (EtOH): 245 nm, 289 nm; UV-Vis dimethylformamide (DMF): 275 nm 371 nm, 702 nm.

[CuTet(bpy)]Br: (5) where bpy = bipyridine To 0.444 g (1 mM) of tetracycline in 20 ml of ethanol (EtOH) was added 0.143 g (1 mM) of Cu(I)Br and the solution was stirred six hours and a dark brown solution was obtain. 0.156 g (1mM) of bpy was dissolved in 4ml ethanol and added as solution. Stirring continue for four hours, thirty minutes and a brownish solution was form. The solution was filtered and the filtrate was kept and the precipitated brown powder was filtered. Yield: (0.350 g, 52.71%). UV-Vis dimethylformamide (DMF): 242 nm, 296 nm, 391.4 nm, 544.4 nm, 599 nm.

[VoTet]SO_4 (6); To 0.444 g (1 mM) of tetracycline in 20 ml of ethanol (EtOH) was added 0.163g (1 mM) of $VOSO_4$ and the solution was stirred 6 hours, a deep brown solution was obtained. The brown filtrate was kept in a cupboard for 96 hours and the precipitated deep brown powder was filtered. Yield: (0.395 g, 77%) UV-Vis (H_2O): 270 nm; UV-Vis dimethylformamide (DMF): 275 nm, 471 nm.

[VoCim$_2$]SO_4 (7); 0.504 g (2 mM) Cimetidine was added into 15ml solution of sodium hydroxide (NaOH) (0.2 M) in a round bottom and stirred for 5mins. 0.163 g (1mM) $VoSO_4$ was added as solid to the solution and stirred for 1 hour and a brown colour solution was obtained. The solution was filtered and the filtrate was kept in a cupboard for crystallization. Yield (0.072 g, 12.63%). UV-Vis dimethylformamide (DMF) 258 nm, 315 nm, 410 nm.

[VoCim$_2$phen]SO_4 (8); 0.504 g (2 mM) Cimetidine was added into 15ml solution of sodium hydroxide (NaOH) (0.2M) in a round bottom and stirred for 5mins. 0.163 g (1mM) $VoSO_4$ was added as solid to the solution and stirred for 1 hour and a brown colour solution was obtained. 0.180 g (1 mM) phenathrolin was dissolve in 4 ml EtOH and added as a solution and stirred for 2 hours 30 mins, a deep brown solution was formed. The solution was filtered and the filtrate was kept in a cupboard for crystallization. Yield (0.032 g, 4.2 %). UV-Vis (DMF) 258 nm, 315 nm, 541 nm.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 PHYSICO-CHEMICAL CHARACTERIZATION

The newly synthesized complexes **1-8** are colored, stable at room temperature except complex **1** that decompose and is partially soluble in common organic solvents such as ethanol (EtOH) and appreciably soluble in dimethylformamide (DMF) and dimethylsulphide (DMSO).

Table 4.1 Solubility of the ligands and metal complexes in different solvents

Compounds	**Water**	**Ethanol**	**Acetone**	**Acetonitrile**	**DMF**
Tetracycline	S	S/S	S/S	S/S	S
Theophylline	S	S	S	S	S
Cimetidine	S/S	S	-	-	S
Phenanthrolin	S/S	S	S	S	I
Bipyridine	S/S	S	S	S	S
Imidazole	S	S	S	S	I
$[CoTet(H_2O)_4]CO_3.5H_2O$ Complexe 1	S/S	I	I	I	S
$[CoTet(H_2O)_3Im]CO_3.5H_2O$ Complexe 2	S/S	S/S	I	I	S
$[CuTheo_2]Br$ Complexe 3	I	S/S	I	I	S
[CuTet]Br Complexe 4	I	S/S	I	I	S
[CuTet(bpy)]Br Complexe 5	I	S/S	I	I	S
$[VoTet]SO_4$ Complexe 6	S/S	I	I	I	S
$[VoCim_2]SO_4$ Complexe 7	I	I	I	I	S
$[VoCim_2phen]SO_4$ Complexe 8	I	I	I	I	S

S/S represents slightly soluble, S represents soluble and I represent insoluble

The solubility results show that tetracycline, theophylline and imidazole are soluble in water; their metal complexes are slightly soluble in water, soluble in dimethylformamide and insoluble in ethanol. Also cimetidine, bipyridine and phenanthroline are soluble in ethanol, acetone and their metal complexes are slightly soluble in ethanol but soluble in dimethylflormamide. The solubility of the metal complexes showed a different pattern whereby their solubility varied from slightly soluble to being soluble.

4.2 SPECTRAL CHARACTERIZATION

The complexes were characterized using Uv-Vis spectroscopy

4.2.1 Electronic Spectra

The electronic absorption spectral data of their metal complexes in dimethylformamide are listed in Table 4.2.

Table 4.2 Spectroscopic data of complex 1-8

Complex	Product yield (%)	Colour	Appearance	Ligands Transitions (nm)	Charge Transfer (nm)	Metal-Lgand charge transfer (nm)
1	32	Orange decompose to brown	Crystalline	269	384	453.9
2	68	Brown	Powdery	275	371	446
3	49.64	Green	Crystalline/powdery	257	371	446
4	46.94	Dark brown	Powdery	275	371	702
5	52.71	Brown	Powdery	242, 296	391.4	544.4, 599
6	77	Reddish brown	Powdery	275	-	471
7	12.63	Lemon green	Powdery	258	315	410

8	4.2	Brown	Powdery	258	-	540

UV-Visible spectra of complex 1-8

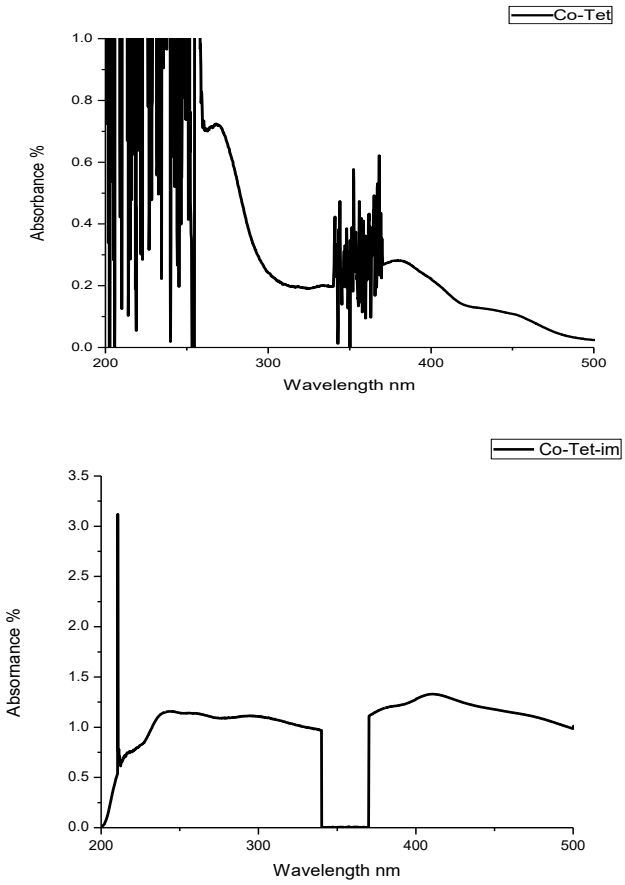


Fig 4.1: Electronic absorption spectra of ligand (Tetracycline) and Cobalt complexes (1 &2)

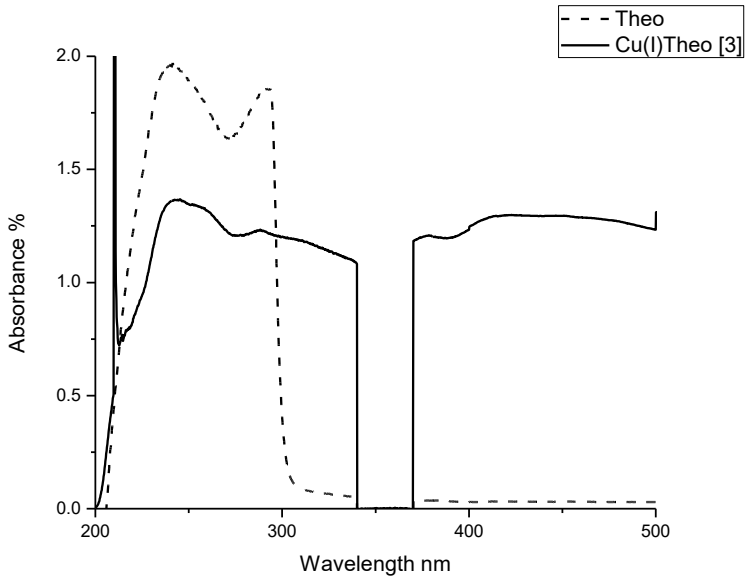


Fig 4.2: Electronic absorption spectra of Theophylline and Copper complex (3)

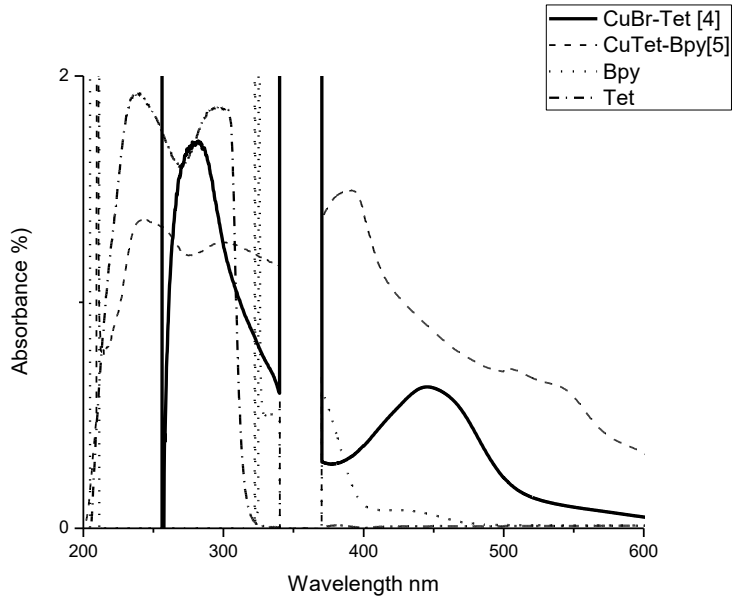
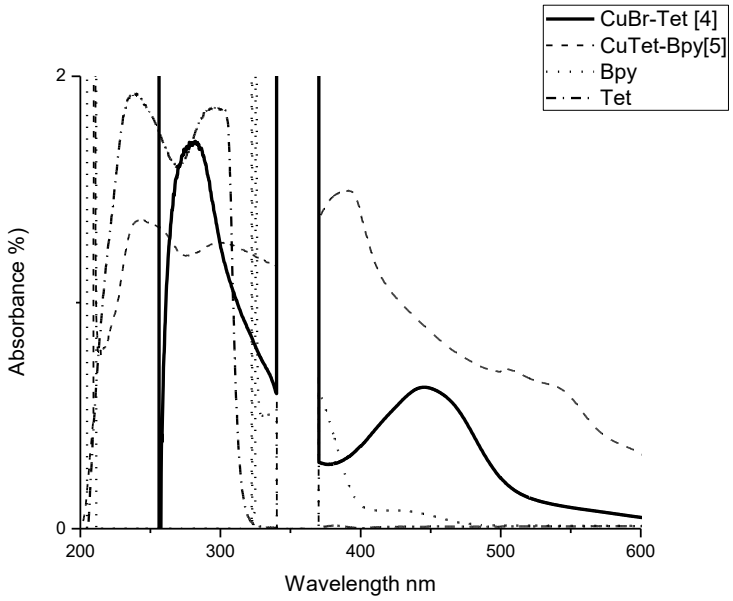


Fig 4.3: Electronic absorption spectra of Tetracycline and Copper complexes (4&5)


CuBr-Tet [4]
CuTet-Bpy[5]
Bpy
Tet
Absorbance %)
2
0
200
300
400
500
600
Wavelength nm

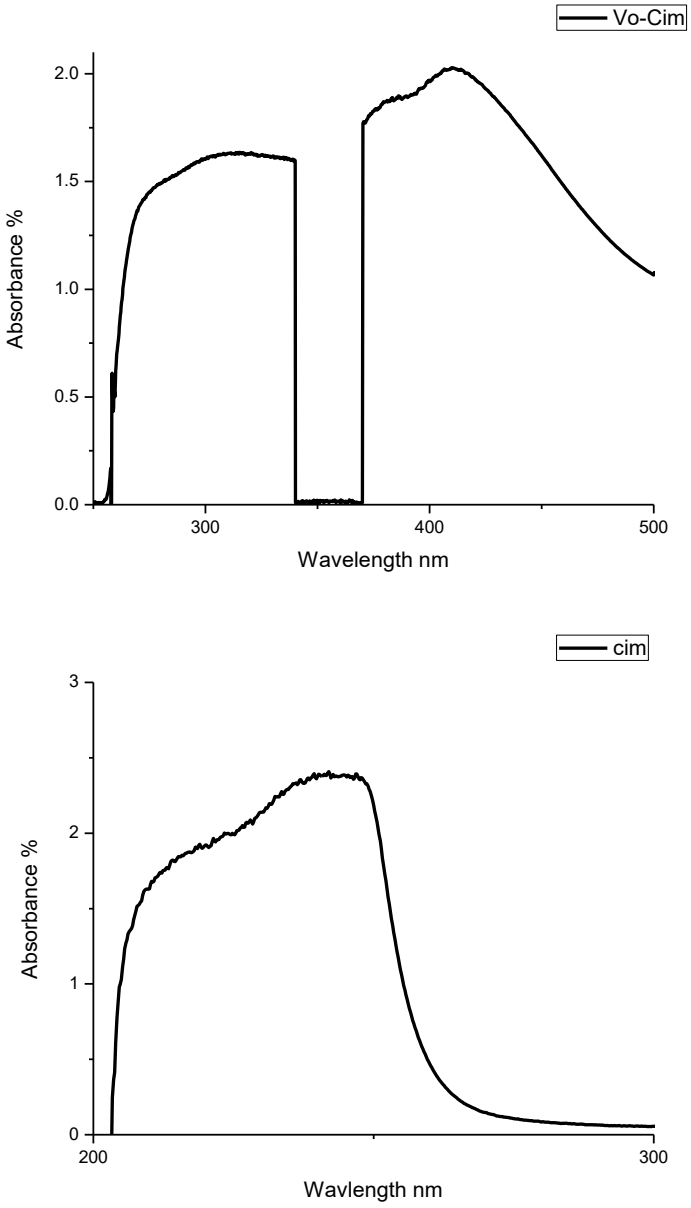


Fig 4.4: Electronic absorption spectra of Cimetidine and Vanadium complexes (7)

The absorption spectra of the complexes and respective ligands were recorded in the range of 200-800nm. The absorption spectra have been recorded in DMF. The electronic spectra of these ligands and their complexes were illustrated in Table 4.2. In the ultraviolet region (200-400nm), peaks ranging from 200-300nm indicates intra-ligands transition (π-π*), peaks at 301-399nm indicates charge transfer of ligands.

While peaks at 400-800nm (Visible region) indicates metal-ligand charge transfer which involve d-d transitions (as a result of electron transition in the d-metal ion). The changes in the absorption spectra confirm that new complexes have been formed.

In complexes **1** & **2,** there are ligand transitions (π-π*) at 269 and 275 nm and charge transfer at 371 and 384 nm in the UV region. At 453.9 and 446 nm for **1** and **2** respectively, there was metal-ligand charge transfer which indicates a d-d transition (due to Co^{3+} which is d^6). These changes indicate formation of new products and that metal-ligand bonds were formed in both **1** and **2.**

In complex **3**, there is a ligand transition (π-π*) at 257 nm while a charge transfer appears at 371 nm. At 446 nm there was metal-ligand charge transfer who corresponds to d-d transition (due to Cu^{+} which is d^{10}), This change indicates a new product has been formed.

In complexes **4** & **5**, ligand transition bands are at (π-π*) at 275 nm and 242 & 296 nm, while a charge transfer at 371 nm for complex **4** and 391.4nm for complex **5**. d-d transition band appear at 702 nm for complex **4**, 544.4 and 599 nm for complex **5** which indicate formation of complexes **4** and **5.**

In complex **6**, there is a ligand transition (π-π*) at 275 nm and another band at 471 nm (due to vanadium). These indicate a new product has been formed.

In complexes **7** & **8**, there is ligand transition (π-π*) at 258 nm, while a charge transfer at 315nm for complex **7**. In complex **7** there is a metal-ligand charge transfer at 410 nm and for complex 8 there is a metal-ligand charge transfer at 540 nm.

4.2.2 FTIR Spectra

The FTIR spectrum of the newly synthesized metal complexes was taken on Shimadzu-8400 FTIR spectrometer in the region 400-4000 cm^{-1}. The comparison of FTIR spectrum of each of the ligands with that of its respective metal complexes revealed certain characteristics differences. One of the significant differences to be expected between the IR spectrum of the parent ligands and its metal complexes is the presence of bands due to heteroatoms (oxygen and nitrogen) of both the O-H and N-H of the ligands which are involved in coordination bond with the transition metal ion. The FTIR spectra of the free ligands (tetracycline, theophylline and cimetidine) and its complexes are presented in the appendix and summarized in tables 4.3-4.5.

Table 4.3: FTIR spectra of tetracycline and its complexes

Tetracycline (cm^{-1})	**Co-Tet (cm^{-1}) 1**	**Co-Tet-Im (cm^{-1}) 2**	**Cu-Tet (cm^{-1}) 4**	**Cu-Tet-Bpy (cm^{-1}) 5**	**Vo-Tet (cm^{-1}) 6**	**Assignment**
3342	3356.25	3396.24			3398.69	O-H stretching
3064	3043.77		3099.71	3072.71	3088.14	C-H stretching of

						aromatic ring
2740	2713.93	2723.56	2775.66	2779.52		C-H stretching
1612	1604.83	1597.11	1614.47	1600	1624.12	C=O stretching of an amide
1176	1186.26	1176.62	1170.83	1172.76	1130.32	C-N stretching
				769.62		Cu—N stretching of bipydrine
		746.48				Co—N stretching of imidazole
					974.08	V=O stretching
	486.08	495.72	451.36	418.57	503.44	M—L bond formation. (M=metal ions and L= ligand)

Table 4.4: FTIR spectra of cimetidine and its complexes

Cimetidine (cm^{-1})	**Vo-Cim (cm^{-1}) (7)**	**Vo-Cim-phen (cm^{-1}) (8)**	**Assignment**
3144.37	3157.56	3151.79	N-H stretching of amines
2177.24	2166.06	2168.06	N-C≡N stretching of isothiocyanates
1590.99	1597.11	1604.83	N-H stretching of primary amine

	977.94	970.29	V=O stretch
		767.69	VO—N stretching of phenanthrolin
	598.88	434.00	VO—N stretching

Table 4.5: FTIR spectra of theophylline and its complexes

Theophylline (cm^{-1})	**Cu-Theo (cm^{-1}) 3**	**Assignment**
3315.04	3348.54	N-H stretching of amine
3107.41	3115.14	N-H stretching of either primary or secondary amine
2000.93	2000.25	C=C stretch
1417.00	1427.37	$-CH_3$ bending
	515.25	Cu-N stretching

From table **4.3**, The FTIR spectrum of free tetracycline is compared with the spectra of its complexes (**1, 2, 4, 5, & 6**), the absorption band at 3342 cm^{-1} in the spectrum of tetracycline has been attributed to O-H. This band have shifted to 3356.25 cm^{-1}, 3396.24 cm^{-1}, 3398.69 cm^{-1} in complex **1, 2** and **6** respectively, and the shifting of this vibrational band have provided evidence that this group is one of the coordination sites of tetracycline. Also the spectrum of tetracycline shows a strong absorption at 1176 cm^{-1} which is attributed to C-N which is another bonding site for tetracycline for coordination. This band has shifted to 1186.26 cm^{-1}, 1176.62cm^{-1}, 1170.83 cm^{-1}, 1172.76 cm^{-1}, 1130.32 cm^{-1} in the complexes (**1, 2, 4, 5, & 6**). And also at 1612cm^{-1} which is attributed to C=O is another coordination site for tetracycline. At 486.08 cm^{-1} and 495.72 cm^{-1} for complexes **1** & **2** respectively, these bands is as a result of metal to ligand bond formation (Co—O stretching), while at 451.36 cm^{-1} and 418.57 cm^{-1} there a Cu—O bond formation for complexes **4** & **5** respectively and at 503.01 cm^{-1} their VO—O bond formation for complex **6.**

At 746.82cm^{-1}, this band is as a result of Co—N stretch of imidazole in complex **2**. And at 769cm^{-1}, this band is as a result of Cu—N stretch of bipyridine in complex **5.**

From table **4.4**, The FTIR spectrum of free cimetidine is compared to the spectra of its complexes (**7,** & **8**), the absorption band at 3144.37 cm^{-1} in the spectrum of cimetidine has been attributed to N-H stretching. This band shifted to 3157.56 cm^{-1} and 3151.79cm^{-1} for both complex **7** and complex **8** respectively and the shifting of this vibrational band have provided evidence that this

group is one of the coordination sites of cimetidine. At 970 cm^{-1} and 977cm^{-1} there is V=O stretching for complex **7** and complex **8** respectively, while at 598 cm^{-1} and 434.00 cm^{-1} for complexes **7** & **8**. These there is metal to ligand bond formation (VO—N stretching) for complex **6.** At 767.69cm^{-1}, this band is as a result of VO—N of phenanthrolin in complex **8.**

From table **4.5**, The FTIR spectrum of free theophylline is compared to the spectrum of its complex (**3**), the absorption band at 3315.04 cm^{-1} in the spectrum of theophylline has been attributed to N-H stretching. This band has shifted to 3348.54 cm^{-1} for complex **3** and the shifting of this vibrational band have provided evidence that this group is the coordination site of theophylline. While the band at 515.01 cm^{-1} shows there is a metal to ligand bond formation (Cu—N stretching).

CHAPTER FIVE

CONCLUSION AND RECOMMENDATION

5.1 CONCLUSION

This project has been able to achieve a synthetic method that is of low cost and saves time and environmentally friendly for the synthesis of new metal complexes. It is an environmentally friendly synthesis because of the use of non-toxic solvent, water. In this research, eight new metal complexes were synthesized. The first synthesized compounds was cobalt complex of tetracycline and also copper (I) complex with tetracycline. The ligands and its metal complexes which are newly prepared were characterized using UV-Visible spectrophotometer and FTIR spectrometer, the electronic data of the ligands were compared to that of the newly synthesizes metal complexes. The other synthesis was centered on using copper (I) bromide, vanadyl sulfate with theophylline, and cimetidine. The ligands and metal complexes were characterized by similar procedure above. The solubility test of the complexes and their ligands were tested in different solvents and they were soluble in dimethylflomamide.

5.2 RECOMMENDATIONS

Since the kind of work done in this project involves inorganic and biological sciences expertise, a good collaboration between these two fields will be helpful for a thorough investigation starting from preparation, characterization and biological analysis of the compounds. The spectra characterization of the ligands and the complexes formed has proved that new products were formed with good stability, comparing these results reveal the need to evaluate the activities of the metal complexes and see how active they are toward biological organism.

Further analyses of these complexes using more sophisticated techniques such as mass spectroscopy (ESI-MS), electron paramagnetic resonance (EPR), powdered X-ray diffraction methods, biological and catalytic studies are recommended as this will give more insight into the structure and phase purity of the new complexes.

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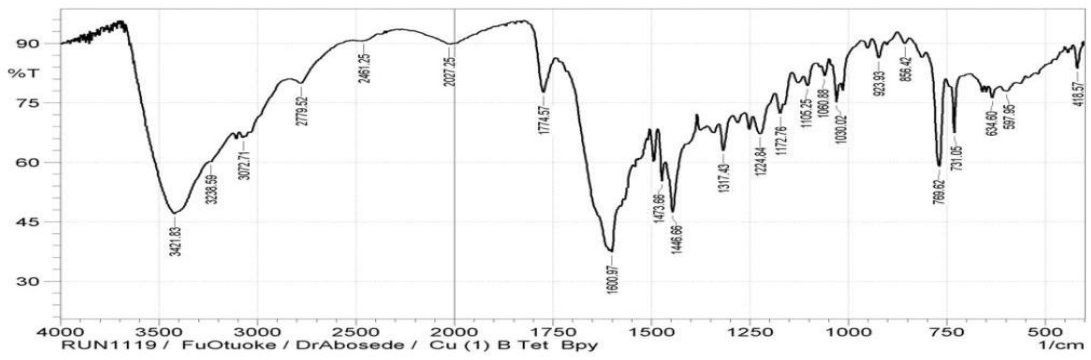
APPENDIX



	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	418.57	83.69	6.32	430.14	403.14	1.56	0.33
2	597.95	77.94	0.45	601.81	576.74	2.58	0.03
3	634.6	76.3	2.88	644.25	615.31	3.09	0.16
4	731.05	67.46	12.54	740.69	711.76	3.21	0.48
5	769.62	58.97	24.23	802.41	754.19	6.27	2.67
6	856.42	89.99	1.99	875.71	844.85	1.24	0.15
7	923.93	86.32	4.47	941.29	908.5	1.67	0.29
8	1030.02	75.21	6.89	1041.6	1020.38	2.08	0.28
9	1060.88	81.87	3.23	1068.6	1049.31	1.51	0.17
10	1105.25	79.31	3.41	1114.89	1084.03	2.64	0.19
11	1172.76	72.39	3.34	1186.26	1165.04	2.73	0.21
12	1224.84	67.16	6.32	1242.2	1188.19	7.87	0.98
13	1317.43	62.94	7.46	1329	1294.28	5.83	0.61
14	1446.66	47.43	14.26	1464.02	1415.8	11.95	2.06
15	1473.66	55.31	8.58	1485.24	1464.02	4.52	0.43
16	1600.97	37.38	1.62	1602.9	1581.68	7.48	0.1
17	1774.57	77.64	12.89	1809.29	1741.78	4.7	1.79
18	2027.25	89.86	0.05	2060.04	2025.32	1.56	0.01
19	2461.25	90.73	0.01	2463.18	2459.32	0.16	0
20	2779.52	79.95	2.1	2808.45	2685	10.29	0.61
21	3072.71	66.24	0.77	3093.92	3063.06	5.41	0.07
22	3238.59	60.15	0.3	3242.45	3124.79	23.01	0.11
23	3421.83	47.02	1.2	3564.57	3416.05	38.44	2.44

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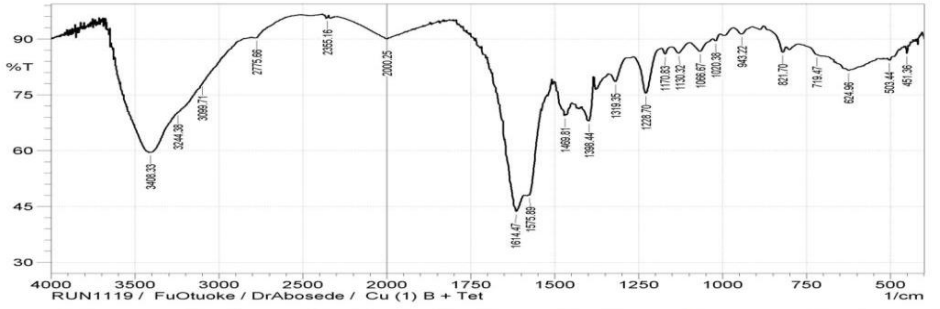

	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	451.36	86.15	2.03	455.22	447.5	0.46	0.04
2	503.44	84.31	0.68	509.22	493.79	1.11	0.03
3	624.96	81.56	0.44	634.6	613.38	1.85	0.02
4	719.47	85.8	0.15	746.48	717.54	1.76	-0.01
5	821.7	86.41	2.49	864.14	810.13	2.53	0.1
6	943.22	91.32	1.81	966.37	910.43	1.93	0.2
7	1020.38	89.45	1.13	1030.02	1006.88	1.03	0.05
8	1066.67	86.68	2.8	1097.53	1030.02	3.66	0.41
9	1130.32	86.19	2.13	1151.54	1097.53	3.12	0.24
10	1170.83	85.94	1.73	1182.4	1151.54	1.85	0.09
11	1228.7	75.4	10.86	1265.35	1182.4	7.05	1.79
12	1319.35	78.57	3.7	1340.57	1282.71	5.13	0.39
13	1398.44	67.96	8.79	1419.66	1384.94	5.25	1.06
14	1469.81	69.42	1.36	1500.67	1465.95	4.78	0.25
15	1575.89	48.07	1.07	1577.82	1523.82	10.89	0.11
16	1614.47	43.68	12.42	1685.84	1591.33	23.25	3.66
17	2000.25	90	0.41	2019.54	1992.53	1.21	0.03
18	2355.16	95.66	0.4	2360.95	2347.45	0.25	0.02
19	2775.66	90.33	0.09	2777.59	2729.37	1.87	0
20	3099.71	77.97	0.11	3101.64	2983.98	10.47	0.02
21	3244.38	70.23	0.18	3246.31	3103.57	18.95	0.34
22	3408.33	59.51	0.09	3412.19	3404.47	1.74	0

Comment;
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No. of Scans;
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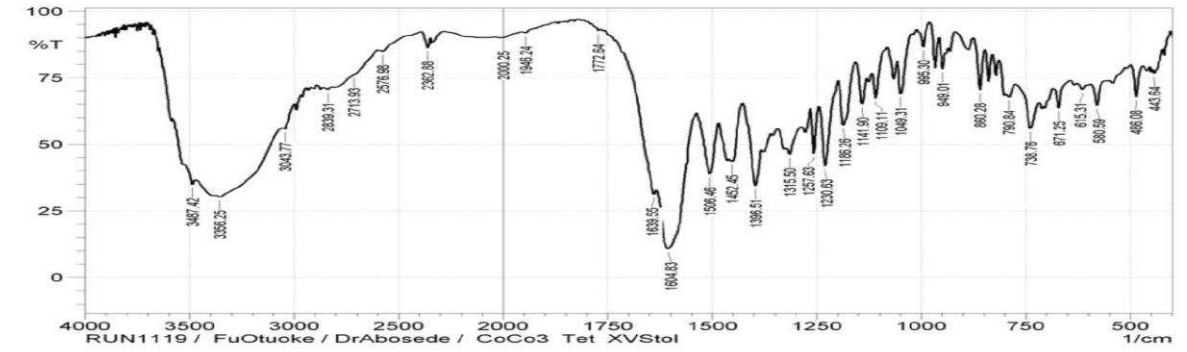
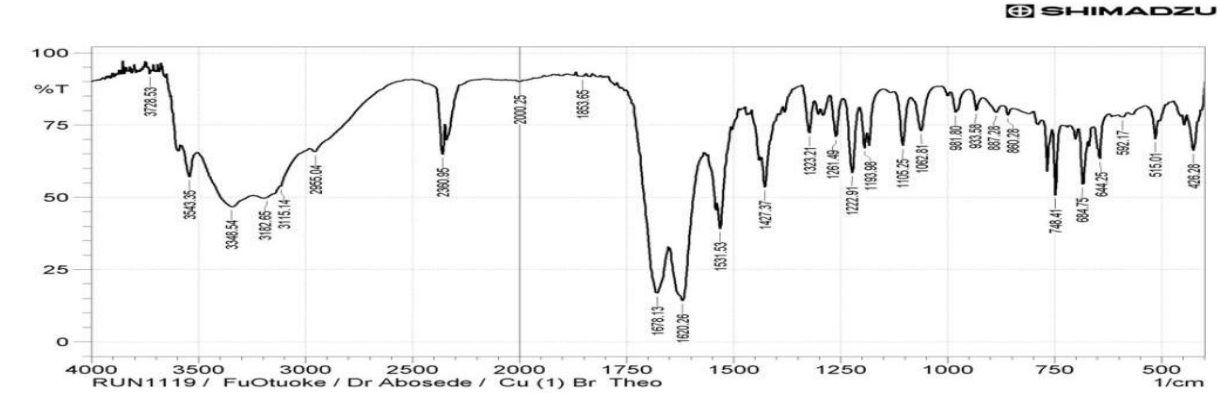


	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	443.64	76.63	2.74	447.5	422.42	2.43	0.26
2	486.08	67.79	11.91	499.58	470.65	3.52	0.67
3	580.59	64.48	8.64	594.1	559.38	5.29	0.6
4	615.31	70.54	2.05	628.81	605.67	3.34	0.13
5	671.25	63.63	8.31	684.75	644.25	6.21	0.55
6	738.76	56.03	12.03	773.48	719.47	10.31	1.55
7	790.84	67.73	2.47	798.56	775.41	3.64	0.16
8	860.28	70.42	17.08	875.71	848.71	2.5	0.97
9	949.01	78.32	8.46	956.72	943.22	1.11	0.3
10	995.3	86.61	7.9	1010.73	979.87	1.17	0.41
11	1049.31	69.01	14.7	1057.03	1024.24	3.33	1.22
12	1109.11	67.32	11.46	1116.82	1082.1	3.67	0.57
13	1141.9	65.06	12.39	1157.33	1130.32	3.8	0.86
14	1186.26	57.11	18.79	1197.83	1159.26	6.65	2.36
15	1230.63	41.88	25.07	1244.13	1199.76	10.77	3.6
16	1257.63	46.52	17.21	1265.35	1246.06	4.85	1.08
17	1315.5	46.1	3.64	1321.28	1286.56	9.89	0.26
18	1396.51	34.41	18.91	1427.37	1383.01	14.53	3.38
19	1452.45	43.5	5.93	1460.16	1427.37	9.34	0.56
20	1506.46	38.86	20.38	1537.32	1487.17	15.56	4.29
21	1604.83	10.74	30.86	1633.76	1539.25	57.53	24.99
22	1639.55	31.21	3.88	1712.85	1635.69	19.52	0.37
23	1772.64	92.63	0.68	1778.43	1770.71	0.23	0.01
24	1946.24	91.84	0.77	1955.88	1926.95	0.97	0.04
25	2000.25	90	0.2	2006.04	1996.39	0.44	0
26	2362.88	86.22	4.54	2387.95	2349.38	1.97	0.4
27	2576.98	84.89	0.99	2590.49	2468.97	6.889	0.08
28	2713.93	76.04	0.16	2715.86	2602.06	10.73	0.13
29	2839.31	70.49	0.89	2856.67	2818.09	5.74	0.09
30	3043.77	55.69	1.13	3047.63	2999.41	10.49	0.12
31	3356.25	30.2	1.63	3369.75	3063.06	125.83	9.02
32	3487.42	34.91	3.21	3525.99	3473.91	21.61	0.55



	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	426.28	66.21	13.09	441.71	408.92	4.45	1.16
2	515.01	70.17	7.77	536.23	507.3	3.25	0.3
3	592.17	77.75	1.07	601.81	580.59	2.26	0.07
4	644.25	63.43	12.73	659.68	621.1	5.25	0.78
5	684.75	54.49	17.44	694.4	671.25	4.55	1.19
6	748.41	50.76	23.15	756.12	737.97	4.13	1.13
7	860.28	78.39	2.77	873.78	848.71	2.37	0.1
8	887.28	79.4	3.15	918.15	873.78	3.88	0.31
9	933.58	80.02	5.78	950.94	918.15	2.45	0.28
10	981.8	79.38	7.3	993.37	950.94	3.19	0.6
11	1062.81	72.97	12.97	1085.96	1022.31	5.31	1.28
12	1105.25	67.92	17.65	1124.54	1085.96	3.9	1.29
13	1193.98	66.99	8.19	1205.55	1188.19	2.34	0.32
14	1222.91	58.51	23.99	1244.13	1205.55	5.35	2.16
15	1261.49	70.98	13.89	1274.99	1244.13	3.14	0.93
16	1323.21	72.22	13.33	1340.57	1311.64	2.84	0.95
17	1427.37	53.5	13.31	1435.09	1396.51	6.63	1.01
18	1531.53	39.16	12.31	1537.32	1506.46	7.95	1.02
19	1620.26	14.29	30.69	1651.12	1570.11	40.99	14.2
20	1678.13	16.92	30.03	1749.49	1653.05	39.57	13.57
21	1853.65	91.83	0.45	1859.44	1844.01	0.55	0.02
22	2000.25	90	0.54	2017.61	1992.53	1.13	0.04
23	2360.95	64.85	12.47	2428.46	2349.38	7.22	0.41
24	2955.04	65.74	2.72	2982.05	2594.34	43.04	1.23
25	3115.14	53.79	0.49	3119	2982.05	28.21	0.02
26	3182.65	49.89	0.11	3184.58	3155.65	8.6	0.02
27	3348.54	46.76	0.24	3504.77	3346.61	41.7	1.12
28	3543.35	57.09	9.56	3578.07	3510.56	13.87	1.97
29	3728.53	92.75	1.77	3736.24	3722.74	0.38	0.05

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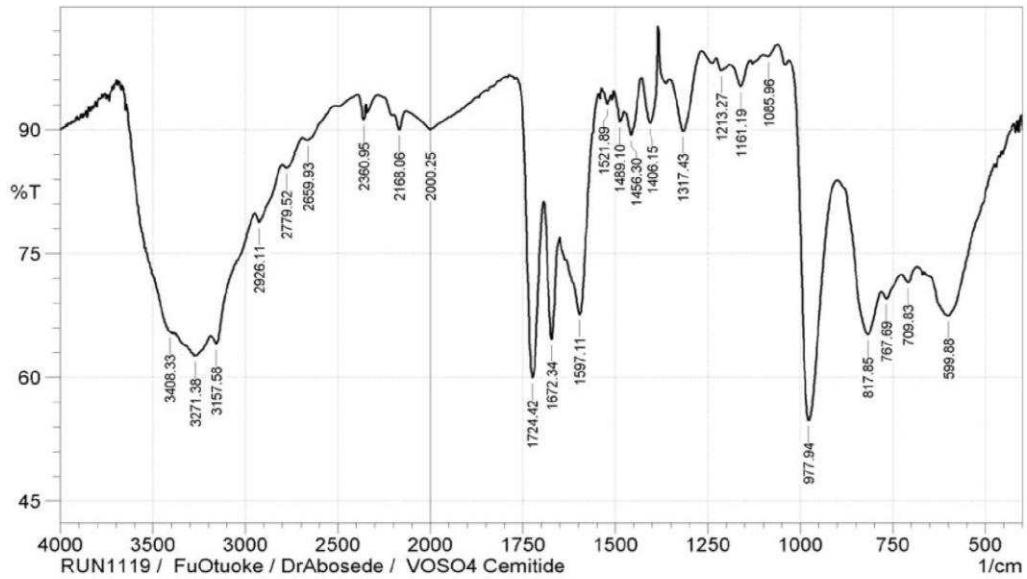

	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	599.88	67.46	1	605.67	476.43	15.58	0.48
2	709.83	71.52	1.31	725.26	684.75	5.7	0.15
3	767.69	69.51	1.31	779.27	725.26	8.05	0.17
4	817.85	65.18	9.41	898.86	781.2	16.38	2.97
5	977.94	54.77	37.8	1030.02	900.79	17.16	11.72
6	1085.96	98.85	0.65	1099.46	1060.88	0.1	0.04
7	1161.19	95.23	2.94	1190.12	1136.11	0.76	0.32
8	1213.27	97.15	1.24	1226.77	1190.12	0.38	0.1
9	1317.43	89.82	7.72	1352.14	1267.27	2.24	1.43
10	1406.15	90.77	8.75	1429.3	1384.94	1.32	1.19
11	1456.3	89.3	4.62	1475.59	1429.3	1.68	0.48
12	1489.1	90.92	2.55	1502.6	1475.59	0.94	0.14
13	1521.89	93.13	1.38	1537.32	1512.24	0.67	0.07
14	1597.11	67.62	14.81	1631.83	1546.96	9.49	3.03
15	1672.34	64.6	14.55	1693.56	1651.12	6.06	1.72
16	1724.42	59.99	27.34	1766.85	1695.49	8.5	4.67
17	2000.25	90	0.2	2013.75	1994.46	0.87	0.01
18	2168.06	89.98	2.04	2195.07	2139.13	2.28	0.26
19	2360.95	91.2	2.23	2387.95	2349.38	1.29	0.19
20	2659.93	88.74	0.07	2661.85	2532.62	5.5	0.04
21	2779.52	85.36	0.28	2798.8	2766.01	2.23	0.02
22	2926.11	78.76	1.98	2947.33	2798.8	13.02	0.87
23	3157.58	64.02	3.05	3190.37	2955.04	34.03	0.83
24	3271.38	62.62	0.34	3282.95	3242.45	8.18	0.06
25	3408.33	65.53	0.18	3520.21	3406.4	18.14	0.25

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No. of Scans;

Declarations

Ethical Approval

Ethical approval: not applicable.
This study did not involve human participants, animal subjects, or any procedures requiring institutional ethical clearance.

Consent to Participate

Consent to participate: not applicable.
No human participants were involved in this research.

Consent to Publish

Consent to publish: not applicable.
This manuscript does not contain any individual person's data, images, or identifiable information.

Data Availability

All data generated or analysed during this study are included in this published article and its supplementary information files.