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Design, synthesis and antibacterial activity of novel metal complex of 3-amino-2-methyl 6-1odo quinazolin-4(3H)-one

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Abstract

Introduction: 4(3H)-quinazolinone rings have been reported to possess different biological activities such as antibacterial, antifungal, antitubercular, antiviral, anticancer. These activities also include antihypertensive, diuretic, antimicrobial, pesticidal, anticonvulsant, anaesthetic and sedative activities, anti-malarial, and anti-diabetic.The above observations and findings stimulated my interest to synthesize these novel, Co (ll) , Cu (ll) and Zn (ll) complexes of 3-amino-2-methyl-6-lodo-quinazolin-4 (3H)-one compounds.

Methods: A new Ligand 3-amino-2-methyl 6-Iodo quinazolin-4(3H)-One (L) has been synthesized in good yield by the reaction of methyl 2-amino 5-Iodo benzoate with acetic anhydride, then replace the oxygen with nitrogen of hydrazine. When the ligand react with Co (11), Zn (11) and Cu (11) new complexes are formed. The chemical structure of all prepared compounds were characterized by elemental analysis, IR, UV/visible, ^{1}H-NMR, ^{13}C-NMR, and GCMS, moreover, molar ration M: L were also determined. The free Ligand and their metal complexes were tested in vitro against a number of *microorganisms, gram positive bacteria (Staphylococcus aureus, Bacillus species and Enterococcus feacalis)*, gram negative bacteria *(Escherichia coli, Klebsiella pneumonia, and pseudomonas aeruginosa)* and fungi (*Candida albicans)* in order to assess their antibacterial properties. All our complexes showed considerable activity against all bacteria.

Conclusions: From our findings, all the complexes synthesized have higher activities against the test microorganisms as compared to the ligand activity.

Keywords: 3- amino-2-methyl-6-Iodo quinazolin-4(3H)-One; Metal complexes; 2-amino 5-Iodo benzoate; Nucleophile; Antimicrobial activity; Synthesis; 2-methyl 6-Iodo 4H-benzo [D][1;3]-Oxazin-4-one

1 Introduction

Bacterial and fungal infections have been for many centuries a major cause of death in humans. It was found in late 19th century that many common diseases are caused by microscopic pathogens which led to introduction of antiseptic procedures in order to diminish mortality related to postsurgical infections. Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. Among heterocyclic compounds five-membered heterocycles constitute a wide and differentiated group with broad spectrum of biological activity. Compounds from this class are present in nature as constituents of nucleic acids, some important amino acids, alkaloids and hormones. This paper presents the information regarding the Heterocyclic compounds that constitute the largest family of organic compounds. These are extremely important with wide array of synthetic, pharmaceutical and industrial applications [1].

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Quinazoline are well known and important nitrogen containing heterocyclic compound made chemical formula C8H6N2 and various methods have been worked out for their synthesis. Quinazoline has become a popular topic up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring having due to its manifold uses. Numerous quinazoline derivatives have been found to possess a broad spectrum of biological activities, which stimulated the research activity in this field. Quinazolines and its derivatives represent one of the most active classes of compounds, which possess wide range of biological activities like anti-bacterial, analgesic, anti-microbial, anti-inflammatory, anticancer, and anti-hypertensive ,antifungal, anti-HIV, antioxidant, analgesic, anticonvulsant, antimalarial, antitumor, anti-tubercular activities [2].

Quinazolinone nucleus is a very attractive and useful scaffold in medicinal chemistry. It had been a pharmacophore in a wide variety of biologically active compounds. Peptides are key regulators in cellular and intercellular physiological responses and possess enormous promise for the treatment of pathological conditions. [3].

Wide range of quinazolinone biological properties including: antibacterial, anticancer, and anti-inflammatory activities encouraged us to synthesis some fused quinazolinone derivatives. The synthesized compounds were evaluated against six strains of bacteria (three Gram positive and three Gram-negative) and one strain of fungi. Overall results of antimicrobial tests showed that the compounds had better bacteriostatic activity against both the Gram positive and Gram-negative bacteria [4].

Owing to the significant biological activities, quinazoline derivatives have drawn more and more attention in the synthesis and bioactivities research. This review summarizes the recent advances in the synthesis and biological activities investigations of quinazoline derivatives [5].

Heterocyclic compounds form a major class of organic compounds. An enormous number of heterocyclic compounds are known today and this number is increasing rapidly due to their synthetic utility. Heterocyclic compounds dominate the field of biochemistry, medicinal chemistry, dyestuff, agricultural sciences and are of increasing importance in many other areas including polymers, adhesives and molecular engineering. Heterocyclic compounds played a vital role in the metabolism of all living cells. This review article covers the most active heterocyclic compounds that have shown substantial biological actions as antifungal, anti-inflammatory, antibacterial, antidepressant, antiulcer, antihelmintic and anticancer activity [6].

Promising antimicrobial and antifungal activities have been reported in many substituted quinazoline derivatives. Earlier, Quinazoline-4-ones has been a subject of extensive pharmacological evaluation, as well as, toxicological studies for antimicrobial and antifungal activities [7].

Interest in coordination chemistry is increasing continuously with the preparation of organic ligands containing a variety of donor groups [8 - 10], and it is multiplied into many folds when the ligand has biological importance [11, 12].

In this paper, we synthesized quinazolinone ligand and its complexes as potential anti-bacterial agents starting from Methyl 2-Amino-5-lodobenzoate. The validity of the hypothesis was confirmed through preliminary in vitro anti-microbial and anti-fungi screening of the ligand and its complexe.

2 Material and methods

2.1 Experimental

2.1.1 Chemistry

All reagents and solvents were purchased from sigma-Aldrich chemical supplier in Germany. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Buck scientific IR M500 instrument. The ^{1}H and ^{13} C N M R spectra were recorded in D M S O at 400 MHz with HAZ VOLATILE V2.M. Chemical shifts are reported in ppm relative to tetramethylsilane. Gas chromatography Mass (GC/MS) spectra were obtained on a Finingem MAT 44S nass spectrometer operating at 70eV. Elemental analysis agreed favourable with the calculated values. Analytical thin layer chromatography (TLC) was used to monitor the reactions.

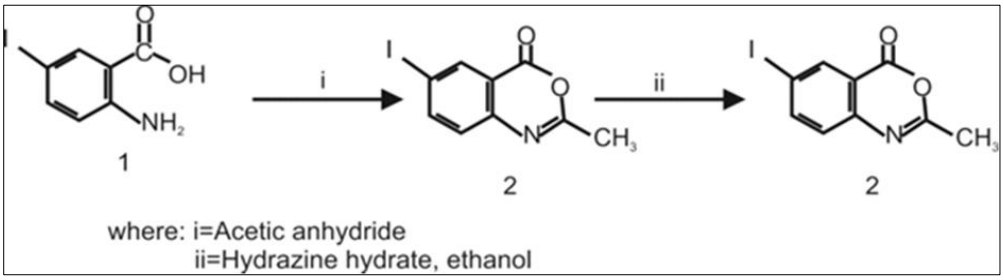
2.1.2 Synthesis of 2-methyl-6-Iodo 4H-benzo [D] [1, 3]-Oxazin-4-One (1) and Synthesis of 3-amino-2-methyl 6-Iodo quinazolin-4(3H)-One (2).

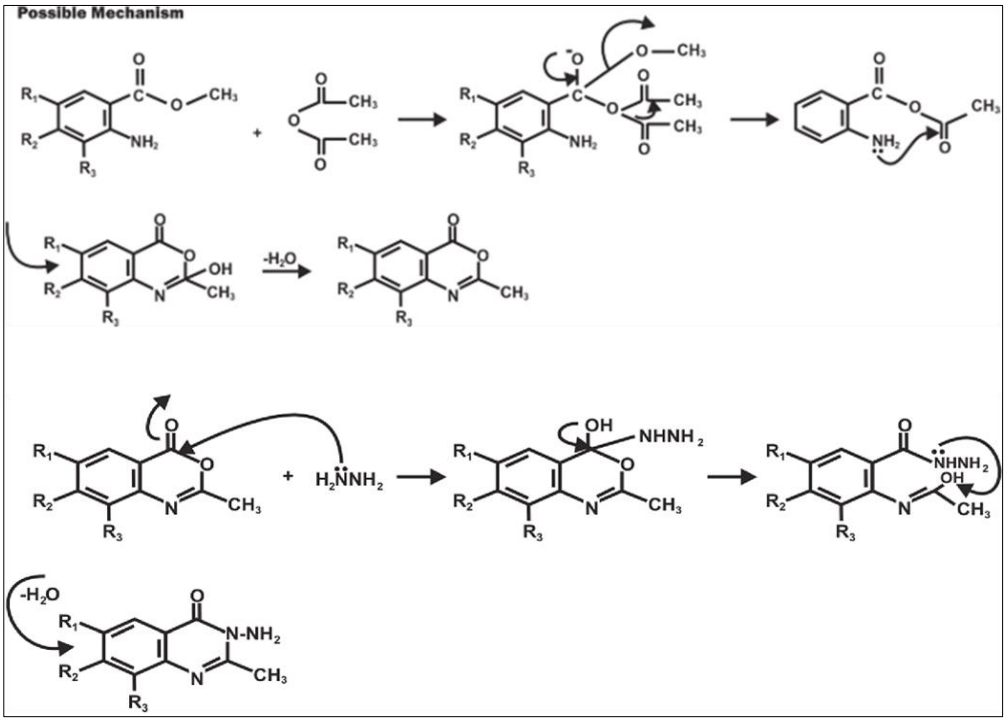
A mixture of 1 (0.01mole) and acetic anhydride (0.02mole) in 30 mL ethanol was heated under reflux with stirring using magnetic stirrer until the reaction mixture show no trace of starting material when TLC was developed (about 2 h). Ethanol was removed in vacuum and the solid product was recrystallized from proper solvent. Yield (75%), m.p 154-155^{0}C.

A mixture of equimolar amounts of benzoxazinone (1) (2.87g, 0.01mole) and hydrazine hydrate (1g, 0.02mole) was heated under reflux in absolute 30 mL ethanol and heated under reflux with stirring using magnetic stirrer until the reaction mixture showed no trace of starting material when TLC was developed (about 3 h). The white precipitate formed was then filtered, washed three times with 20ml of distilled water [20ml x 3]. The white crystals were dried and recrystallized from dimethylformamide (DMF) to give pure 3-amino-2-methylquinazolin-4 (3H) –one. Yield (80%, m. p. 158^{0}C.

2.1.3 Design, Synthesis and Bioassay of Novel Metal Complexes

A 0.0l mol) in 30 mL boiling ethanol was stirred using a magnetic stirrer until the reaction mixture showed no trace of starting material when by TLC data (about 3 h). The reaction mixture was concentrated in vacuum under reduced pressure using rotary evaporator. The solid product (white crystals) was dried and recrystallized from proper solvent. Yield, 1.20g (80%); mp, 97 – 99°C.





Where R1 = I, R2 =H, R3 =H

Figure 1 Synthesis of Metal Complexes

2.1.4 Synthesis of Metal Complexes

A mixture of hot ethanol solution of the Ligand (0.01 Mole) and hot ethanol solution (20 mL) of corresponding metal salt (0.005 Mole) was heated under reflux on a water bath with stirring using a magnetic stirrer until the reaction mixture showed no trace of starting material when the TLC was developed (5 hours). On cooling the content the coloured complex was separated out in each case. The product was filtered, washed with 50% ethanol and dried in vacuum over $P_4 O_{10}$ [13].

2.1.5 Study of Complexes Formation in Solution

Using the molar ratio method [14], Study of the Complexes of ligand with metal ions in solution of DMF as solvent were done in order to determine the (M: L) ratio. Various solutions at contant concentration (10^3M) of metal ion and Ligand (L) were prepared. From the relationship between the absorbance and the mole ratio, the (M/L) ratio were determined Table 1.

2.1.6 Evaluation of Antibacterial Activity

Antibacterial activities were done using t**he** Agar wall diffusion method [15]. Seven species: *Staphylococcus aureus*, (ATCC10145) *Bacillus species*, (NCTC 8236) *Enterococcus feacalis*, (NCTC 6571) *Escherichia coli*, (ATCC 25922) *Klebsiella pneumonia*, (NCTC 10418) *pseudomonas aeruginosa* (ATCC 10145) and *candida albicans* (ATCC24433) Stock cultures were used. The test organisms were obtained from the Pharmaceutical Microbiology Department of the University of Benin, Benin City, Nigeria. The test organisms were cultured overnight in nutrient broth, diluted to the turbidity of 0.5 MarFarland standard. Broth culture (0.5mL) were seeded on nutrient agar and allowed to dry. Then various concentrations of the compounds (20 – 640 mg/mL) were introduced. The culture plates were then incubated at 37^0c for 24hours. The results were taken by considering the zone of inhibition by the test compounds. Ciproflaxin (20mg/ML) was used as positive control while the vehicle (10% DMSO) was used as negative control [16]. Activity and inactivity were observed in accordance with the standard and accepted method. Figure 1.

3 Results and Discussion

The reaction of the methyl 2-amino 5-Iodobenzoate with acetic anhydride yield the cyclic compound 2-methyl 6-Iodo 4H-benzo [D] [1,3]-Oxazin-4-one as shown in the mechanism. The reaction of this compound with hydrazine yield the novel ligand 3-amino-2-methyl 6-Iodo quinazolin 4(3H)-one as shown in the mechanism

3.1 Synthesis of complexes

Mixture of Ligand and metal ions in 1 : 2 molar ratio were refluxed in an ethanol medium to produce the complexes.The ligand behaves as bidentate and coordinate through oxygen and nitrogen donor atoms. The complexes can be stored for a long period of time, being fairly stable at room temperature. In a similar study carried out by me [13] in 2015 the same procedure was used to synthesize 3-Amino 6,8-dibromo-2-methyl quinazolin-4(3H)-One Ligand and its complexes.

Table 1 Physical Characteristics of Complexes

No	Complexes	Colour	M.P.OC	Yields (%)	M.L
C1	CuL2 U2	Brown	216-219	86	1:2
C2	ZnL2 U2	White	245-243	81	1:2
C3	CoL2 U2	Green	254-257	83	1:2

3.2 Elemental analysis

Elemental analysis of C, H and M contents (both theoretically calculated values and actual values) are in accordance with the formula ML_2CL_2 indicating that the ligand is neutral. This is due to the absence of any deprotonating agent during the synthesis. Generally, the complexes are soluble in common organic solvents. Table 2.

Table 2 Elemental Chemical Analysis Data of the Metal Complexes

Elemental Analysis							
No	**Complexes**	**Theoretical calculated values**			**Actual calculated values**		
		C%	H%	M%	C%	H%	M%
C1	CuL2U2	48.92	5.41	12.00	49.13	5.21	11.96
C2	ZnL2U2	45.04	5.39	13.11	45.10	5.14	12.93
C3	CoL2U2	44.59	5.12	12.27	44.11	5.21	11.93

3.3 Infrared Spectra

From this study and IR spectra of the ligand and its complexes, it shows that the ligand is bidentate, with the carbony-oxygen and nitrogen as coordination sites. The ring vibrations and C-H absorption make the spectra fairly complicated for complete assignment of individual bonds. The IR data are partly presented in Table 3. In the IR spectra of the complexes a considerable negative shift in V(C=O) is observed, indicating a decrease in the stretching force constant of the C=O bond as a consequence of co-ordination through the carbonyl-oxygen atom of the free base. The band which occurs at 1503cn-1 is attributed to V(C=N) azomethine mode [17 - 18] and remains unaffected after complexation. The band due to NH-stretching in free ligand occurs in the 3301cm^{-1} region, in the spectra of all the complexes. The band is shifted to lower frequency and appears in the 3205-3260cm^{-1} region indicating the presence of the N-atom of coordination.

Table 3 Infrared absorption frequencies (cm-1) of ligand and it complexes

No	**Complexes**	**V(NH)**	**V(C=N**	**V(C=O)**	**M-O**	**M-N**
L	C_9 H_8 N_3 IO	3301	1503	1678	-	-
C1	CuL_2U_2	3273	1536	1632	447	426
C2	ZnL_2U_2	3274	15.14	1620	430	487
C3	CoL_2U_2	3222	1514	1620	440	470

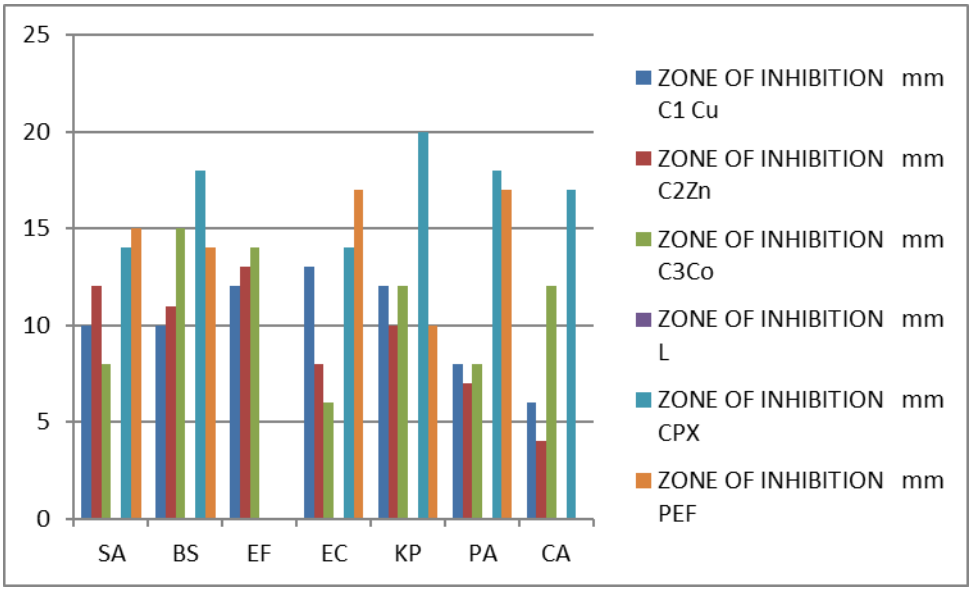
3.4 UV-Vis Spectra

The synthesized Ligand shows in DMF two absorption bands in the UV Spectrum. The first band observed at 240nm represents the (transition while the second and third bands (which have higher intensity than the first band due to conjugated system) appear at 330nm which represents the (transition. Generally, the bands of the newly synthesized complexes are either shifted to shorter or longer wavelengths than that of ligands, but the high intensity of these bonds is indicative for complex formation. The origin of the band observed at about 700nm in the electron spectra of complexes has been identified as d-d transition. In these spectra, the bands observed at 300-400nm could be assigned to nitrogen-metal charge transfer absorption. The electronic absorption bands for the ligand and complexes are classified into two distinct groups, those belonging to liquid transitions appeared in the UV region while d-d transitions appeared in the visible region. These transitions are assigned in relevance to the structures of complexes [13].

3.5 Evaluation of Antibacterial Analysis

3.5.1 Antibacterial Activity of Ligand and Tested Complexes against Tested Standard Organisation

- Control Drugs
- Ciprofloxicin (CPX) For Bacteria
- Ketonaxol (PEF) For Fungus
- Ligand (L), Complex 1 (4bCu), Complex 2 (4bZn), Complex 3 (4bCo)



Significantly different from Ligand at P< 0.05, values are in mm

Figure 2 The effect of Ligand toward studied bacteria. SA=Staphylococcus aureus, BS=Bacillus species, EF=Enterococcus feacalis, EC=Escherichia coli, KP=Klebsiella pneumonia, PA= pseudomonas aeruginosa and CA=candida albicans (4c = L)

All the compounds synthesized have antibacterial activities, but the metal chelates show higher activities than the parent Ligands. The higher activity of the metal chelates can be discussed on the basis of chelation theory. It is known that chelation makes the complexes more powerful and potent bactericidal agents, thus killing more of the bacteria than the ligand. It was discovered that, in a complex, the positive charge of the metal is partially shared with the donor atoms present in the ligands, and there may be -electron delocalization over the whole chelate [19]. This higher Lipophilic character of the metal chelate favours its permeation through the lipoid layer of the bacterial membranes. This higher lipophilic character is responsible for their enhanced antibacterial activity. It may be suggested that these complexes deactivates various cellular enzymes, which play a vital role in various metabolic pathways of these microorganisms. It has also been proposed that the ultimate action of the toxicant is the denaturation of one or more proteins of the cell, which as a result, impairs normal cellular processes. Other factors which also increase the activity, include solubility, conductivity and bond length between the metal and the ligand.

Activities of the ligand and metal complexes were tested against some human pathogenic microbes including Gram positive (*Staphylococcus aureus*, *Bacillus species* and *Enterococcus aureus)*, Gram negative *(Eschorichia coli, Klebsiella pneumonia*, *pseudomonas atriginosa)* and fungi *candida albicans* by the Agar wall diffusion method Figure 2. From the result obtained by the method, it was found that some of the tested complexes were highly active even at low concentrations.

3.6 Statistical analysis

All data were expressed as the mean ± SEM; the student's t-test was applied to determine the significance of the difference between the Ligand and the test compounds.

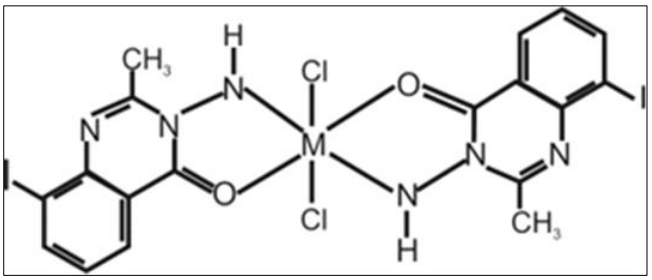


Figure 3 Proposed structure for the complexes

Abbreviations

- TLC: Thin Layer Chromatography
- SEM: Standard error mean
- IR: Infrared Spectra
- UV/Visible: UV-Visible Spectra
- ^{1}H NMR: Proton Nuclear Magnetic Resonance
- ^{13}C NMR: Carbon thirteen Nuclear Magnetic Resonance
- GCMS: Gas Chromatography Mass Spectroscopy
- L: Ligand
- 4bCu: Copper complex 1
- 4bZn: Zinc complex 2
- 4bCu: Colbert complex 3

4 Conclusion

In conclusion, all the complexes synthesized have higher activities against the test microorganisms as compared to the ligand activity. This is because, the Ligand act as bidendate uni-negative ligand, coordinated through one of nitrogen and oxygen. All the complexes are found to be mononuclear, based on the IR spectroscopy data. Based on the physicochemical and the spectra studies the proposed structure for the complexes is shown in Figure 3.

Compliance with ethical standards

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Disclosure of conflict of interest

The author declares there is no conflict of interest.

Author declarations

The author hereby declares that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by me.

Availability of data and material

No other data and material is available.

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Authors Contributions.

Dr. Osarumwense Peter Osarodion did the work while Dr. Marvis help in the spectral analysis of the samples.

Statement of ethical approval

Ethical approval, and the procedure used were approved by the ethical approval committee of Ondo State University of Science and Technology, Okitipupa, Ondo State, Nigeria.

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