COORDINATION CHEMISTRY OF SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY OF CHLOROQUINE AND SELECTED D-BLOCK METALS.

A REPORT SUBMITTED

BY

ONIKEDE, BASIT OLAYODE
HND/23/SLT/FT/1100

TO THE DEPARTMENT OF SCIENCE LABORATORY TECHNOLOGY, INSTITUTE OF BASIC AND APPLIED SCIENCES, KWARA STATE POLYTECHNIC, ILORIN.

IN PARTIAL FUFILMENT OF THE REQUIREMENT FOR THE AWARD OF HIGHER NATIONAL DIPLOMA [HND] IN SCIENCE LABRORATORY TECHNOLOGY.

JUNE, 2025

CERTIFICATION

This is to certify that this project work was carried out by **ONIKEDE, BASIT OLAYODE** under the supervision of

MR. OGUNYEMI O.J — DATE
(PROJECT SUPERVISOR)

MRS. SALAHUDEEN K.A — DATE
(HEAD OF UNIT)

DR. USMAN A.O — DATE
(HEAD OF DEPARTMENT)

EXTERNAL EXAMINER — DATE

DEDICATION

This research work is dedicated to the Almighty God, I also dedicate it to my beloved parents MR and Mrs. Onikede for their care and support towards me right from my childhood

ACKNOWLEDGEMENT

My sincere heart of gratitude goes to the Almighty Allah who gave me knowledge and strength for the successful completion of this Higher National Diploma program.

This project work would not have been possible without the cooperation of a very large number of people. My greatest debt in this regard however, is to my supervisor, in person of Mr. Ogunyemi O.J whose patient criticisms and comments played a big role towards the completion of this project work. I am extremely grateful to him.

An immeasurable debt of appreciation is due to my Godly parents, Mr. and Mrs. Olayode, without their long-term patience and encouragement through many vicissitudes of life, this project could never have been completed. I pray you will live long to eat the fruits of your labour over me. May the Almighty Allah bless and protect you. (Amin).

ABSTRACT

Some Choroquine complexes of Ni[ii], Cu[ii] and Iron[ii] were prepared from the reaction of chloroquine and metal salts.
The complexes were characterized using physical properties like melting point and solubility test.

LIST OF ABBREVIATONS

Ni	**Nickel**
Zn	**Zinc**
Fe	**Iron**
S	**Soluble**
Ns	**Not Soluble**
Ss	**Slightly Soluble**
Uv	**Ultraviolet**
IR	**InfraRed**
g/mol	**Gram per mole.**

TABLE OF CONTENT

CHAPTER ONE

1.1 INTRODUCTION

Chloroquine is a medication primarily used to prevent and treat malaria in areas where malaria remains sensitive to its effects.[1] Certain types of malaria, resistant strains, and complicated cases typically require different or additional medication.[1] Chloroquine is also occasionally used for amebiasis that is occurring outside the intestines, rheumatoid arthritis, and lupus erythematosus.[1] While it has not been formally studied in pregnancy, it appears safe.[1][2] It was studied to treat COVID-19 early in the pandemic, but these studies were largely halted in the summer of 2020, and the NIH does not recommend its use for this purpose.[3] It is taken by mouth.[1]

Common side effects include muscle problems, loss of appetite, diarrhea, and skin rash.[1]Serious side effects include problems with vision, muscle damage, seizures, and low blood cell levels.[1][4] Chloroquine is a member of the drug class 4-aminoquinoline.[1] As an antimalarial, it works against the asexual form of the malaria parasite in the stage of its life cycle within the red blood cell.[1] How it works in rheumatoid arthritis and lupus erythematosus is unclear.[1]

Chloroquine was discovered in 1934 by Hans Andersag.[5][6].It is on the World Health Organization's List of Essential Medicines.[7]It is available as a generic medication.[1]

Chloroquine has been used in the treatment and prevention of malaria from *Plasmodium vivax*, *P. ovale*, and *P. malariae*. It is generally not used for *Plasmodium falciparum* as there is widespread resistance to it.[9][10]

Chloroquine has been extensively used in mass drug administrations, which may have contributed to the emergence and spread of resistance. It is recommended to check if chloroquine is still effective in the region prior to using it.[11]In areas where resistance is present, other antimalarials, such as mefloquine or atovaquone, may be used instead. The Centers for Disease Control and Prevention recommend against treatment of malaria with chloroquine alone due to more effective combinations.[12]

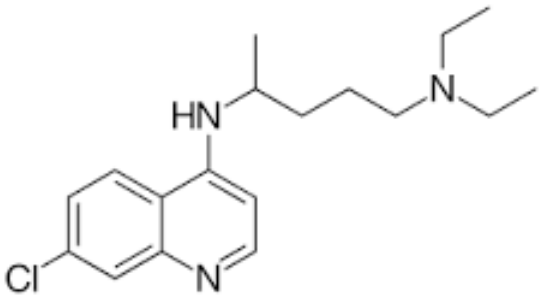

Fig. 1 Structure of Chloroquine.

1.2 Rheumatic disease

As it mildly suppresses the immune system, chloroquine is used in some autoimmune disorders, such as rheumatoid arthritis and has an off-label indication for lupus erythematosus.[1]

1.3 Side effects

Side effects include blurred vision, nausea, vomiting, abdominal cramps, headache, diarrhea, swelling legs/ankles, shortness of breath, pale lips/nails/skin, muscle weakness, easy bruising/bleeding, hearing and mental problems.[14][15]

- Unwanted/uncontrolled movements (including tongue and face twitching, diskenesia, and dystonia)[14][16]
- Deafness or tinnitus[14]
- Nausea, vomiting, diarrhea, abdominal cramps[15]
- Headache[14]
- Mental/mood changes (such as confusion, personality changes, unusual thoughts/behavior, depression, feeling being watched, hallucinating)[14][15]
- Signs of serious infection (such as high fever, severe chills, persistent sore throat)[14]
- Skin itchiness, skin color changes, hair loss, and skin rashes[15][17]

    - Chloroquine-induced itching is very common among black Africans (70%), but much less common in other races. It increases with age, and is so severe as to stop compliance with drug therapy. It is increased during malaria fever; its severity is correlated to the malaria parasite load in blood. Some evidence indicates it has a genetic basis and is related to chloroquine action with opiate receptors centrally or peripherally.[18]
- Triggering of a severe psoriasis attack in those with psoriasis[16]
- Unpleasant metallic taste
    - This could be avoided by "taste-masked and controlled release" formulations such as multiple emulsions.[19]
- Chloroquine retinopathy (irreversible retinal damage)[16]
- Electrocardiographic changes[20]
    - This manifests itself as either conduction disturbances (bundle-branch block, atrioventricular block) or cardiomyopathy — often with hypertrophy, restrictive physiology, and congestive heart failure. The changes may be irreversible. Only two cases have been reported requiring heart transplantation, suggesting this particular risk is very low. Electron microscopies of cardiac biopsies show pathognomonic cytoplasmic inclusion bodies.

- Pancytopenia, aplastic anemia, reversible agranulocytosis, low blood platelets, neutropenia[16]
- Worsening of the condition for those with porphyria[16]

1.4 Pregnancy

Chloroquine has not been shown to have any harmful effects on the fetus when used in the recommended doses for malarial prophylaxis.[21] Small amounts of chloroquine are excreted in the breast milk of lactating women. However, this drug can be safely prescribed to infants, the effects are not harmful. Studies with mice show that radioactively tagged chloroquine passed through the placenta rapidly and accumulated in the fetal eyes which remained present five months after the drug was cleared from the rest of the body.[16][22] Women who are pregnant or planning on getting pregnant are still advised against traveling to malaria-risk regions.[21]

1.5 Elderly

There is not enough evidence to determine whether chloroquine is safe to be given to people aged 65 and older. Since it is cleared by the kidneys, toxicity should be monitored carefully in people with poor kidney functions, as is more likely to be the case in the elderly.[16]

1.6 Drug interactions

Chloroquine has a number of drug–drug interactions that might be of clinical concern

- Ampicillin – levels may be reduced by chloroquine;[16]
- Antacids – may reduce absorption of chloroquine;[16]
- Cimetidine – may inhibit metabolism of chloroquine; increasing levels of chloroquine in the body;[16]
- Cyclosporine – levels may be increased by chloroquine;[16] and
- Mefloquine – may increase risk of convulsions.[16]

1.7 Overdose

Chloroquine, in overdose, has a risk of death of about 20%.[23] It is rapidly absorbed from the gut with an onset of symptoms generally within an hour.[24] Symptoms of overdose may include sleepiness, vision changes, seizures, stopping of breathing, and heart problems such as ventricular fibrillation and low blood pressure.[23][24] Low blood potassium may also occur.[23]

While the usual dose of chloroquine used in treatment is 10 mg/kg, toxicity begins to occur at 20 mg/kg, and death may occur at 30 mg/kg.[23] In children as little as a single tablet can be fatal.[24][16]

Treatment recommendations include early mechanical ventilation, cardiac monitoring, and activated charcoal.[23] Intravenous fluids and vasopressors may be required with epinephrine being the vasopressor of choice.[23] Seizures may be treated with benzodiazepines.[23] Intravenous potassium chloride may be required, however this may result in high blood potassium later in the course of the disease.[23] Dialysis has not been found to be useful.[23]

Absorption of chloroquine is rapid and primarily happens in the gastrointestinal tract.[25] It is widely distributed in body tissues.[26] Protein binding in plasma ranges from 46% to 79%.[27] Its metabolism is partially hepatic, giving rise to its main metabolite, desethylchloroquine.[28] Its excretion is ≥50% as unchanged drug in urine, where acidification of urine increases its elimination. It has a very high volume of distribution, as it diffuses into the body's adipose tissue.

Accumulation of the drug may result in deposits that can lead to blurred vision and blindness.[29] It and related quinines have been associated with cases of retinal toxicity, particularly when provided at higher doses for longer times. With long-term doses, routine visits to an ophthalmologist are recommended.

Chloroquine is also a lysosomotropic agent, meaning it accumulates preferentially in the lysosomes of cells in the body. The pKa for the quinoline nitrogen of chloroquine is 8.5, meaning it is about 10% deprotonated at physiological pH (per

the Henderson-Hasselbalch equation). This decreases to about 0.2% at a lysosomal pH of 4.6. Because the deprotonated form is more membrane-permeable than the protonated form, a quantitative "trapping" of the compound in lysosomes results.

1.8 Malaria

The lysosomotropic character of chloroquine is believed to account for much of its antimalarial activity; the drug concentrates in the acidic food vacuole of the parasite and interferes with essential processes. Its lysosomotropic properties further allow for its use for *in vitro* experiments pertaining to intracellular lipid related diseases,[30][31] autophagy, and apoptosis.[32]

Inside red blood cells, the malarial parasite, which is then in its asexual lifecycle stage, must degrade hemoglobin to acquire essential amino acids, which the parasite requires to construct its own protein and for energy metabolism. Digestion is carried out in a vacuole of the parasitic cell.[*citation needed*]

Hemoglobin is composed of a protein unit (digested by the parasite) and a heme unit (not used by the parasite). During this process, the parasite releases the toxic and soluble molecule heme. The heme moiety consists of a porphyrin ring called Fe(II)-protoporphyrin IX (FP). To avoid destruction by this molecule, the parasite

biocrystallizes heme to form hemozoin, a nontoxic molecule. Hemozoin collects in the digestive vacuole as insoluble crystals.

Chloroquine enters the red blood cell by simple diffusion, inhibiting the parasite cell and digestive vacuole. Chloroquine (CQ) then becomes protonated (to CQ2+), as the digestive vacuole is known to be acidic (pH 4.7); chloroquine then cannot leave by diffusion. Chloroquine caps hemozoin molecules to prevent further biocrystallization of heme, thus leading to heme buildup. Chloroquine binds to heme (or FP) to form the FP-chloroquine complex; this complex is highly toxic to the cell and disrupts membrane function. Action of the toxic FP-chloroquine and FP results in cell lysis and ultimately parasite cell autodigestion.[33] Parasites that do not form hemozoin are therefore resistant to chloroquine.[34]

1.9 Resistance in malaria

Since the first documentation of *P. falciparum* chloroquine resistance in the 1950s, resistant strains have appeared throughout East and West Africa, Southeast Asia, and South America. The effectiveness of chloroquine against *P. falciparum* has declined as resistant strains of the parasite evolved.

Resistant parasites are able to rapidly remove chloroquine from the digestive vacuole using a transmembrane pump. Chloroquine-resistant parasites pump chloroquine out at 40 times the rate of chloroquine-sensitive parasites; the pump is

coded by the *P. falciparum* chloroquine resistance transporter (*PfCRT*) gene.[35] The natural function of the chloroquine pump is to transport peptides: mutations to the pump that allow it to pump chloroquine out impairs its function as a peptide pump and comes at a cost to the parasite, making it less fit.[36]

Resistant parasites also frequently have mutation in the ABC transporter *P. falciparum* multidrug resistance (*PfMDR1*) gene, although these mutations are thought to be of secondary importance compared to *PfCRT*. An altered chloroquine-transporter protein, *CG2* has been associated with chloroquine resistance, but other mechanisms of resistance also appear to be involved.[37]

Verapamil, a Ca2+ channel blocker, has been found to restore both the chloroquine concentration ability and sensitivity to this drug. Other agents which have been shown to reverse chloroquine resistance in malaria are chlorpheniramine, gefitinib, imatinib, tariquidar and zosuquidar.[38]

As of 2014 chloroquine is still effective against poultry malaria in Thailand. Sohsuebngarm et al. 2014 test *P. gallinaceum* at Chulalongkorn University and find the parasite is not resistant.[39]: Sertraline, fluoxetine and paroxetine reverse chloroquine resistance, making resistant biotypes susceptible if used in a cotreatment.[40]

1.10 Antiviral

Chloroquine has antiviral effects against some viruses.[41] It increases late endosomal and lysosomal pH, resulting in impaired release of the virus from the endosome or lysosome — release of the virus requires a low pH. The virus is therefore unable to release its genetic material into the cell and replicate.[42][43]

Chloroquine also seems to act as a zinc ionophore that allows extracellular zinc to enter the cell and inhibit viral RNA-dependent RNA polymerase.[44][45]

1.11 Chemical synthesis

The first synthesis of chloroquine was disclosed in a patent filed by IG Farben in 1937.[44] In the final step, 4,7-dichloroquinoline was reacted with 1-diethylamino-4-aminopentane.By 1949, chloroquine manufacturing processes had been

1.12 Formulations

Chloroquine comes in tablet form as the phosphate, sulfate, and hydrochloride salts. Chloroquine is usually dispensed as the phosphate.[36]

1.13 Names

Brand names include Chloroquine FNA, Resochin, Dawaquin, and Lariago.[37]

Chloroquine, in various chemical forms, is used to treat and control surface growth of anemones and algae, and many protozoan infections in aquariums,[38] e.g. the fish parasite *Amyloodinium ocellatum*.[39] It is also used in poultry malaria.[39]:

Chloroquine was proposed as a treatment for SARS, with *in vitro* tests inhibiting the severe acute respiratory syndrome coronavirus (SARS-CoV).[30][31] In October 2004, a published report stated that chloroquine acts as an effective inhibitor of the replication of SARS-CoV in vitro.[60] In August 2005, a peer-reviewed study confirmed and expanded upon the results.[22]

Chloroquine was being considered in 2003, in pre-clinical models as a potential agent against chikungunya fever.[23]

Chloroquine and hydroxychloroquine are anti-malarial medications also used against some auto-immune diseases.[64] Chloroquine, along with hydroxychloroquine, was an early experimental treatment for COVID-19.[45] Neither drug has been useful to prevent or treat

SARS-CoV-2 infection.[46] Administration of chloroquine or hydroxychloroquine to COVID-19 patients has been associated with increased mortality and adverse effects, such as QT prolongation.[42][43] Researchers estimate that off-label use of hydroxychloroquine in hospitals during the first phase of the pandemic caused 17,000 deaths worldwide.[44] The widespread administration of chloroquine or hydroxychloroquine, either as monotherapies or in conjunction with azithromycin, has been associated with deleterious outcomes, including QT interval prolongation. As of 2024, scientific evidence does not substantiate the efficacy of hydroxychloroquine, with or without the addition of azithromycin, in the therapeutic management of COVID-19.[42]

Cleavage of the SARS-CoV-2 S2 spike protein required for viral entry into cells can be accomplished by proteases TMPRSS2 located on the cell membrane, or by cathepsins (primarily cathepsin L) in endolysosomes.[45] Hydroxychloroquine inhibits the action of cathepsin L in endolysosomes, but because cathepsin L cleavage is minor compared to TMPRSS2 cleavage, hydroxychloroquine does little to inhibit SARS-CoV-2 infection.[45]

Several countries initially used chloroquine or hydroxychloroquine for treatment of persons hospitalized with COVID-19 (as of March 2020), though

the drug was not formally approved through clinical trials.[46][47] From April to June 2020, there was an emergency use authorization for their use in the United States,[48] and was used off label for potential treatment of the disease.[49] On 24 April 2020, citing the risk of "serious heart rhythm problems", the FDA posted a caution against using the drug for COVID-19 "outside of the hospital setting or a clinical trial".[40]

Their use was withdrawn as a possible treatment for COVID-19 infection when it proved to have no benefit for hospitalized patients with severe COVID-19 illness in the international Solidarity trial and UK RECOVERY Trial.[41][42] On 15 June 2020, the FDA revoked its emergency use authorization, stating that it was "no longer reasonable to believe" that the drug was effective against COVID-19 or that its benefits outweighed "known and potential risks".[43] In fall of 2020, the National Institutes of Health issued treatment guidelines recommending against the use of hydroxychloroquine for COVID-19 except as part of a clinical trial.[44]

In 2021, hydroxychloroquine was part of the recommended treatment for mild cases in India.[46]

In 2020, the speculative use of hydroxychloroquine for COVID-19 threatened its availability for people with established indications (malaria and auto-immune diseases).[48]

1.14 AIM OF PROJECT

The aims of this research work are

(i) To synthesis novel complexes of chloroquine

(ii) To characterize the resulting complexes using standard analytical techniques such as solubility, melting point, infrared and ultraviolet .

CHAPTER TWO

2.1 MATERIALS AND METHODS

2.1.1 APPARATUS

The following apparatus were used in the formation of the complexes and further analytical studies were carried out.

APPARATUS	MANUFACTURER
Beakers	Pyrex scientific Ltd. England
Conical Flasks	Simax company Ltd. England
Capilary tube	Silber brand Ltd, England
Dessicator	Moncrief Scientific, England
Electrothermal melting point	Gallenkamp Ltd ,England
Round bottom flasks	Pyrex scientific Ltd, England

Hot plate with magnetic stirrer	Gallenkamp Ltd, England
Measuring cylinder	Technico scientific Ltd, England
Plastic condenser	
Reflux condenser	Moramber (Mbc) Ltd
Test tube	Pyrex scientific Ltd, England
Thermometer	Uniscope scientific Ltd, England
Infrared	Duck V Scientific 500 infrared
Ultraviolet	Jenwoy 6405 UV spectrophotometer.

2.1.2 REAGENTS

The following reagents were collected from chemistry department, Kwara State Polytechnic.

Reagent	**Manufacturer**
Nickel Sulphate Hexahydrate	
Molecular Formular- $NiSO_4.6H_20$	J.T Barker Chemical C.O Philliburg

Molecular mass =262.71g/mol

Copper Sulphate

Molecular formula = $CuSO_4$. Eagle Scientific England

Molecular Mass= 159.60g/mol

Iron Sulphate Heptahydrate East Aglia, Chemicals Hadheigh

Molecular Formular= $FeSO_4.7H_20$

Molecular Mass =278.02g/mol.

Ethanol East Aglia, Chemicals Hadheigh

Methanol East Aglia, Chemicals Hadheigh

Distilled water

2.1.3 MATERIALS

Chloroquine

Molecular formular= $C_{18}H_{26}CIN_3$

Molecular Mass=319.872g/mol

Source Chemistry department, University of Ilorin.

2.2 EXPERIMENTAL PROCEDURES

All apparatus were cleaned thoroughly before use. The retort stand was set properly and a round bottom flask clamped to it. This was further positioned onto the hotplate with a magnetic stirrer. A reflux condenser was fixed into the round bottom flask containing the solution and clamped onto the retort stand. Water pipes were connected, one into the inlet and the other into the outlet with both connected to full bucket of water and an empty bucket respectively.

2.2.1 CHLOROQUINE Ni (ii) COMPLEX FORMATION

3.52g of choroquine was weighed using a digital pocket scale and was then dissolved in 10cm3 of distilled water using a clean dried round bottom flask.

2.38g of $NiSO_4.6H_2O$ was also weighed using a digital pocket scale and was then dissolved in 10cm3 of distilled water in a beaker.

The Nickel solution was added to the ibuprofen solution and shaken vigorously for it to mix well. The magnetic stirrer was placed in the mixture and it was refluxed for 1 hour after which the solution was allowed to cool and a light green color was observed. The resulting solution was filtered using a filter paper. The precipitate was then washed off with methanol.

The complex obtained was weighed and put in a container which was labeled CHLNi(ii) complex.

The weight of the complex obtained was 1.7g of methanol.

2.2.2 CHLOROQUINE Cu (ii) COMPLEX FORMATION

3.52g of chloroquine was weighed using a digital pocket scale and was then dissolved in 10cm3 of distilled water using a clean dried round bottom flask.

1.6g of $CuSO_4$ was also weighed and was then dissolved in $10cm^3$ of distilled water in a beaker. The magnetic stirrer was placed in the mixture and it was refluxed for 1 hour after which the solution was allowed to cool and a light green

color was observed. The resulting solution was filtered using a filter paper. The precipitate was then washed off with methanol. The complex obtained was weighed and put in a container which was labeled IBCu(ii) complex. The copper solution was added to the chloroquine solution and shaken vigorously. The weight of the complex obtained was 3.5g.

2.2.3 CHLOROQUINE(Fe) FORMATION

3.52g of Chloroquine was weighed using a digital pocket scale and was then dissolved in 10cm3 of distilled water using a clean dried round bottom flask.

3.8g of $FeSO_4$ was also weighed and was then dissolved in $10cm^3$ of distilled water in a beaker. The magnetic stirrer was placed in the mixture and it was refluxed for 1 hour after which the solution was allowed to cool and a light brown color was observed. The resulting solution was filtered using a filter paper. The precipitate was then washed off with methanol. The complex obtained was weighed and put in a container which was labeled CHLFe(ii) complex. The copper solution was added to the ibuprofen solution and shaken vigorously. The weight of the complex obtained was 3.2g.

2.3 CHARACTERIZATION METHODS

2.3.1 SolubilityTest.

The solubility of the complexes was determined in the following solvents. Ethanol, benzene, methanol, petroleum ether, acetone, distilled water and chloroform

2.3.2 MELTING POINT DETERMINATION

The melting point of the complexes were determined using Gallenkamp melting point apparatus, thermometer and capillary tubes

2.3.3 METHOD

One side of the capillary tubes was sealed and the samples were introduced through the open and to a depth of about 1cm of the tube. The thermometer and the capillary tubes were inserted in the hole provided in the apparatus. The apparatus was switched on and the temperature at which the sample starts to melt and ends was taken as the melting point range of the sample. The melting point temperatures were taken for both the ligand and the complexes.

CHAPTER THREE

3.1 RESULTS AND DISCUSSION

The following are the results of the analysis conducted on some of the complexes formed

3.1.1 RESULTS OF SOLUBILITY TEST

Complex	Ethanol	Benzene	Methanol	Pet. Ether	Acetone	Distilled water	Chloroform
Chloroquine ligand	NS	NS	NS	NS	NS	S	NS
CHLNi(ii)	SS	NS	NS	NS	NS	SS	NS
CHLCu(ii)	SS	NS	NS	NS	NS	SS	NS
CHLFe(ii)	SS	NS	NS	NS	NS	SS	NS

Key S= soluble, SS=slightly soluble NS= not soluble

3.1.2 INTEPRETATION OF SOLUBIITY TEST

From the results obtained from the solubility test, it was evident that all complexes and the ligand were slightly soluble in methanol. Solubility of the ligand and the complexes were poor in ethanol, benzene, petroleum ether, acetone and chloroform.

3.2 RESULTS OF MELTING POINT TEST

COMPLEX	MELTING POINT RANGE
CHLOROQUINE LIGAND	190-192
CHLNi(ii) COMPLEX	158-160
CHLCu(ii) COMPLEX	160-162
CHLFe(ii) COMPLEX	211-213

3.2.1 INTERPRETATION OF MELTING POINT RANGE

From the results obtained, it showed that the melting point of the complexes were higher than those of the ligand. This shows that there was coordination.

Ligands/Complex	Wavelenght(nm)	Absorbance	Transition Assignment
Chloroquine	299.0	0.60	n-π* transition
	260.0	1.756	π-π* transition
CHLNi(ii)	278	2.916	n-π* transition
	233.5	0.932	π-π* transition
CHLCu(ii)	296	0.996	n-π* transition
	251.5	0.638	π-π transition
CHLFe(ii)	284	2.328	n-π* transition
	219	1.738	π-π transition

CHAPTER FOUR

4.1 CONCLUSION

Chloroquine formed stable complexes with Ni (ii), Cu (ii) and Fe (ii) ions. The solubility test and melting point determination showed that coordination has taken place. Further spectroscopic analysis like IR, UV and NMR is required in order to give a complete structure of the complexes.

REFERENCES

1. Adelusi SA, Salako LA (November 1982). "Tissue and blood concentrations of chloroquine following chronic administration in the rat". The Journal of Pharmacy and Pharmacology. **34** (11): 733–735.

2. Ajayi AA (September 2000). "Mechanisms of chloroquine-induced pruritus". Clinical Pharmacology and Therapeutics. **68** (3): 336.

3. Al-Bari MA (February 2017). "Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases". *Pharmacology Research & Perspectives*. **5** (1): e00293.

4. Alcantara LM, Kim J, Moraes CB, Franco CH, Franzoi KD, Lee S, et al. (June 2013). "Chemosensitization potential of P-glycoprotein inhibitors in malaria parasites". Experimental Parasitology. **134** (2): 235–243. .

5. Amebic Hepatic Abscesses~treatment at eMedicine.Drugs.com. Retrieved 22 March 2020.

6. Andersag, Hans; Breitner, Stefan & Jung, Heinrich, "Process for the preparation of quinoline compounds containing amino groups with basic substituents in the 4-position", issued 1939-11-13, assigned to IG Farbenindustrie AG Bhattacharjee M (2016). Chemistry of Antibiotics and Related Drugs. Springer. p. 184. ISBN 978-3-319-40746-3. Archived from the original on 1 November 2018. Retrieved 9 September 2017.

8. CDC. Health information for international travel 2001–2002. Atlanta, Georgia: U.S. Department of Health and Human Services, Public Health Service, 2001.

9. Chloroquine or Hydroxychloroquine". COVID-19 Treatment Guidelines. National Institutes of Health. Archived from the original on 28 August 2020. Retrieved 14 February 2021.

10. dailymed.nlm.nih.gov. Archived from the original on 8 December 2015. Retrieved 4 November 2015.. DailyMed. 8 October 2018. Retrieved 7 April 2020.

11. Chloroquine Use During Pregnancy". Drugs.com. Archived from the original on 16 April 2019. Retrieved 16 April 2019. There are no controlled data in human pregnancies.

12. Chloroquine. 6.1 Absorption by route of exposure. Retrieved 24 April 2020.

13. Chloroquine" nih.gov. National Institutes of Health. Retrieved 24 March 2020.

14. Chloroquine: MedlinePlus Drug Information". medlineplus.gov. Retrieved 22 March 2020.

15. Frequently Asked Questions (FAQs): If I get malaria, will I have it for the rest of my life?". US Centers for Disease Control and Prevention. 8 February 2010. Archived from the original on 13 May 2012. Retrieved 14 May 2012.

16. The History of Malaria, an Ancient Disease". Centers for Disease Control. 29 July 2019. Archived from the original on 28 August 2010.

17. Chen PM, Gombart ZJ, Chen JW (March 2011). "Chloroquine treatment of ARPE-19 cells leads to lysosome dilation and intracellular lipid accumulation: possible implications of lysosomal dysfunction in macular degeneration". Cell & Bioscience. **1** (1): 10.

18. Fern K (2010–2020). "Cinchona officinalis – L." Plans for a Future. Archived from the original on 25 August 2017. Retrieved 2 February 2020.

19. Fredericksen BL, Wei BL, Yao J, Luo T, Garcia JV (November 2002). "Inhibition of endosomal/lysosomal degradation increases the infectivity of human immunodeficiency virus". Journal of Virology. **76** (22): 11440–11446.

20. Handzel DM, Romanou-Papadopoulou V, Briesen S (September 2021). "[Visual loss under chloroquine treatment-and not (only) due to bull's eye maculopathy!]" [Visual loss under chloroquine treatment-and not (only) due to bull's eye maculopathy!]. Der Ophthalmologe (in German). **118** (9): 953–955.

21. Hempelmann E (March 2007). "Hemozoin biocrystallization in Plasmodium falciparum and the antimalarial activity of crystallization inhibitors". Parasitology Research. **100** (4): 671–676.

22. Huang Z, Srinivasan S, Zhang J, Chen K, Li Y, Li W, et al. (2012). "Discovering thiamine transporters as targets of chloroquine using a novel functional genomics strategy". PLOS Genetics. **8** (11):83.

23. Institute of Medicine (US) Committee on the Economics of Antimalarial Drug (2004). Arrow KJ, Panosian C, Gelband H (eds.). Saving lives, buying time : economics of malaria drugs in an age of resistance. National Academies Press.

24. Kenyon RL, Wiesner JA, Kwartler CE (1 April 1949). "Chloroquine manufacture". Industrial & Engineering Chemistry. **41** (4): 654–662.

25. Kim EL, Wüstenberg R, Rübsam A, Schmitz-Salue C, Warnecke G, Bücker EM, et al. (April 2010). "Chloroquine activates the p53 pathway and induces apoptosis in human glioma cells". Neuro-Oncology. **12** (4): 389–400.

26. Kouznetsov VV, Amado Torres DF (September 2008). "Antimalarials: construction of molecular hybrids based on chloroquine". Universitas Scientiarum. **13** (3): 306–320.

27. Kurup P, Zhang Y, Xu J, Venkitaramani DV, Haroutunian V, Greengard P, et al. (April 2010). "Abeta-mediated NMDA receptor endocytosis in Alzheimer's disease involves ubiquitination of the tyrosine phosphatase STEP61". *The Journal of Neuroscience*. **30** (17): 5948–5957.

28. Lin JW, Spaccapelo R, Schwarzer E, Sajid M, Annoura T, Deroost K, et al. (June 2015). "Replication of Plasmodium in reticulocytes can occur without hemozoin formation, resulting in chloroquine resistance" (PDF). The Journal of Experimental Medicine. **212** (6): 893–903. (PDF) from the original on 22 September 2017. Retrieved 4 November 2018.

29. Ling Ngan Wong A, Tsz Fung Cheung I, Graham CA (February 2008). "Hydroxychloroquine overdose: case report and recommendations for management". European Journal of Emergency Medicine. **15** (1): 16–18. Smith

ER, Klein-Schwartz W (May 2005). "Are 1-2 dangerous? Chloroquine and hydroxychloroquine exposure in toddlers". *The Journal of Emergency Medicine*. **28** (4): 437–443.

30. Manson P, Cooke G, Zumla A, eds. (2009). Manson's tropical diseases (22nd ed.). [Edinburgh]: Saunders. p. 1240. . Archived from the original on 2 November 2018. Retrieved 9 September 2017.

31. Martin RE, Marchetti RV, Cowan AI, Howitt SM, Bröer S, Kirk K (September 2009). "Chloroquine transport via the malaria parasite's chloroquine resistance transporter". Science. **325** (5948): 1680–1682.

32. McDougald LR, Cervantes HM, Jenkins MC, Hess M, Beckstead R (22 November 2019). "Protozoal Infections". Diseases of Poultry (14 ed.).

33. Mittra RA, Mieler WG (2013). "Chapter 89 – Drug Toxicity of the Posterior Segment". Retina (Fifth ed.). W.B. Saunders. pp. 1532–1554.

34. Munoz-Bellido JL, Munoz-Criado S, Garcìa-Rodrìguez JA (April 2000). "Antimicrobial activity of psychotropic drugs: selective serotonin reuptake inhibitors". *International Journal of Antimicrobial Agents*. **14** (3). *International Society of Chemotherapy (Elsevier):* 177–180.

35. Plowe CV (2005). "Antimalarial drug resistance in Africa: strategies for monitoring and deterrence". Malaria: Drugs, Disease and Post-genomic Biology. Current Topics in Microbiology and Immunology. Vol. 295. Springer. pp. 55–79.

36. Pou S, Winter RW, Nilsen A, Kelly JX, Li Y, Doggett JS, et al. (July 2012). "Sontochin as a guide to the development of drugs against chloroquine-resistant malaria". Antimicrobial Agents and Chemotherapy. **56** (7): 3475–3480.

37. Projean D, Baune B, Farinotti R, Flinois JP, Beaune P, Taburet AM, et al. (June 2003). "In vitro metabolism of chloroquine: identification of CYP2C8, CYP3A4, and CYP2D6 as the main isoforms catalyzing N-desethylchloroquine formation". Drug Metabolism and Disposition. **31** (6): 748–754.

38. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R (November 2003). "Effects of chloroquine on viral infections: an old drug against today's diseases?". The Lancet. Infectious Diseases. **3** (11): 722–727.

39. Shafik SH, Cobbold SA, Barkat K, Richards SN, Lancaster NS, Llinás M, et al. (August 2020). "The natural function of the malaria parasite's chloroquine resistance transporter". Nature Communications. **11** (1): 3922.

40. Sneader W (2005). Drug Discovery. A History. Wiley. The American Society of Health-System Pharmacists. Archived from the original on 8 December 2015. Retrieved 2 December 2015.

41. Tönnesmann E, Kandolf R, Lewalter T (June 2013). "Chloroquine cardiomyopathy - a review of the literature". Immunopharmacology and Immunotoxicology. **35** (3): 434–442.

42. Tripathi KD (2003). Essentials of Medical Pharmacology (fifth ed.). Jaypee Brothers Medical Publisher Ltd. pp. 739–740.

43. Uhlemann AC, Krishna S (2005). "Antimalarial Multi-Drug Resistance in Asia: Mechanisms and Assessment". Malaria: Drugs, Disease and Post-genomic Biology. Current Topics in Microbiology and Immunology. Vol. 295. Springer. pp. 39–53.

44. Ullberg S, Lindquist NG, Sjòstrand SE (September 1970). "Accumulation of chorio-retinotoxic drugs in the foetal eye". Nature. **227** (5264): 1257–1258.

45. Vaziri A, Warburton B (1994). "Slow release of chloroquine phosphate from multiple taste-masked W/O/W multiple emulsions". Journal of Microencapsulation. **11** (6): 641–648.

46. Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ (November 2010). "Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture". PLOS Pathogens. **6** (11): e1001176.

47. Walker O, Birkett DJ, Alván G, Gustafsson LL, Sjöqvist F (March 1983). "Characterization of chloroquine plasma protein binding in man". British Journal of Clinical Pharmacology. **15** (3): 375–377.

48. World Health Organization (2019). World Health Organization model list of essential medicines: 21st list 2019. Geneva: World Health Organization. . WHO/MVP/EMP/IAU/2019.06.

49. Xue J, Moyer A, Peng B, Wu J, Hannafon BN, Ding WQ (1 October 2014). "Chloroquine is a zinc ionophore". PLOS ONE. **9** (10):10918