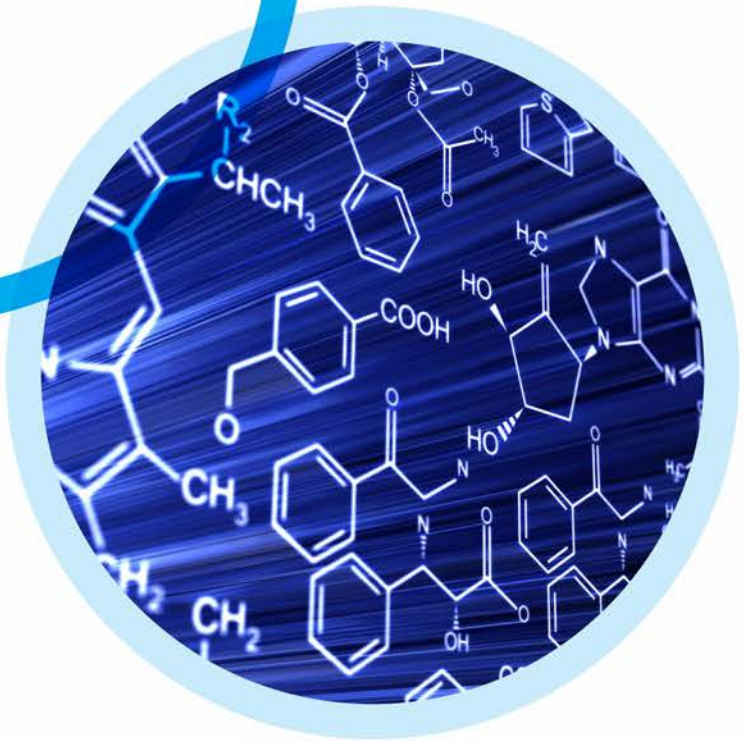

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Research Article
Novel Metal^{2+} complexes of N-(1,4-dihydro-1,4- oxonaphthalen-3-yl) pyrazine-2-carboxamide: Synthesis, structural characterization, magnetic properties and antimicrobial activities

[1]Chioma Festus, [2]Ozioma A. Ekpete and [3]Chioma D. Don-Lawson

[1]Inorganic Unit, Department of Chemistry, Ignatius Ajuru University of Education, PMB 5047, Rumuolumeni, Port Harcourt, Rivers State, Nigeria
[2]Analytical Unit, Department of Chemistry, Ignatius Ajuru University of Education, PMB 5047, Rumuolumeni, Port Harcourt, Rivers State, Nigeria
[3]Department of Science laboratory Technology, School of Science and Technology, Port Harcourt, Polytechnic, Nigeria

Abstract

Background and Objective: Heterocyclic nitrogen-bearing cyclic compounds mostly of amine derivatives have long been associated with biological and industrial applications as antimycobacterial, fungicides, growth inhibitors, perfumes, cosmetics, insecticides and to impact flavour in pharmaceuticals. Hence, this research study tends to synthesize and characterize divalent metal complexes of N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide and evaluate same for bactericidal and fungicidal properties. **Materials and Methods:** The Elementar instrument; model Vario EL III and micrOTOF-Q II 10390 was adopted for the elemental and electron impact mass spectra analyses at North-West University, South Africa. Proton and carbon-13 NMR spectra were determined on Bruker DRX-300, 300 MHz NMR spectrometer, while vibrational bands stood evaluated on Shimadzu FTIR 8000 spectrophotometer as KBr pellets. The Lambda 25 UV/visible spectrophotometer was used to obtain the electronic spectra. The *in vitro* antibacterial and antifungal activities of the synthesized compounds were investigated against the strains of *B. cereus*, *P. mirabilis*, *E. coli*, *S. aureus*, *K. oxytoca*, *P. aeruginosa*, *A. niger*, *A. flavus* and *R. stolonifer*. **Results:** A new Fe^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} complexes of LH type ligand, derived from the condensation of 2-hydroxy-1,4-naphthoquinone with pyrazine-2-carboxamide were synthesized. Physical and analytical (molar conductance and magnetic moment measurements, melting point and solubility determination, elemental analysis) and spectral (^{1}H-^{13}C-NMR, mass, UV-visible and FTIR) data were used to confirm the formation of the synthesized compounds. On spectral basis, the ligand LH, acts as bi-dentate, coordinating through the deprotonated secondary amide nitrogen and ketonic oxygen atoms, while analytical and spectral data indicate that all the complexes were mononuclear, non-electrolytic in dimethyl sulfoxide $(CH_3)_2SO$, coordinated with the ligand in 2L:1M molar ratio and also the presence of coordinated water molecule(s) in Fe^{2+}, Co^{2+} and Cu^{2+} complexes. Furthermore, tetrahedral geometry for Ni^{2+} and Co^{2+} and octahedral geometry for Fe^{2+} and Cu^{2+} complexes were proposed. **Conclusion:** Generally, the metal^{2+} complexes exhibited moderate to good activity against the microorganisms better than the metal free ligand in one form or the other. The studied cobalt and nickel complexes had the best antibacterial and antifungal activities against the screened microbes with inhibitory zones of 25.0 and 22.0 mm separately.

Key words: Naphthoquinone, pyrazine, mass spectrometry, antifungal, metal^{2+} complexes

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Corresponding Author: Chioma Festus, Inorganic Unit, Department of Chemistry, Ignatius Ajuru University of Education, PMB 5047, Rumuolumeni, Port Harcourt, Rivers State, Nigeria

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Poor hygiene and safety and environmental pollutions have led to increase in life-threatening infectious diseases. The latter in recent times have developed pathogenic resistance to known compounds/drugs through a number of macromolecular secretion mechanisms[1], i.e., mutation of their genome, trans-locating proteins and nucleoprotein complexes from the bacterial cytosol to the host cell, plasmid deoxyribonucleic acid (DNA) transfer from one cell to another, inactivation and efflux of antibiotics[2,3]. Hence, it has become necessary for new drugs with low molecular weights for easier diffusion across bacterial intracellular membranes[4], low toxicity with improved selectivity and broad spectrum activity to be designed and synthesized as to combat the numerous infectious diseases[5] ravaging humanity. *In vivo* research studies have shown that heterocyclic compounds bearing nitrogen and oxygen atoms and -C=N- groups are biologically and pharmacologically active agents[6-8] due to their high degree of binding affinity to biological systems[9]. For example 5-fluorouracil combined with bevacizumab is used for metastatic colorectal cancer treatment[10], N-[(1E)-(5-nitro-1-naphthyl) methylene]-1-[2-(trifluoromethyl) phenyl]methanamine has been reported operational antimalarial agent[11], etc. The compounds become complexes and are known to exhibit more bacteriostatic and pharmacologically significant activity upon chelation[12] due hyper conjugation and enhanced lipophilicity[13]. Pyrazines are naturally ubiquitous as part of various polycyclic compounds[14]. They make-up a vital sort of heterocyclic nitrogen-encompassing aromatic compounds, especially their amine analogues and have long been recognized to exhibit fascinating biological and/or industrial applications as anti-mycobacterial, fungicides, growth inhibitors and to impact flavour in pharmaceuticals, perfumes, cosmetics, insecticides, etc.[15-18]. Consequently, 2-hydroxyl-1,4-naphthoquinone have been incorporated to enhance pharmacological activity in different compounds/drugs due to their antitumor, allelopathic, entomological and antibacterial activity often attributed to both inter and intra molecular proton bonding[19-21]. Due to the enhanced pharmacological potentials of aminopyrazine-hydroxynaphthaldehyde ligands compared to their precursors, research interests have been more pronounced towards their compounds. However, transition metal complexes of the latter are lacking in literature. The exceptional antioxidant potentials of metallic assemblages often attributed to proton atom release to unchelated radicals, solitary electron transfer to chelated radicals and metallic chelation influence has gained a place in the treatment of chronic diseases. Design and synthesis of transition metal complexes for novel antibiotics or to improve on existing active antibiotic derivatives still appears the best practice and the largest contribution to medicinal therapeutics[22]. This research work is concerned with the syntheses of a new ligand; N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide and its divalent complexes. The compounds will be evaluated for various magnetic interactions. Finally, the potency of the bidentate LH and its divalent complexes as bactericidal and fungicidal pro-agents will be explored as a continuation of these research activities in discovering lead compounds for antibiotics[9,23]. This research study is tends to synthesize and characterize divalent metal complexes of N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide and evaluate same for bactericidal and fungicidal.

MATERIALS AND METHODS

The used reagents; $Co^{2+}(Cl)_2.4H_2O$, $Fe^{2+}SO_4.7H_2O$, $Ni^{2+}(Cl)_2.4H_2O$,$Cu^{2+}(Cl)_2.2H_2O$,2-hydroxy-1,4-naphthoquinone (HNQ), pyrazine-2-carboxamide (PCA) and $(C_2H_5)_3N$ were all procured from Aldrich and BDH companies. The solvent, CH_3OH was distilled using standard methods[24]. All laboratory experiments were carried out within 2 months (February-March, 2019) at the research laboratory of the Department of Chemistry, Ignatius Ajuru University of Education, Rivers State, Nigeria. The characterizations were done at Nelson Mandela Metropolitan University, South Africa while the antimicrobial studies were carried out at the microbiology laboratory of University of Ibadan, Oyo State Nigeria.

Syntheses

Synthesis of N-(1,4-dihydro-1,4-oxonaphthalen-3-yl) pyrazine-2-carboxamide: Established reaction procedure [25] was followed in the synthesis of the ligand, LH. Equimolar amount of pyrazine-2-carboxamide (0.0183 mol, 2.00 g) was neatly added to a stirring 15 mL CH_3OH solution of 0.0183 mol (3.192 g) of 2-hydroxy-1,4-naphthoquinone. The mixture stayed refluxed for 6 h at 60°C on a magnetic hot plate stirrer. Afterwards, yellow shade solid product N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide was obtained on cooling in ice (19°C), filtered, recrystallized with cold CH_3OH and stored in desiccators over drying agents.

Synthesis of M^{2+} complexes: The $Fe^{2+}(SO_4).7H_2O$ (5.39 mmol, 0.149 g) dissolved in dehydrated CH_3OH, 10 mL was neatly dropped in bits into a stirring 10 mL $CH_3OH$of N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide (5.39 mmol, 3.00 g) at 50°C. About3 mL of $(C_2H_5)_3N$ was adopted to raise and stabilize the reaction to a pH of 9. Consequently, the resultant solution stood refluxed on magnetic-stirrer hot plate for 6 h with continuous stirring. The solid precipitates formed were collected by filtration, recrystallized with CH_3OH and stored over drying agents in a desiccators. The Co^{2+}, Ni^{2+} and Cu^{2+} complexes were all prepared from their chloride salts via the same procedure. All syntheses were carried out at the Chemistry Department, Ignatius Ajuru University of Education, Rumuolumeni, Port Harcourt, Rivers State, Nigeria.

Physical measurements: The analysis for elemental compositions were obtained on elementar instrument, model Vario EL III, while the electron impact mass spectra (EIMS) of the ligand, HL was recorded on micrOTOF-Q II 10390 at North-West University, South Africa. The elemental proportions of C, H, N existing in N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide (LH) and its metal^{2+} complexes were determined. The percentage metal ion contents in the complexes were obtained titrimetrically. Measurements for magnetic vulnerability stood determined for powdery metallic assemblages on a Johnson Matthey magnetic susceptibility apparatus with diamagnetic corrections calculated using Pascal's constants, proton and carbon-13 NMR spectra of the synthesized LH were determined on Bruker DRX-300, 300 MHz NMR spectrometer, while the chemical shifts were obtained with reference to the internal standard, tetramethylsilane (TMS) in $(CH_3)_2SO$-d6 as solvent. Vibrational bands (400-4000 cm^{-1}) for the compounds stood evaluated on Shimadzu FT-IR 8000 spectrophotometer as KBr pellets, while Lambda 25 UV/visible spectrophotometer was used to obtain the electronic spectra. Melting points (uncorrected) and molar conductance measurements were verified on Electro-thermal Temp-Mel melting point machine and Systronic Conductivity Bridge 304, respectively.

- N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide: Yield (69.30%), shade (Light Brown), melting point: 145-147°C, IR(cm^{-1}): νHH(3531_m), ArC-H(3052), νC=O(1676_s), νC=N(1641_s), νC-C(1588s), δC-H(1023), electronic (cm^{-1}): 27548 (n-π*) 31348, 37037(π-π*). Molecular weight (g moL^{-1}): 279.252. The ^{1}H-NMR (δ ppm): 6.149 (s, H_{15}), 7.76-7.83 (m, $H_{17\&18}$) and 7.90-7.98 (m, $H_{16\&19}$), 8.68 (s, H_6), 8.83 (s, H_5), 9.17 (s, H_3), 11.69 C-13NMR (75 MHz, $(CH_3)_2SO$-d_6) δ ppm: 111.00 (C_{15}), 125.96-125.42 ($C_{17,18}$), 131.91-130.59 ($C_{16,19}$), 133.24 ($C_{12,13}$), 134.49 (C_{10}), 143.39 (C_6), 145.10 (C_3), 147.40 (C_2), 159.58 (C_5), 165.08 (C_7=O), 181.29 (C_{11}=O) and 184.70 (C_{14}=O)
- $[Fe(L)_2(H_2O)_2]$: Molecular weight (g moL^{-1}): 648.36, yield% (64.06), shade: Sandy brown, mp: 320-322°C, FTIR(ν/cm^{-1}): 3428(OH), 3038(Ar-CH), 1633(C=O), 1591(C=N), 1564(C=C), 1400 (C-N),983(δC-H), 618 (Fe-N), 497(Fe-O), CHN(%)-Anal(Cald): C, 55.93 (55.52), H, 3.37(3.11), N, 13.82(12.96), %Fe (cald) 8.76 (8.61), electronic (cm^{-1}): 36918 (π→π*), 26064 (n→π*), 20530 ($^5T_{2g}\rightarrow{}^5B_{1g}$), 14502 ($^5T_{2g}\rightarrow{}^5A_{1g}$), μ_{eff}(B.M.): 5.09, mc (ohm^{-1} mol^{-1} cm^2): 12.03
- $[Co(L)_2].H_2O$: Molecular weight (g moL^{-1}): 633.434, yield% (52.90), shade: Sinopia brown, mp: 300-302°C, FTIR(ν/cm^{-1}): 3435(OH), 2925(Ar-CH), 1612(C=O), 1589(C=N), 1556(C=C), 1282, 1244(C-N), 986(δC-H), 523(Co-N), 424(Co-O), CHN(%)-Anal(Cald): C, 56.99(56.86), H, 3.05(2.86), N, 13.64(13.27), %Co (cald) 9.55(9.30), electronic (cm^{-1}): 45045 (CT), 29673 (n→π*), 18553 ($^4A_2\rightarrow{}^4T_1$(P)), 12788 ($^4A_2\rightarrow{}^4T_1$), μ_{eff}(B.M.): 4.31, mc (ohm^{-1} $mol^{-1}cm^2$): 10.57
- $[Ni(L)_2]$: Molecular weight (g mol^{-1}): 615.198, yield% (69.10), shade: Magenta red, mp: 167-170°C, FTIR(ν/cm^{-1}): 3040, 2928 (Ar-CH), 1625(C=O), 1587(C=N), 1564(C=C), 1372, 1278(C-N), 9 94(δC-H), 549 (Ni-N), 451(Ni-O), CHN(%)-Anal(Cald): C, 59.03 (58.51), H, 2.88 (2.62), N, 13.91(13.66), %Ni (cald) 9.46(9.54), electronic(cm^{-1}): 43691 (C.T), 31016 (π→π*), 25060 (n→π*), 16207 ($^3T_1\rightarrow{}^3A_2$), 12626 ($^3T_1\rightarrow{}^3T_2$), μ_{eff}(B.M.): 3.98, mc ($ohm^{-1}mol^{-1}cm^2$): 9.14
- $[Cu(L)_2(H_2O)_2]$: Molecular weight (g moL^{-1}): 656.06, yield% (56.45), shade: Rose-quartz gray, mp: 206-208°C, FTIR(ν/cm^{-1}):3425(OH), 3032, 2956(Ar-CH), 1657(C=O), 1627(C=N), 1591, 1559(C=C), 11369, 1260(C-N), 984(δC-H), 572(Cu-N), 452(Ni-O), CHN(%)-Anal(Cald): C, 55.77(54.87), H, 3.13(3.07), N, 12.85 (12.81), %Cu (cald) 9.91(9.69), Electronic (cm^{-1}): 48543 (C.T), 27855 (n→π*), 20964 ($^2E\rightarrow{}^2T_2$), μ_{eff}(B.M.): 2.29, mc (ohm^{-1} mol^{-1} cm^2): 15.05

Pharmacological studies

Antibacterial activity: The N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide and its metallic assemblages were verified *in vitro* against 4 Gram-negative and 2 Gram-positive bacteria at the microbiology laboratory, University of Ibadan, Nigeria. The bacteria species were carefully selected due to their pharmacological importance: *K. oxytoca*, a rod shaped Gram-negative bacterium is responsible for various tract infections (urinary, respiratory and gastrointestinal), the intestinal bacterium, *E. coli*, which

causes bloody diarrheal is often linked with hemolytic uremic syndrome, a toxic substance that destroys red blood cells, leading to kidney injury/failure and even death of the host, *P. mirabilis* is one of the most common infectious causing bacteria associated with both wound, eyes and burn infections, catheter-associated urinary tract infections, prostatitis, etc; *P. aeruginosa*, a multi-antibiotic resistant pathogen known for its ubiquity causes various sepsis syndromes, pneumonia, urinary tract and; skin and soft tissue infections, food borne illnesses bacterium *B. cereus* causes severe nausea, vomiting, chills, abdominal pain and diarrhea in children; while *S. aureus*is associated with different skin infections such as cellulitis, folliculitis, impetigo and boils[26-29].

Reported procedure was adopted for the antibacterial screening of the compounds[30] with slight modifications. Nutrient agar medium was used to grow the bacteria organisms for 24 h at 35°C adopting the agar well diffusion technique[31]. The surfaces of the Muller Hinton's agar in petri cups remained homogeneously inoculated with 0.2 mL of the 24 h grown test bacteria cultures with pasteurized cotton pads. After which, holes were made into the solidified agar using a sterile cork borer (7 mm). Consequently, $(CH_3)_2SO$ solution of the test compounds (10 mg mL^{-1} each) was poured into the dug holes. The cups stood equilibrated for 30 min prior to incubation at 35°C for 24 h. Inhibition growth zones in diameter (mm) were acquired as the sensitivity of the bacterial organisms to the test/synthesized compounds. The bactericide 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid (ciprofloxacin), a second generation fluoroquinolone was used as standard drug concomitantly with the test samples. The growth of the tested microbes was not influenced by the concentration of $(CH_3)_2SO$ used for the medium. The experimentations were carried out in duplicates and values <7 mm were considered inactive.

Antifungal activity: The *in vitro* antifungal actions of the synthesized compounds were measured using disc technique. Unpeeled but washed-sliced potatoes (250 g), dextrose (25 g) and agar (25 g) in 1250 mL purified H_2O were used to prepare the 'potato dextrose agar (PDA) medium' adopted for the antifungal screening. The antifungal screening (*in vitro*) was carried out against *A. niger*, *A. flevus* and *R. Stolonifer*. The pure cultures of fungal isolates were uniformly inoculated on the surface of the PDA solution petri dish. The 15 µg of the stock solutions of each test sample (1 mg mL^{-1}) prepared by liquefying 10 mg of the synthesized compound in 10 mL of $(CH_3)_2SO$ solvent was poured into a 6 mm holes dug on the PDA with a 6 mm disinfected metallic borer. All the plates inoculated were incubated at 35°C for 48 h after which inhibition zone growth in diameter (mm) was obtained as the sensitivities of fungal isolates toward the test compounds with antibiogram zone scale. All antifungal activities were determined as mean of 3 replicates. The drug fluconazole was used as standard, while $(CH_3)_2SO$ was used as a negative control and all values <6 mm were considered inactive.

RESULTS AND DISCUSSION

General: Figure 1 and 2 showed the synthesized ligand and its M^{2+} complexes. The synthesized compounds were generally coloured solids that are soluble in $(CH_3)_2SO$ and dimethyl formamide but fairly soluble in other organic solvents, stable in air and amorphous in nature. Analytical and elemental data suggest molar ratio 1:2 of M-L corroborating stoichiometry of the sort $[M(L)_2]$ for Ni^{2+}, $[M(L)_2(H_2O)_2]$ for Fe^{2+} and Cu^{2+} and $[M(L)_2]H_2O$ for Co^{2+} complexes, respectively, (L = deprotonated ligand). Varied melting points were observed for compounds which were distinct from their starting materials, while the molar conductance values obtained in $(CH_3)_2SO$ were very low to accommodate dissociation of the complexes (9.14-15.05 ohm^{-1} cm^2 moL^{-1}), confirming the non-electrolytic nature of the complexes. The elemental analyses results for the compounds and the percentage metal compositions in the $metal^{2+}$ complexes indicate good agreement between the experimental and theoretical values.

Infrared spectra: The apportioning of bands within M^{2+} complexes were made by relating their spectra to that of the LH and documented works on related assemblages as to ascertain coordination atoms of LH involved in complexation[32-34]. The -NH band of LH was detected at 3531 cm^{-1} but disappeared in the spectra of the complexes corroborating deprotonation of the N-H moiety and possible chelation of the N-atom to M^+ ions[35]. However, the bands at 3424-3435 cm^{-1} with the exclusion of the Ni^{2+} complex were apportioned to νO–H of coordinated/hydrated water molecules[9]. The LH band at 3052 cm^{-1} allotted to cyclic C–H stretching vibrations still remained in the metal complexes but shifted with ±5-18 cm^{-1} owing to complexation effect[25]. Similarly, shrill to average bands detected at 1676, 1641 and 1588 cm^{-1} in LH spectrum were attributed to uncoordinated νC=O, pyrazinyl ring ν=N and cyclic νC=C stretching vibrations separately. The bands were still observed in the spectra of the M^{2+} complexes however suffered lesser frequency shifts to 1657-1611, 1626-1587, 1591-1564 cm^{-1}, thus confirming complexation of LH to M^{2+} ions[35]. The δC-H vibration around

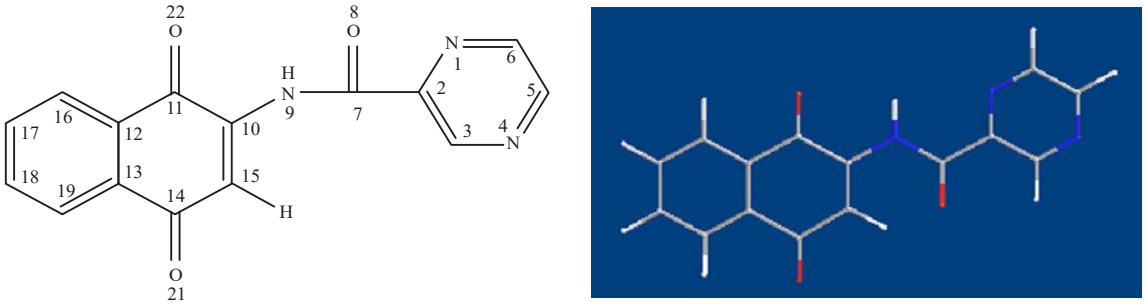

Fig. 1: N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide, HL

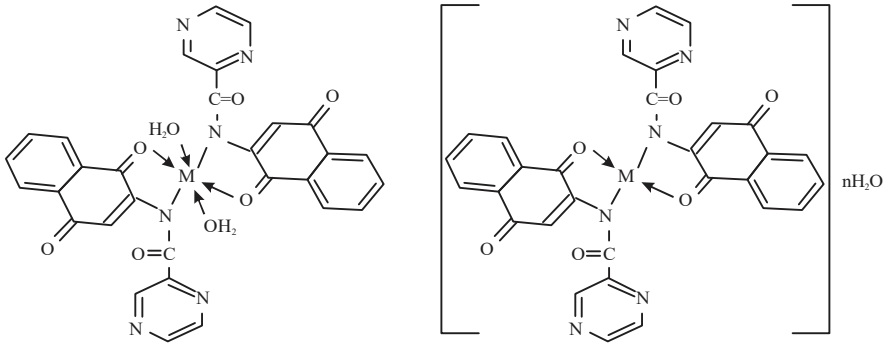

Fig. 2: Proposed structure of the metal^{2+} complexes

1023 cm^{-1} displayed by LH, was detected at the array of 994-982 cm^{-1} in the complexes due to the pseudo-cyclic status of the chelates[35]. Additional proof of chelation was the appearance of non-LH bands arising from ν(M-O) and ν(M-N) at 497-423 and 619-522 cm^{-1} stretching vibrations correspondingly in the spectra of the complexes owing to the participation of carbonyl oxygen and deprotonated amine nitrogen atoms coordination to the M^{+} ions.

Electronic spectra and magnetic moment measurements: The electronic spectra of LH, N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide and its Fe^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} complexes were recorded as solid reflectance. Absorption bands of the compounds which are direct consequences of electrons' movement within the LH ($n\rightarrow\pi$, $n\rightarrow\pi^*$), M^{2+} complexes (d-d transitions) and transitions of electron(s) transfer (L→M and M→L electron transfer) have been determined. The ligand was characterized by two fold peaks in the ultraviolet spectrum at 27548 cm^{-1} and 31348-37037 cm^{-1} allotted to $\pi^*\leftarrow n$ and $\pi^*\leftarrow\pi$ transitions separately[35].

Similarly, the electronic spectrum of cobalt^{2+} complex exhibited dual absorptions within the ultraviolet province at 29673 and 45045 cm^{-1} assignable to $\pi^*\leftarrow n$ and electron transfer (CT) transitions, respectively. The visible spectra of cobalt ($3d^7$) complexes both in octahedral and tetrahedral environments with ^4T and ^4A ground terms are expected to display 3 transitions each with the absorption bands of the latter appearing at lower frequencies and more intense[36,37]. In the ligand field spectrum of the cobalt complex studied, characteristic absorption bands at 12788 and 18553 cm^{-1} were detected. The observed bands above corroborates 4 coordinate tetrahedral geometry with $^4A_2\rightarrow{}^4T_1$ (υ_2) and $^4A_2\rightarrow{}^4T_1(P)$ (υ_3) transitions individually[35,37] corresponding to the electronic configuration of e^4t^3 (high spin). However, the band within 5000-6000 cm^{-1} frequently linked to the transition $^4A_2\rightarrow{}^4T_2$ in 4-coordinate Co^{2+} assemblages remained unseen as it tailed into the vibrational region[38]. The apportioning of high spin tetrahedral structural assemblage to the Co^{2+} complex studied was validated by the experimental μ_{eff} value of 4.31 B.M since μ_{eff} of Co^{2+} complexes are projected to be greater than spin-only value of 3.87 B.M for tetrahedral complexes due to orbital contributions[39].

The ultraviolet spectrum of the synthesized copper^{2+} complex had 2 absorptions at the 27855 and 48543 cm^{-1} assignable to $\pi\leftarrow$n and charge transfer transitions. Regular divalent tetrahedral copper complexes usually display lone broad band below 10000 cm^{-1}, while their octahedral counterparts often exhibits lone broad band above 10000 cm^{-1} and square-planar complexes are associated with two bands between 10000-20000 cm^{-1}. Furthermore, copper^{2+} ligand field spectra are more complicated to interpret due to unsymmetrical overlapping bands resulting from distortions[40]. Distortions in Cu^{2+} complexes are direct result of uneven sharing of electrons in the e_g set of the 3d orbitals[41]. Single absorption band around 20964 cm^{-1} was detected in the visible spectrum of the divalent copper complex studied and was consequently octahedral with band assigned as $^2E\rightarrow{}^2T_2$. A μ_{eff} of 1.9-2.2 B.M. is usually observed for mono-nuclear divalent copper assemblages[42]. This complex had a μ_{eff} of 2.29B.M and corroborates the geometry.

The electronic spectrum of Fe^{2+} complex displayed double absorptions each in the ultraviolet and visible regions. The absorptions around 26064 and 36918 cm^{-1} were corroborative with $\pi^*\leftarrow$n and $\pi^*\leftarrow\pi$ transitions, while those observed at 14502 and 20530 cm^{-1} corroborates high spin octahedral geometry and were consequently apportioned to $^5T_{2g}\rightarrow{}^5A_{1g}$ and $^5T_{2g}\rightarrow{}^5B_{1g}$ transitions. Divalent iron bearing $3d^6$ electron configuration exhibits μ_{eff} of 5.20 B.M for high spin octahedral complexes. The experimental μ_{eff} of 5.09 B.M. was supportive of this geometry [43].

Three dissimilar absorptions stood observed within the ultraviolet section of the nickel^{2+} complex which corroborates $\pi^*\leftarrow$n, $\pi^*\leftarrow\pi$ and electron transfer transitions. The visible spectrum of nickel assemblages consisting $3d^8$ electron formations with 3F and 3P terms experience basic switches square planar to tetrahedral or to octahedral[44]. Consequently, $^3T_1$ ground term nickel^{2+} complexes of tetrahedral geometry exhibits absorptions around 12000, 17500 and 21000 cm^{-1} ascribed to $^3T_1(F)\rightarrow{}^3T_2(F)$, $^3T_1(F)\rightarrow{}^3A_2(F)$ and $^3T_1(F)\rightarrow{}^3T_1(P)$ transitions, while square planar divalent nickel complexes are expected only to display single characteristic band around 20000 cm^{-1} due to $^1A_{1g}(D)\rightarrow{}^1A_{2g}(D)$ transition. The visible spectrum of the nickel^{2+} complex studied displayed two absorption bands at 12626 and 16207 cm^{-1} consistent tetrahedral geometry typical of the transitions; $^3T_1(F)\rightarrow{}^3T_2(F)$ and $^3T_1(F)\rightarrow{}^3A_2(F)$. The observed μ_{eff} value of 3.98 B.M corroborates the assigned tetrahedral geometry.

^{1}H NMR and^{13}C NMR spectroscopy: The NMR spectra of the ligand were measured in $(CH_3)_2SO$-d_6 and all hydrogen atoms were observed in their predictable regions. The naphthoquinone phenyl protons (H_{15}, $H_{17\&18}$ and $H_{16\&19}$) stood observed as a singlet at 6.149 ppm, multiplet at 7.76-7.83 ppm and multiplet at 7.90-7.98 ppm separately. Equally, the cyclic hydrogen atoms' peaks of the PCA assemblage remained recognised as singlets at 8.68, 8.83 and 9.17 ppm for H_6, H_5 and H_3 atoms. The peak arising from O-H group common of HNQ remained absent in LH spectrum rather a broad peak at 11.69 ppm typical of amide (s, H, CON_9H) moiety was noticed. The broad amide N-H peak validates the suggested ketoimine tautomeric assemblage for LH in solution rather than its enolimine tautomer. The ^{13}C NMR spectrum showed resonance signals of the naphthoquinone carbonyl groups (C_{14}, C_{11}) at 184.70 and 181.29 ppm while the signal at 165.08 was typical of the secondary amide carbon atom (C_7). Furthermore, observed resonance signals at 134.49, 133.24, 131.91-130.59, 125.96-125.42 and 111.00 ppm were attributed to C_{10}, $C_{12\&13}$, $C_{16\&19}$, $C_{17\&18}$ and C_{15} atoms, respectively of the naphthoquinone moiety. However, the resonance signals due to C_5, C_2, C_3 and C_6 of the pyrimidine moiety were seen at 159.58, 147.40, 145.10 and 143.39 ppm accordingly.

Mass spectra: Mass spectrometry was acquired for LH, N-(1, 4-dihydro-1, 4-oxonaphthalen-3-yl) pyrazine-2-carboxamide to as certain its molecular weight and patterns of fragmentation. Obtained molecular ion peak of m/e 280.047 corroborates the formula weight (FW) for the proposed ligand structure which was in agreement with the calculated m^+ value. The low intensity of the molecular ion with extra mass unit may be attributed to cleaved bonds and consequently presence of ^{13}carbon isotope. The ligand mass spectrum also displayed (m/z) peaks at 175, 227 and 263 corresponding to $[C_{13}H_5N]$, $[C_{13}NO_3H_7]$ and $[C_{15}H_9N_3O_2]$ fragments, respectively.

Antibacterial studies: The antibacterial activity of LH, N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide and its metal^{2+} complexes (Fig. 3) tested *in vitro* against Gram-positive microbes "*S. aureus* and *B. cereus*" and Gram-negative microbes "*P. mirabilis*, *K. oxytoca*, "*E. coli* and "*P. aeruginosa*" are presented in Table 1. Generally, the metal^{2+} assemblages demonstrated adequate to excellent antibacterial actions towards the microorganisms better than the metal free ligands in one form or the other. This could be attributed to chelation effect which increases antimicrobial activities mainly arising from partial distribution of oxidative charge resident on the Mn^+ with chelate atoms of LH and probable electron delocalisation on the cyclic rings[35]. Though, Ni^{2+} and Fe^{2+} complexes remained insensitive against *B. cereus*, *E. coli*, *K. oxytoca* and *S. aureus* and *S. aureus* and *B. cereus*. The sensitivity of Fe^{2+} and Ni^{2+} complexes could be accredited to production of potent protein toxins by the

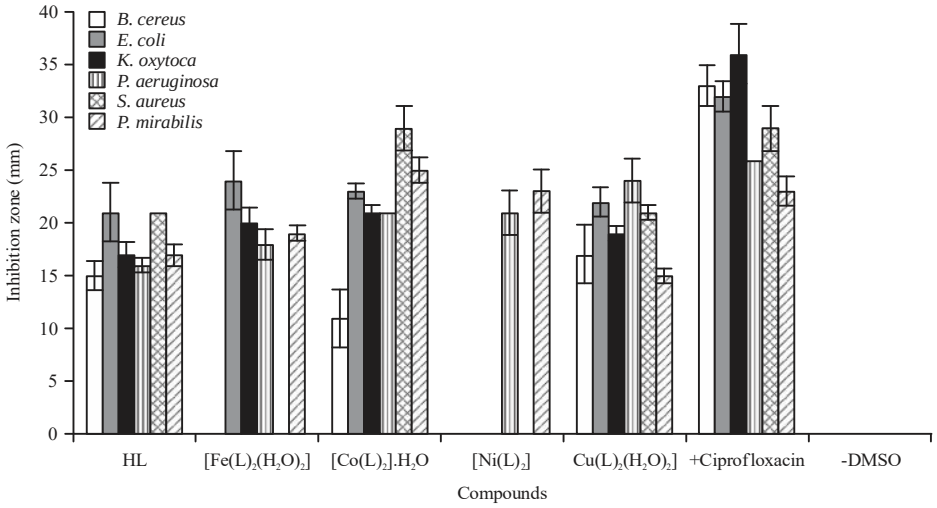

Fig. 3: Antibacterial actions' column chart for the synthesized compounds

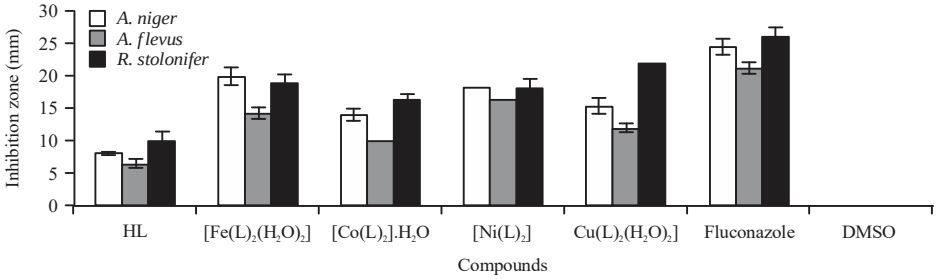

Fig. 4: Vertical bar graph of the antifungal actions of the synthesized compounds

Table 1: Antimicrobial data for LH and its M^{2+} complexes

	Antibacterial activity						Antifungal activity		
Compounds	*B. cereus*	*S. aureus*	*K. oxytoca*	*P. aeruginosa*	*E. coli*	*P. mirabilis*	*A. niger*	*A. flevus*	*R. stolonifer*
LH	15.0±1.4	2.01±0.0	17.0±2.1	16.0±0.7	21.0±2.8	17.0±1.0	8.1±0.2	6.5±0.7	10.0±1.4
$[Fe(L)_2(H_2O)_2]$	0.0±0.0	0.00±0.0	20.0±1.4	18.0±1.4	24.0±2.8	19.0±0.7	20.0±1.4	14.2±0.9	19.0±1.2
$[Co(L)_2].H_2O$	11.0±2.8	29.00±2.1	21.0±0.7	21.0±0.0	23.0±0.7	25.0±1.2	14.0±0.9	10.0±0.0	16.4±0.7
$[Ni(L)_2]$	0.0±0.0	0.00±0.0	0.0±0.0	21.0±2.1	0.0±0.0	23.0±2.1	18.2±0.0	16.4±0.0	18.2±1.4
$[Cu(L)_2(H_2O)_2]$	17.0±2.8	21.00±0.7	19.0±0.7	24.0±2.1	22.0±1.4	15.0±0.7	15.4±1.2	12.0±0.7	22.0±0.0
$^{+}$Ciprofloxacin/fluconazole	33.0±1.9	29.00±2.1	36.0±2.8	26.0±0.0	32.0±1.4	23.0±1.4	24.5±1.2	21.2±0.9	26.0±1.4
$-(CH_3)_2SO$	0.0±0.0	0.00±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0

bacterial organisms to activate their cell surface proteins which in turn prevent adequate permeation of the metal complexes into the bacteria cells and lesser lipophilicity of the complexes which also decreases their penetration through the lipid cell membrane[45,46]. Thus, the Co^{2+} complex presented greater actions compared to LH toward *S. aureus* (29.0 mm), *P. Aeruginosa* and *K. oxytoca* (21.0 mm), *E. coli* (23.0 mm) and *P. mirabilis* (25.0 mm). Equally, Cu^{2+} complex demonstrated actions greater than LH against *B. cereus*, *E. coli*, *K. oxytoca* and *P. aeruginosa,* with inhibitory zones of 17.0, 22.0, 19.0 and 24.0 mm individually. Fascinatingly, the Co^{2+} complex had significant and enhanced broad spectrum actions than LH against all the tested microbial organisms and greater than of the standard drug against *P. mirabilis* (25.0 mm).

Antifungal studies: The synthesized LH ligand and its divalent metal complexes stood screened for their antifungal actions against the fungal strains *A. niger*, *A. flevus* and *R. stolonifer* and are presented in Fig. 4. The compounds generally displayed good antifungal inhibitory activities (Table 1) against the fungal strains. Careful examination of the

antifungal data acquired, showed the ligand had a weak inhibitory effect against the fungus with inhibition zones range of 6.5-10.0 mm. However, the activity of the latter became effective and more pronounced on coordination with the metal ions. Toxicity of the complexes, which is a consequence of synergistic effect involving the metal ion and the Lewis bases, may be accountable for this boost. Other factors which may have played significant role in the enhanced antifungal action of the complexes include, chelation improves the lipophilic character of central metal atoms in complexes, hereafter increasing their hydrophobic character and liposolubility which in turn favours easy permeation of the complexes through the lipid layers of the cell membrane and higher steadiness constant of the complexes than the ligand[47,48]. The metal complexes had inhibitory zones in the range 10.0-22.0 mm comparable to that of the standard drug.

CONCLUSION

The ketoimine tautomeric Schiff base: N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide (LH)coordinates to the Fe^{2+}, Co^{2+}, Ni^{2+} and Cu^{2+} ions in a bi-dentate fashion through the deprotonated amide N and ketonic O atoms. The apportioning of a 4-coordinate tetrahedral to the Co^{2+} and Ni^{2+} complexes and 6-coordinate octahedral to Cu^{2+} and Fe^{2+} complexes were corroborated by spectroscopic and physical measurements. The latter also corroborated the Schiff base structural assemblage. Analytical and spectral data designates all complexes mononuclear, non-ionic in $(CH_3)_2SO$, 2L:1 M molar ratio chelation fashion and likewise the existence of hydrated water molecule(s) in Fe^{2+}, Co^{2+} and Cu^{2+} complexes. The *in vitro* antibacterial and antifungal activities of the synthesized compounds were investigated against the strains of *B. cereus*, *P. mirabilis*, *E. coli*, *S. aureus*, *K. oxytoca* and *P. aeruginosa* and *A. niger*, *A. flavus* and *R. stolonifer*. Generally, the metal^{2+} complexes exhibited moderate to good activity against the microorganisms better than the metal free ligand in one form or the other. The studied cobalt and nickel complexes had the best antibacterial and antifungal activities against the screened microbes with inhibitory growth zones of 25.0 and 22.0 mm.

SIGNIFICANT STATEMENT

This study established the bidentate coordinative nature of N-(1,4-dihydro-1,4-oxonaphthalen-3-yl)pyrazine-2-carboxamide through its ketoimine tautomeric assemblage and making the synthesized Schiff base an excellent chelate. The study discovered potent cobalt and nickel complexes with the best antibacterial and antifungal activities against screened microbes with fascinating inhibitory growth zones that could be exploited by researchers for further drug designs and synthesis.

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