Network for Research and Development in Africa
International Journal of Pure and Applied Science Research
ISSN: 2384-5918, Volume 11, Issue 13
PP 309-323 (December, 2024)
DOI: 45727711-11156
arcnjournals@gmail.com
https://arcnjournals.org

SYNTHESIS AND CHARACTERIZATION OF MIXED LIGAND COMPLEX OF CIMETIDINE AND ALLYLTHIOUREA WITH Cu (Ii) ION

Fatima Yadawu Usman[1]. Aisha Muhammad Ngubdo[2], Aisha Musa Bulama[3]. Mohammed Goni[4] and Suleiman Babayo Ali[5]

[1]Department of Science Laboratory Technology, Ramat Polytechnic, Maiduguri, Borno State, Nigeria
[2&3]Department of Remedial Science, Ramat Polytechnic, Maiduguri, Borno State, Nigeria
[4]Department of Remedial and General Studies, Mohammed Goni College of Legal and Islamic Studies, Maiduguri. Nigeria
[5]Department of Chemistr**y,** Nigeria Army University Biyu, Borno State

Abstract*: Mixed-ligand complexes of cimetidine (Cim) and a selected thiourea derivative (Allylthiourea) with Cu(II) hydrated salt were prepered. The complex was characterised using infrared, UV/Visible (electronic spectra), melting point, solubility and conductivity. The IR data showed that the compounds formed by the metal (II) ion (Cu) coordinated through ν(C=N) of imidazole, ν(C-N), ν(C=S), ν(M-N) and ν(M-S) stretching of the ligand. The complex decomposed at high temperatures. The complex was soluble in ethanol and DMSO. The anti-ulcer (anti- histamine) activity of cimetidine and its mixed ligand metal(II) complexes showed that complex of Cu(cim)(thio)Cl_2 have higher effect than that of cimetidine on the histamine induced contraction on the guinea pig ileum.*

Keywords*: Allylthioure; Cimetidine, Copper II, Ligand.*

INTRODUCTION

The field of knowledge concerned with the application of inorganic chemistry to therapy or diagnosis of disease is medicinal inorganic chemistry. The introduction of metal ions or metal ion binding components into a biological system for the treatment of diseases is bioinorganic chemistry (Saddam *et al.,* 2018). *In vitro* refers to biological studies that are carried out in test tube (i.e., in a glass vessel) rather than in a human or animal. *In vitro* studies allow scientists to isolate specific cells, bacteria and viruses and study them without the distractions of having to look at a whole organism. However, as compared to *in vivo* studies, *in vitro* studies are substantially faster, and can be done with fewer ethical and safety concerns (Sumia *et al*., 2018). In context to this, the present study is thus to perform the evaluation of in vitro antiulcer potency of the mixed-ligand complexes of Co(II), Ni(II) and Cu(II) ions with cimetidine and selected thiourea derivatives by assessing its H_2 receptor antagonist activity.

Mixed-ligand (or ternary) complexes are compounds made of a central metal ion and two or more different ligand molecules (Osunlaja, 2008). Cimetidine is a potent histamine receptor antagonist which inhibits excessive acid secretion caused by histamine, and is used for treatment of "peptic ulcer disease", they are also called H_2 blockers (Kanumfre *et al*., 2010).

Thiourea, is an organo-sulphur compound with the formula $SC(NH_2)_2$ (Alkan *et al*., 2011). Derivatives of thiourea are classified into categories on the basis of number of substituents attached to thiourea moiety. 1,3-diphenylthiourea or N,N-diphenylthiourea, is a 1, 3-disubstituted thiourea, which occurs if the hydrogen atom of NH_2 group is replaced by phenyl group and another hydrogen atom of the other NH_2 group is replaced by another phenyl group (Azeem *et al*., 2016). Methylthiourea or 1-methylthiourea is a mono substituted thiourea, which occurs if one hydrogen atom of NH_2 group is replaced by a methyl group. Allylthiourea is also a mono substituted thiourea derivative in which one hydrogen atom of the NH_2 group is replaced by $CH=CHCH_2$ group. Thiourea having a considerably wide range of applications, is a functional organic compound, it is a versatile reagent in inorganic synthesis. Complexes of thioureas are used as precursors and antibacterial agents (Azeem *et al*., 2016). It is also a very common industrial material used in dyes, photographic film, elastomers, plastics and textiles (Musa, 2000).

Peptic ulcer disease (PUD) are sores that develop in the lining of the stomach, lower oesophagus or small intestine. They are usually formed as a result of erosion of inner linning of stomach caused by acids or inflammation caused by bacteria (*Helicobacter-pylori*). PUDs are common health problems, and are of three types, which are; Peptic or stomach ulcer: ulcer that develop inside the stomach. Oesophageal ulcer; ulcer that develop inside the oesophagus. Duodenal ulcer; ulcer that develop in the upper section of small intestines called duodenum (Valencia, 2017). Most common symptoms of PUD is burning, abdominal pain that extends from the navel to the chest which can range from mild to severe. In some cases, the pain may wake a person up at night (Rao, 2014). Small ulcers may not produce any symptoms in the early phases. Other common signs of a PUD include change in appetite, nausea, bloody or dark stools, un-explained weight loss, indigestion, vomiting and chest pain (Najm, 2011).

The medication used to decrease acid is usually either a proton pump inhibitor (PPI) or a H_2 blocker with four weeks of treatment initially recommended (Najm, 2011).

The presence of more than one type of ligand in a complex increases chances of variation in properties expected for the complex. Synthesis and characterisation of mixed-ligand is gaining attention day-by-day. The increased interest in this research area has motivated many researchers to get involved in this field (Valencia, 2017). One of the main goals of the present day inorganic coordination chemists and pharmaceutical investigation is the discovery and development of better drugs to fight diseases and this has led to numerous studies on drug-metal complexes (Dnyaneshwar *et al*., 2014).
Mixed-ligand (or ternary) complexes are compounds made up of a central metal ion and two or more different ligands molecules, Such metal ions are essentially d-block transition metals, especially the first row elements, whose characteristic feature enables them to form complexes with a variety of neutral molecules; such as dienes, CO, H_2O, isocyanides, amines, substituted

phosphine, arsine, Schiff base etc. Atoms such as N, O and S which are of prime importance in biological systems, molecules which act as the ligand, possess lone pairs of electrons through which they covalently coordinate to the central metal ion/ions (Osunlaja, 2008).

Mixed-ligand complexes are characterized by their extreme stability. Mixed-ligand complexes formation are the most general and probable form of existence of elements in solution. Studies of mixed-ligand complex formation makes it possible to estimate the characteristics of the intermediate and final forms of the complexes, and therefore to comprehend the mechanism and kinetics of analytical reaction. Certain peculiarities of elements, which are most pronounced in mixed-ligand complexes, as well as the physical phenomena accompanying the process of mixed-ligand complex formation, open new prospects for the development of selective and sensitive method for the determination, separation and concentration of elements. They have been used to reveal wide range of biological activities, including anti-bacteria, anti-cancer, anti-fungal and anti-inflammatory, anti-viral, and antipyretic properties (Alimarin and Shlenskaya, 1969).

Mixed-ligand metal complexes were found to be particularly useful because of their potential to bind DNA via a multitude of intrinsic chemical, electro chemical and photochemical reactivities (Al-Obaidi, 2012). Mixed-ligand complexes are used as important intermediates in many reactions in analytical chemistry such as analytical methods based on complex formation-separations involving liquid-liquid extraction, titrimetric and gravimetric analysis (Rajkumar and Natarajan, 2016). Stabilities of mixed-ligand are of great importance in the biological systems as many metabolic and toxicological functions depends on this stability (Sunil *et al*., 2009).

Ulcer disease or peptic ulcer disease (PUD) is the disease that develops in the form of sores in the lining of the stomach, oesophagus or small intestine. The most common symptom of this disease is abdominal pain that occurs from stomach region to chest part. If the ulcer is left untreated then it may result in other adverse health conditions such as haemorrhage, perforation, or obstruction in 20-25% of patients. Among these complications, upper gastrointestinal (UGI) bleeding is the most frequently encountered, accounting for about 70% of cases (Huang and Lee, 2014). The peptic ulcer usually occurs as a result of imbalance of acid secretion and mucosal defences that resist the acid digestion, accounting to the developments in the medical treatment of (PUD), some times surgical intervention is confined to the treatment of the complicated disease (Joshita, 2016).

Generally, when the ulcerative condition is left untreated then it may result in further complications like, internal bleeding: Which can occur as slow blood that leads to anaemia or as severe blood loss that may require hospitalization or blood transfusion. Severe blood loss may cause black or bloody vomit or black or bloody stool. Infection: Peptic ulcer can form a hole through perforating the wall of the stomach or small intestine, causing serious infection of the abdominal cavity. Obstruction: Peptic ulcer can lead to swelling, inflammation or scarring that may block passage of food through the digestive tract. A blockage can/may cause vomitting and lose of weight (Valencia, 2017).

Materials and methods

All reagents used were of analytical grade (AR) and were purchased from Sigma-Aldrich, through Ibra Hadad limited, Lagos, Nigeria without further purification. The metal salt was used as chlorides ($CuCl_2.2H_2O$). Cimetidine (anti-ulcer drug) and Allylthiourea (Thio) were used as ligands. Solvents that were used during the synthesis and subsequent analysis are: ethanol, methanol, acetone, ethyl acetate, chloroform, hexane, benzene, DMSO, and distilled water, including other reagents such as glucose, $MgCl_2$, NaH_2PO_4, $NaHCO_3$, $CaCl_2$, KCl and NaCl.

Synthesis of the Complexes

The complex was prepared following a reported procedure (Adediji *et al*., 2009 and Waziri, 2014). The metal salt: $CuCl_2.2H_2O$ (0.008 mmol), was dissolved in 10 ml distilled water in a round bottom flask. Cimetidine (Cim) (0.008 mmol, 2.02g), was dissolved in 20ml of ethanol, thio (0.008 mmol. 1.83g) was also dissolved in 10ml of ethanol then they were mixed together. The solution of the metal salt was added to the dissolved ligands, in 1:1:1 mole ratio. Methanolic ammonia solution 10% was used to maintain the pH (two to three drops). The solution was refluxed for 3 hours at 35 ^oC. The resulting solution was kept for about one week. The precipitate formed was then filtered and washed with ethanol to remove unreacted ligand and metal salts (Adediji, *et al*., 2009; Ibrahim, 2014).

Melting Point Determination

Melting point of all the complexes and their ligands were determined using Gallenkamp melting point apparatus at the Research Laboratory in the Department of Pure and Applied Chemistry, University of Maiduguri, Borno state, Nigeria.

Solubility

The solubility of the complexes and their ligands were determined at room temperature in some polar and non-polar solvents.

Conductivity

Molar conductivity of the complexes and the ligands were measured using DDS-307 conductivity meter, at room temperature (10^{-3} Scm^2 mol^{-1}) at the Department of Pure and Applied Chemistry, University of Maiduguri, Borno state, Nigeria.

Infrared Spectra

The infrared (IR) spectra were recorded as KBr disc on SHIMADZU FTIR-8400S TRANSFORM INFRARED SPECTROPHOTOMETER at National Research Institute for Chemical Technology (NARICT) Zaria, Kaduna State, Nigeria.

Electronic spectra

Electronic spectra of all the ligands and their complexes were measured in ethanol at (10^{-3}M) concentration in the wavelength range of 200-700 nm at National Research Institute for chemical technology (NARICT) Zaria, Kaduna State, Nigeria.

***In vitro* Anti-ulcer (anti-Histamine) Investigation**

Animal and Drugs: A healthy guinea pig was obtained from animal house of Faculty of Pharmacy, University of Maiduguri. The Guinea pig was killed through humane killing at which the ileum was removed for experimental purpose. Promethazine were purchased at Zaima Pharmacy, Maiduguri, Borno State. The ileum was prepared and experiment were carried out following a reported procedure (Timothy *et al*., 2015; Jeannot *et al.,* 2016).

Guinea Pig Ileum: A piece of guinea pig ileum, 10-20cm long, about 15 cm proximal to the ileo-cecal junction, was removed from the abdominal chamber. The proximal ileum was washed and placed in tyrode solution and the mesenteric residuor 5 min after each administration of either the standard drug or test drugs. The isolated ileum was contracted with 0.1ml, 0.2ml, 0.4ml and 0.8ml (final concentration in the bath) of histamine (5µg/ml) for 2min for the viability test. The organ was rinsed three times and allowed to rest and return to its initial tension. After washing, the tissue was pretreated with 0.1ml cimetidine (10µg/ml) and 0.4ml histamine (5µg/ml), 0.1ml promethazine (10mg/ml) and 0.4ml histamine (5µg/ml) followed by 0.1ml test drug (each synthesized complex A-I) (10µg/ml) and 0.4ml histamine. The effects of the drugs were recorded on a kymograph by means of an isotonic frontal writing lever (Timothy *et al*., 2015; Jeannot *et al.,* 2016).

In case of competitive inhibition (the extract applied was epected to compete about the occupation of H_2 type histaminic receptors within the intestine smooth muscles of the guinea pig isolated ileum). In case of non-competitive inhibition, the extract EC_{50} value is the parameter to be evaluated (extract concentration which inhibits up to 50% of the maximum contraction induced by the histamine without complex) (Timothy *et al*., 2015).

Statistical Analysis

Data obtained for anti-ulcer study were expressed in mean ± SEM and subjected to inferential statistics (ANOVA followed by fisher) using SPSS version 20. P less than 0.05 was considererd significant.

RESULTS

4.1. Physical properties of the Ligands and their Metal(II) Complexes

The physical properties of ligand and its synthesised metal complexes are presented in Table 1.

4.2 Solubility of the Ligand and its Metal (II) complexes

The solubility tests carried out on the ligands and metal complexes at room temperature showed that they are soluble or slightly soluble in most of the organic solvents used but dissolved more readily in DMSO as shown in Table 2.

Infrared spectra

The relevant infrared spectra bands of the ligand and their metal(II) complex was obtained in the 400 – 4000 cm^{-1} range and the results are presented in Table 3.

Electronic spectra

The result for UV/Visible absorption spectra in wavelength (nm) together with band assignments are presented in Table 4.4.

Effect of Histamine on the Guinea Pig Ileum

The agonistic effect of histamine at the concentrations of 20, 40, 80 and 160 ng/ml produced dose dependent contraction of the guinea pig ileum for 10mm (37%), 12mm (44%), 20mm (74%) and 27mm (100%) respectively (Table 4.5; Appendix 1). The extrapolated EC_{50} was found to be 50.1 ng/ml (Figure 4.5).

Effect of Cimetidine and its Mixed Ligand Metal (II) Complexes on Histamine Induced Contraction

The antagonistic effect of cimetidine and its mixed ligand complex on the isolated tissue of guinea pig ileum is shown in Table 4.6 Cimetidine and promethazine were able to reduce contractions due to histamine by 60 and 25% respectively. However, when cimetidine and promethazine were

combined together, the effect of histamine was completely blocked. The complex of $Cu(cim)(thio)Cl_2$ reduced the contraction induced by histamine up by 75%.

Table 1 Physical Properties of the Ligands and their Metal(II) Complexes

Compound	Molar mass of Ligand & complex (g/mol)	Metal % found (cal)	Colour	M.P (°C)	Yield (%)	Conductivity ($Scm^2\ mol^{-1}$)
Cim	252.11		White	105	4	
Thio	116.19		White	72	4	
$Cu(cim)(Thio)Cl_2$	502.98	13.6(12.6)	Light green	110	70.0	10

Table 2 Solubility of the Ligands and their Metal (II) complexes

Compounds	Water		Methanol		Ethanol		Acetone		Ethyl-acetate		Chloroform		n- Haxane		Benzene		DMSO	
	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C
Cim	s	ss	s	ss	s	s	s	ss	is	is	is	is	s	ss	ss	ss	s	s
Thio	ss	s	s	s	s	s	s	s	s	s	s	s	s	s	s	ss	s	s
$Cu(cim)(Thio)Cl_2$	s	ss	ss	ss	s	ss	s	ss	ss	ss	is	is	ss	ss	s	ss	s	s

Cim
$Thio_1$

Key: C= cold, H= hot, IS= insoluble, SS=Slightly soluble, S=Soluble

Discussion

Table 4.1 shows some of the physical properties of the ligand and its metal (II) complex. The mixed-ligand complexes of cimetidine (cim) and a selected thiourea derivative (thio) was subsequently directly reacted with hydrated salt of Cu(II). The mixed ligand metal (II) complex decomposed at high temperatures, with a yield which ranges between 43.0 – 70.0 %.
The complex prepared is light green in colour. This indicates the typical properties of transition metal compounds. The molar conductance values measured in ethanol solution
(10^{-3}M) for the complexes were in the range "4-12" Scm^2mol^{-1}. This reveals that the complex was non-electrolytes (Osowole, 2008).

The relevant vibrational bands of the free ligands and the complexes were recorded in the region 400 – 4000 cm^{-1} (Raman *et al*., 2001). Comparative studies of IR spectra of each ligand and its metal (II) complexes indicate that several peaks found in the ligands are shifted, either to higher (blue shift) or lower (red shift) frequencies respectively. To ascertain the bonding in the mixed ligand complex of cimetidine and a selected thiourea derivativ (allylthiourea) with metal(II) ion (Cu), a careful comparison of the infrared spectroscopy of the ligand and complex was done.

Cimetidine has several potential donor atoms and can donate to any of the metal center. The donor atoms are sulphur atom in the thiol group, nitrogen atom of imidazole ring and the nitrogen atom of the secondary amine (Adedibu *et al*., 2011). The infrared of cimetidine, selected thiourea derivative and its complex as shown in Table 4.3 have been assigned mainly for those specific

frequencies directly involved in complex formation. The vibrational frequency at 1597cm^{-1} in the free cimetidine ligand which was assigned to ν(C=N) stretching shifted to higher frequencies in the metal (II) complexes (1641-1651 cm^{-1}) region, which suggests the coordination of metal (II) ion through nitrogen of the imidazole group of cimetidine ligand (Adedibu *et al*., 2011; Daniela *et al*., 2013; Hussaini, 2017; Habila *et al.,* 2018; Osunlaja *et al*., 2019,). The principle behind the phenomena is due to donation of the unpaired electrons from one of the nitrogen to the metal (II) ion (Adedibu *et al*., 2011).

The band observed in the free cim ligand at 1388cm^{-1} which was assigned to ν(C-N), shifted to higher frequency in the range of 1402-1419cm^{-1} for all the metal (II) complexes. This is an indication that there was a metal to nitrogen bonding on the N-H group of cimetidine in all the metal (II) complex (Adedibu, *et al.,* 2011; Daniela *et al*., 2013; Jacquline *et al.,* 2015; Habila *et al.,* 2018; Osunlaja *et al*., 2019). The frequencies of the free thioureas (thio at 1433 cm^{-1}) attributed to ν(C-N), was compared to that of the metal(II) complex. It was observed that all the frequencies of the metal complex are in lower frequency range, which is an indication that there is a bond between the metal and the nitrogen of N-H group of the thio metal (II) complexes. (Eltayeeb, 2000; Santha and Riswana, 2012; Rayees 2013; Bushan, 2013).
In the cimetidine, the frequency at 756 cm^{-1} was observed to have found a negative shift for all the frequency of the metal(II) complexes, indicating no bond between the metal to sulphur of cimetidine ligand (Eltayeeb, 2000; Netnapa, 2010; Santha and Rizwana, 2012; Bushan, 2013; Rayees 2013). The frequency of the free thio ligand, for thio at 1433 cm^{-1} which was assigned to ν(C=S) band, the metal to nitrogen ν(M-N) stretching vibrational frequency band were indicated by appearance of new bands observed around 511-630cm-^{1} region. Metal to sulphur ν(M-S) stretching coordination frequency appeared within the range 420-499cm-^{1} (Santha and Rizwana 2012; Ratha Krishnan *et al.,* 2014; Lawal, 2017;Osunlaja *et al*., 2019; Habila 2020).

Proposed structure of Complex;

Electronic spectra of the ligands Cim (cimetidine), thio (allylthiourea), have bands that fall within the range 40832 – 25075 cm-^{1}. In the metal (II) complexes, some of the bands shifted to higher or lower wave lengths due to coordination (Aderoju and Sharifah, 2015).

5.1.3.3 Cu(II) Complexes.

The electronic spectra of Cu(cim)(thio)Cl_2 show an absorption band at 14587 cm^{-1} which is attributed to $^{2}E_{g}\rightarrow{}^{2}T_{2g}$ also corresponding to octahedral geometry (Adedibu *et al*., 2011, Daniela *et al*., 2013, Eltayeeb, 2000, Netnapa, 2010, Habila *et al.,* 2018, Husaini, 2017).

Anti- ulcer Activity of Cimetidine and Its Mixed-Ligand Metal (II) Complexes

The dose dependent contractile effect of histamine on the guinea pig ileum at varying concentrations observed in the present study agrees with several literature reports in which similar observations were made (Maria-jose *et al.,* 1986; Margaret and Vane, 1963; Arul *et al.,* 2004; Saba and Tomori, 2007). The ability of histamine to stimulate H_1 and H_2 receptors found on the smooth muscles of the guinea pig ileum may be responsible for the observed contractions. The extrapolated EC_{50} which was found to be 50.1 ng/ml was lower than those reported by Barka and Hough (1983) and Luiz *et al* (2015), this signifies that the histamine used in the present study

was more potent than those earlier reported (Barka and Hough, 1983; Luiz *et al.,* 2015). However, the EC_{50} of the present study was found to be higher than 1.2 ng/ml as previously reported by Winbery and Barker (1986). The antagonistic effect of cimetidine observed in this research work is in agreement with several literature reports in which similar observations were made (Brimblecombe *et al*., 2010; Wallace and Sharkey, 2011, Thimoty *et al*., 2019).

Conclusion

The mixed-ligand metal (II) complexes derived from Cimetidine and some selected thiourea derivatives and their *in vitro* antiulcer activity have been described. The result shows that the mixed ligand metal (II) complexes have colours which indicates that the metals used in complexation are of transition types. The result of the conductivity suggested that the synthesized compounds are nonelectrolytes which was proved by their low conductivity value. The melting points of the ligands and their mixed ligand complexes decomposed at high temperature. The IR data indicated that the ligands have coordinated to the central metal ion through the imidazole nitrogen, amines and sulphur atoms of the ligands. The electronic spectral bands observed are consistent with an octahedral geometry for all the complexes. The *in vitro* anti-ulcer result demonstrated that cimetidine and its complexes may antagonize contraction against Histamine on the tissue (isolated guinea pig ileum) and compare the anti-ulcer activity of cimetidine and its metal (II) complexes.

It is highlighted that cimetidine reduced Histamine induced contraction on the guinea pig ileum by 60 percent. In comparison, the complex Cu(cim)(thio)Cl_2 with 75 percent is competing with cimetidine since it is a bit higher than the percent reduction response of cimetidine. This indicates that its anti-ulcer effect is more potent to that of cimetidine (60 percent).

5.3 Recommendations

Relative to the experiments and studies conducted, the following recommendations are drown; X-ray diffraction, Nuclear magnetic resonance (NMR) and Mass spectroscopy are recommended to confirm the structure of the complexes. Magnetic susceptibility is recommended in order to ascertain the geometry of the complexes. Micro analysis should be carried out in order to determine exact percentage of C, H, N and S. Anti-bacteria activity on Helicobacter pylori should be carried out on the mixed ligand complex. Further studies to determine the toxicity of the complexes should be done to know the level of safety of the complex.

REFERENCES

Abadia, A., Sancho, A., Soto, L. and Borras, J. (1986). Cimetidine Complexes Derived from Cobalt(II), Nickel(II) and Copper(II) Salts of Polyatomic Anions. *Transition Metal Chemistry,* **11:** pp 8-11.

Adedibu, T. C., Uche, B. E., Aaron, Y. I. and Christianah, A. O. (2011). Mechanically-Induced Solvent-less Synthesis of Cobalt and Nickel Complexes of Cimetidine. *The Electronic journal of Chemistry*, **3**(2): pp 94-103

Adediji, J. F., Olayinka, E. T., Adebayo, M. A. and Babatunde, O. (2009). Antimalarial Mixed-ligand Metal Complexes: Synthesis, Physicochemical and Biological Activities. *International Journal of Physical Sciences*, **4**(9): pp 529-53

Aderoju, A. O. and Sherifa, M. W. (2015). Synthesis, Characterization and Antimicrobial Activity of some Mixed Trimethoprime-Sulfamethozazole Metal Complexes. *Journal of World Applied Science*, 33(2): pp 336-342.

Advenier, C., Gnassounou, P. J. and Scarpignato, C. (1987). Relaxant effect of the H2-receptor Antagonist Oxmetidine on Guinea-pig and Human Airways. Brazilian Journal of Pharmacology, **90:** pp 523-530

Al-Dulaimi, A. A. N. (2010) Synthesis and Characterization of Mecury (ii) Complexes of N-Pheyl-N-(2-pyridyl or 2-benzothiozole) thiourea. *Tikrit Journal of Pure Science*, **15**(1): pp 1813-1866

Al-Obaidi, O. H. (2012). Synthesis Characteriszation and Antimicrobial Screening of Mixed-ligand Cu(II) and Zn(II) complexes*. Open Journal of Inorganic Non-metallic Materials*, 2:59-64.

Alimarin, P. I. and Shlenkskaya, V. I. (1969). The Analytical Chemistry of Mixed-ligand Complex. Institute of analytical chemistry, M.V. Lomonosov Moscow State University, Moscow, PP 462-470.

Alkan, C., Yusuf, T. and Derya, K. (2010). Preparation and Characterization of a series of Thiourea Derivatives as phase change Materials for Thermal Energy Storage. *Turkey Journal of Chemistry*, **35**: pp 769-777.

Anvarhusein, A.I., Fattouhi, M. and Malik, M. R. (2011). Mercury(II) Cyanide Complexes of Thiourea and the Crystal Structure of [(N,methylthiourea)$_2$.Hg(CN)$_2$]. *Russian Journal of Coordination Chemistry,* **37**(3): pp 180-185.

Arul, V., Miyazaki, S. and Dhananjayan, A. (2004). Mechanism of the Contractile Effect of the Alcoholic Extract of Aegle Marmelos Corr. on Isolated Guinea Pig Ileum and Tracheal Chain. *Journal of Phytotherapy and phytopharmacology,* 11(7-8): pp 679-683.

Azeem, S., Ataf, A. A, Ashfaq, M.Q. and Amin, B. (2016). Thiurea Derivatives in Drugs Design and Medicinal Chemistry. *Journal of Drug Design and Medicinal Chemistry*, **2**(1): pp 10-20.

Bailey, R. A. and Peterson, T. R. (1967). Some Complexes of Fe(II) with Thiourea and Methylthiouirea, 1-3-dimethylthiourea and 1-3- diethylthiourea Ligands. *Canadian Journal of Chemistry,* **45***:* pp 1135

Baranska, M. and Proniewcz, L. M. (1999). FT-IR and FT-Raman Spectra of Cimetidine and its Metallocomplexes. *Journal of Molecular Structure*, pp 153-162.

Barker, L. A. and Hough, L. B. (1983). Selectivity of 4-Methyl Histamine at H1 and H2- receptors in the Ileum. *British Journal of Pharmacology*. 80(1): pp 65-71.

Bhushan, K. L., Nirmal, R. Y. and Saudhya, C. (2013). Growth and Characterization of Pure Rare earth Doped Nonlinear Optical Single Crystal: Allylthiourea Cadmium Chloride (ATCC). *International Journal of Science and Research*, **4**(438): pp 2319-7064.

Brimblecombe, W. R., Duncan, A. W., Ganellin, C. R., Leslie, G. B. and Parsons, M. E. and Black, J.W. (2010). The Pharmacology of Cimetidine, a new Histamine H2-receptor Antagonist. *British Journal of Pharmacology*. !60(1): pp 552-553.

Brimblecombe, W. R., Duncan, A. W., Durant, J. G., Emmett, C. J., Ganellin, C. R., Leslie, G. B. and Parsons, M. E. (1978). Characterization and Development of Cimetidine as a Histamine H2-Receptor Antagonist. *American Journal of Gastroenterology,* 74(2): pp 340-347.

Daniela, O. R., Villeda-García, J. C., Colorado-Peralta, R., Solano-Peralta, A., Sanchez, M., Hernández-Ahuactzi, F. I. and Castillo-Blum, S. E. (2013). Spectroscopic Studies and DFT Calculations of Cimetidine Complexes with Transition Metal Ions. *Journal of Mexican Chemical Society***, 57**(3): pp 230-238.

Dnyaneshwar, S., Wankhede, Nileshkumar, D. and Atit H. Q. (2014). Mixed-ligand Complexes derived from 4-(Benzene) Azo, Salicyldehyde and 2-Amino-4-nitropenol using Transition Metal ions. *Journal of Current Chemical and Pharmaceutical Science*, **4**(3): pp 135-141.

Ekakitie, A. O. and Osakwe, A. A. (2014). Isolation of $CuSO_4$, $Cu(NO_3)_2$, $CuCl_2$,$Cu(CH_3COO)$, $CoCl_2$, $Co(NO_3)_2$ from Mixed-ligand of Acetemide and Thiourea*. Research on Science and Technology,* **3**(3): pp 2319-2330.

Eltayeb, M. A. H. (2000). Reaction of Urea, Thiourea and their Derivatives with Tertiary Phosphine Transition Metal Halides. (M.Sc thesis). Department of Chemistry, Faculty of Education, University of Khartoum, Sudan, PP 78-86

Erickson, S., Lanstrom, G., Rikuer, L., Calsson, R. and Nasedal, J. (1996). Omeprazol and H2-Receptor Antagonist in Acute Treatment of Duodenal Ulcer, Gastric Ulcer and Reflux Oesophagitis: a Metal-analysis. *European Journal of Gastro Enterology and Herpetology*, **8**(2): pp 192.

Esbenshade, T. A., Kang, C. H., Krueger, K. M., Miller, T. R., Witte, D. G., Roch, J. M. Masters, J. N. and Hancock, A. A. (2003). Differential Activation of Dual Signaling Responses by Human H1 and H2 histamine receptors. *Journal of Receptor and Signal Trans duct Research,* **23**(1): pp 17-31.

Fun, H. K., Razuk, I. A., Pakawatchai, C., khaokong, C., Chantropromma, S. and Saithong, S. (1998). Tris(N,N,diethylthiourea) Iodo Copper(I) and Tris(N,N,diethylthiourea) Iodo ilver(I). *Acta Crystallographica,* **54**: pp 453-456.

Gilman, A. G., Rall, T. W., Nies, A. S. and Taylor, P. (1990). Goodman and Gilmans the pharmacological basis of therapeutics*.* 8th edition. Pergmon Press. New York, PP 893.

Gutzmer, R., Langer, k., Lisewski, M., Mommert, S., Rieckboprn, D., Kapp, A. and Werfel, T. (2002). Expression and Function of Histamine Receptors 1 and 2 on Human Monocyte-derived Dentritic cells. *The Journal of Allergy and Clinical Immunology,* 109(3): pp 524-531.

Habila A.N.P., Ndahi, N.P., Hauwa, S. B., Grema, M., Osunlaja, A.A., and Hussaini, G. (2020). Synthesis, Characterization and Antimicrobial Analysis of Schiff Bases of o-Phenylenediamine and 2-aminopyridine-3-carboxylic acid with Ofloxacin and their Metal (II) Momplexes. *International Journal of Biological and Chemical Sciences*. 14(1): pp 263-278

Huang, T. C. and Lee, C. L. (2014). Diagnosis, Treatment and Outcome in Patients with Bleeding Peptic Ulcers and Helicobacter Pylori Infections. *Bio Med Research International*, **10**: pp 2-10.

Hussaini G. (2017). Transition Metal Schiff Base Complexes Derived from Trimethoprim and their Antimicrobial Properties (M.Sc. Thesis). University of Maiduguri, Nigeria, PP 43-58.

Ibrahim, W. (2014). Synthesis Characterization and Anti-microbial studies of some Mixed anti-biotic Complexes with Transition Metals (M.Sc. Thesis). University of Maiduguri, Nigeria, PP 48.

Ikokoh, P. P. A, Onigbanjo, H. O, Adedirin, O. Akolade, J. O., Uzo, A. and Fagbohun, A. (2015) Thiourea and Silver(I) Thiourea. *Open Journal of Research*, **6**(1): pp 056-091.

Jacquline, P. R., Kalyanasundharam, S., Santhanalakshmi, K., Muthukumar, S. and Manivannan, P. (2015). *International Letters of Chemistry, Physics and Astronomy,* 49: pp 74-80.

Jantratid, E., Pracongpan, S., Dressman, J. B., Amidon, G. L., Junginger, H. E., Midha, K. K. and Barend, D.M. (2006). Biowaiver Monopraphs for Immediate Release of Solid Oral dosage forms:Cimetidine. *Journal of Pharmaceutical Science*, **95**(5): pp 974-984

Jeannot, B. R., Léa, H. R., Anne, W. L. R., René, R., Louise, F. R. and Amélie, R. (2016). Antispasmodic effects of Sesselin from Cynanchum Ambositrense on Isolated Tissues. *Journal of Pharmacognocy and Phytochemistry*, **5**(6): pp 238-244.

Joshita, S. (2016). A Note on Peptic Ulcer. *Research and Review Journal of Pharmacognosy and Phytochemistry*, **41**(1): pp 47-53

Jorda, P., Ortiz, R. and Borrhs, J. (1991). Study of Copper(II) Ternary Complexes with Cimetidine and L-alanine, Bete-alanide and Phenyl or Hydroxyphenyl Substituted Amino Acids. Evidence of Aromatic Ring Stacking Involving a Coordinated Imidazole Ring. *Journal of Inorganic Biochemistry*, **41**: pp 149-155

Kanumfre, F., Delima, E. M., Scheidt, G., Carneiro, P. I. B. and Rosso, N. D. (2010).Potentiometric and Spectrophototmetric Studies of Mn-II and Ni-II Cimetidine Complexes. *Journal of Brazilian Chemical Society*, **21**(5): pp 800-805.

Khan, M. M. (1999). Rn(III), Pd(II), Pt(III) and Ot(iv) Complexes of a Novel 32-membered Unsymmetrical Dinucleating Macrocyclic ligand, Synthesis and Reactivity in Inorganic, Metal-Organic and Nano-Metal Chemistry. *Applied Journal of Chemistry,* **40**(5): pp 148-152.

Luiz, H.C.V., Ana, C. C., Lara, L. L. S., and Maria, C. C. S. (2015). Flavonoid Gelatin 3,6- Dimethyl Ether Attenuates Guinea Pig Ileum Contraction through K(+) Channel Activation and decrease in Cytosolic Calcium Concentration. *European Journal of Pharmacology*. 767(52): pp 60

Margaret, D. and Vane, J. R. (1963). An analysis of the direct and indirect actions of drugs on the isolated guinea-pig ileum. *British Journal of Pharmacology,* 20:150-170.

Maria-Jose, A. Francisco, J. Morale-Olivas and Elena, R. (1986). Pharmacological Investigation into the Effect of Histamine and Histamine Analogues on Guinea pig and Rat colon *Invitro. Britsih Journal of Pharmacology.* 88: pp 501-506.

Marina, P., Thomas, D. B. L. and Gordon, S. F. (1997). Nickel Metabolism in Humans. *American Society for Clinical Nutrition,* **66**: pp 616-621.

Marja, L. and Oikari, A. (2010). Microbial Transformation of Pharmaceuticals Naproxen, Bisoprolol, and Diclofenac in Erobic and Anaerobic Environments. *Archives of Environmental Contamination and Toxicology,* **61**(2): pp 2266-2268

Muhammad, H., Muhammad, A. H. N., Maria V. B., Jamshed, I., Alexander, R., Bernhard, K. K. and Christian, G. H. **(**2014). Ruthenium II(η6-arene) Complexes of Thiourea Derivatives: Synthesis, Characterization and Urease Inhibition. *Molecules*, ***19***(3): pp 8080-8092.

Muhammad, S., Trivendra, T., Farrukh, S., Shagufta, M., Mashiatullah, S. and Rahat, A. K. (2009). Histamine, Histamine Receptors, and their Role in Immunomodulation: An Updated Systematic Review. *Open Journal of Immunology,* 2: pp 9-41

Musa, E. M. B. (2000). Organometallic Complexes of the Thiocarbanilides and Substituted Thiocarbanilides-using Manganese(II) Chloride (M.Sc. Thesis). University of Khartoum, Sudan, PP 1-5.

Najm, W. (2011). Peptic Ulcer Disease Primary Care. *Review Journal Article*, **38**(3): pp 383-394.

Nenad, S. K., Ružica S. N., Maja, N. S., Nada, G. N. and Dragan, M. D. (2015). Coordination Compounds of M(II) Biometal Ions with acid-type Anti-inflammatry Drugs as Ligands. *Tropical Journal of Pharmaceutical Research,* **14**(2): pp 337-349

Netnapa, E. (2010). Silver(I) Complexes containing Triphenylphosphine and N,N,diphenylthiourea (MSc. thesis). Prince of Sonkla University, Thailand, PP 80-83.

Osowole, A. A. (2008). A studies on some VO(IV), Ni(II), and Cu(II) complexes of Non-Symmetrical Tetradentate Schiff-Bases. *Bulletin of the chemical society of Ethiopia*, 22, 219-224.

Osunlaja, A. A. (2008). Synthesis, Physio-chemical and Antimicrobial Properties of Co(II), Ni(II) and Cu(II) Mixed-ligand Complexes of Dimethyl Glyoxime (M.Sc. Thesis). University of Maiduguri, Nigeria, PP 5-7.

Osunlaja, A.A., Ndahi, N.P., Ameh, A. J. and Adetoro, A. (2011). Synthesis, Physico-Chemical and Antimicrobial Properties of Co(II), Ni(II), and Cu(II) Mixed-Ligand Complexes of Dimethylglyoxime. *Research Journal of Applied Sciences, Engineering and Technology* **3**(11): pp 1233-1238.

Raman, C. Gorlitz A. Vogels, J. M., Leanhardt A. E., Gustavson, T. L., Abo-Shaeer, J. R., Chikkatur, S., Gupta, S., Inouye, S., Rosenband, T. and Ketterle, W., (2001) Realization of Bose-Einstein Condensates in Lower Dimensions. *Physical Review letters*. **87**: 130402.

Rayees, A. S., Ismail, A. R., Maqsood, A. M., Norhayati, L.uddin1, Sam'an, M. M. and Shaeel Al-Thabaiti, A. (2013). Transition Metal Complexes with Mixed Nitrogen-Sulphur (NS) Donor Macrocyclic Schiff Base Ligand: Synthesis, Spectral, Electrochemical and Antimicrobial Studies. *International Journal of Electrochemical Science.* 8**:** pp 6972 – 6987.

Rao, D. S. (2014). Clinical Manual of Surgery. 1st edition. Elsevier Health Sciences, PP 962.

Rossi, S. (2005). Australian Medicines Handbook. 5th edition. Adelaide: Australian Medicines Handbook, PP 184.

Ruyuktimkin, S. (1991). Quinazolinones. 18. Synthesis and H1/H2 Anti-histamine Action of Omega -[2- anryl -2 -2, 3- dihydro -4(1H)- Quinazolinone -1- yl] Alkyl Substituted Ureas and Cyanoguanidines. *Archives of Pharmacology*, **2**(34): pp 92-143.

Saba, A. B., and Tomori, O. A. (2007). The Contractile Effect of Ethanolic Extract of West African Black Papper (piper guineense) on Isolated Guinea pig Ileum. *Pakistan Journal of Nutrition*, 6(4): pp 366-369.

Saidul, I., Belayet, H. and Yamin, R. (2003). Antimicrobial Studies of Mixed-ligand Transition Metal Complexes of Maleic Acid and Heterocyclic Amine Bases. *Journal of Medical Science*, **3**(4): pp 289-293.

Saddam H. M., Zakaria, C. M. and Kudrat-E-Zahan M. D. (2018). Metal Complexes as Potential Antimicrobial Agent: A Review. *American Journal of Heterocyclic Chemistry,* **4**(1): pp 1-21

Shamin, H., Aslam, R., Kurshid, A., Kudirat, Z., Sarkar, S. and Akhtar, F. (2004). Antimicrobial and Cytotoxic Activities of 2-aminobenzoic and 2-aminophenol and their Coordination Complexes with Magnesium. *Pakistan Journal of Biological Science*, **7**(1): pp 25-27.

Sharma, P. D., Srivastava, S. and Singh, P. P. (2009). Molecular Mechanics and Quantum Chemistry Based Study of Nickel-*N*-Allyl Urea and *N*-Allyl Thiourea Complexes. *E-Journal of Chemistry,* **6**(3): pp 753-758.

Singh, H., Pahwa, S., Dhamija, K. and Arora, V. (2018). Cimetidine: A Review. *International Journal of Chemical and Technical Research*, **11**(2):115-123.

Stephen, G. N. and Carol, B. (1981). H2 Receptor Blockade and Bronchial Hyperreactivity to Histamine in Asthma. *Thorax*, **36**: pp 268-271

Sumia, F., Dr. Ramesh, C. and Salheel, Q.A. (2018). In vitro evalution of Anti-ulcer Activity of polyherbal mixture. *IOSR Journal of Pharmacy*, **8**(12): pp 55-59

Sunil, S., Ganish, A., Thakur, and Vishwanath, R. P. (2009). Synthesis, Spectral and Biological Studies on some Mixed-ligand Ni(II) complexes. *Acta Polaniea Pharmaceutica-Drug Researh*, **66**(3): pp 271-277.

Syed, A.T., Feroza, H. W., Muhammad, H. Sarwar, W., Saadia, S., Allah-Nawaz, M. and Allah-Bux, G. (2012). Spectrophotometric Study of Stability Constant of Cimetidine-Ni(II) Complexes at different Temperatures. *Arabian Journal of Chemistry*, **5**(2): pp 309-314.

Timothy, S.Y., Attah, M.O. and Shamaki, K.B. (2015). Antiulcer and Antibacterial Screening of the Seed Coat and Leaf Extracts of *Tamarindus indica* linn. *Asian Journal of Pharmaceutical Research*, **8**(6): pp 55-59

Valencia, H. (2017). Peptic Ulcer. 1st edition. Medically Reviewed by Graham Rogers: Health line. Hamdard Turkey, PP 3-10.

Venkappayya, D. and Brown, H. D. (1974). Some Metal Halide Complexes of Morpholine-4-thiocarbonic acid Anilide. *Journal of Inorganic and Nuclear Chemistry,* **36**: pp 1023-1030

W.H.O. (2003). W.H.O. model list of essential medicines, 13th edition. Available from URL:http://www.who.int/medicnes/organization/per/edl/expcom13/em/13-wn.doc.

Walece, J. L. and sharkey, K. A. (2011). Pharmacotherapy of Gastric Peptic Ulcers and Gastro Oesophageal Reflux Disease. In Goodman and Gilman's the Pharmacological Basis of Therapeutics, 12th edition, 45: pp 1309-1322.

Wang, A. and Peura, Y. D. A. (2011). The Prevalence and Incidence of Helicobacter Pylori associated Peptic Ulcer Disease and Upper Gastrointestinal Bleeding throughout the World. *Gastro Intestinal Clinics of North America*, **24**(4): pp 613-835

Waqar, A., Shakeel A. K., Khurram, S. M., Asma, K. C. and Sadia K. (2017). Synthesis,Characterization and Pharmacological Evaluation of Mixed-ligand Metal Complexes Containing Omeprazole and 8-hydroxyquinoline. *Tropical Journal of Pharmaceutical Researc,.* **16**(5): pp 1137-1146

Yagupsky, G., Negrotti, R. H. and Levitus, R. (1964). Polymeric Complexes of Cobalt II Thiocyanate with Thiourea, N,methylthiourea, and N,N,ethylenethiourea. *Journal of Inorganic and Nuclear Chemistry*, **27**(3): pp 2603-2616

Yagupsky, G. and Levitus, R. (1972). N,N,diphenylthiourea and N,N,dicyclohexylthiourea Complexes of Cobalt(II). *Journal of Inorganic Chemistry*, **4**(11): pp 1589-1594

Yu, Y., Ramsay, J. A. and Ramsay, B. A. (2009). Uses of Allylthiourea to Produce Soluble Methane Mono Oxygenase in the Presence of Copper. *Applied Microbiology and Biotechnology,* **82**(2): pp 333-339.