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SYNTHESIS AND EVALUATION OF ANTIFUNGAL SENSITIVITY OF HALOGENATED IMIDAZOLES AND THEIR TRANSITION METAL COMPLEXES

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Abstract

Microorganisms remain significant contributors to global health challenges, and their control often relies on bioactive agents. However, the long-term effectiveness of these agents is increasingly undermined by resistance, intolerance, and other limitations. This underscores the need to discover new bioactive substances capable of overcoming microbial threats.

This study focused on synthesizing novel metal complexes with potential antifungal activity. Halogenated imidazoles were prepared and characterized using spectroscopic techniques, and their antifungal properties were assessed against *Candida albicans* through measurements of inhibition zones. These halogenated imidazoles then served as ligands for the synthesis of metal complexes, which were subsequently evaluated for antifungal potency. Upon complexation, the IR absorption bands of the halogenated imidazoles showed slight reductions, particularly in the C–N and C=N stretching regions associated with the ligand's donor sites. The initial sensitivity trend among the ligands was TBI > DCI > TII, but this order shifted upon coordination with metals—changing to DCI > TBI > TII for Mn^{2+} complexes and DCI > TII > TBI for Ni^{2+} complexes. Overall, the results demonstrate that the synthesized metal complexes exhibit promising antifungal activity and provide a foundation for further investigation into their potential therapeutic applications.

Keywords: Halogenated imidazoles, antifungal, bioactive complexes

Introduction

Bioactive compounds are hardly sufficient to effectively satisfy the health needs of the world's growing population. A whole lot of the currently existing compounds encounter resistance from the pathogens causing these disorders and some are toxic to human cells and organs which render them not useful as drugs (Guegerich, 2011; Ahmed *et al*., 2024). Thus, there is a need to source for alternative compounds. Synthesis of new compounds and modification of existing compounds play a key role in increasing the number of biologically active substances.

Imidazole ring is present in many natural and synthetic products which include drugs, catalysts, and biologically active substances, appearing as single rings or fused with other alicyclic or heterocyclic entities, thus gaining much recognition and importance in the area of medicinal and pharmaceutical chemistry. Imidazole derivatives have shown various forms of bioactivities such as antimicrobial (Chidambaranathan *et al*., 2015; Aboagye *et al*., 2023; Faleye *et al*., 2024), anticancer and antiviral (Haryadi and Pranowo 2023; Hassan *et al*., 2021), and antidiabetic (Suhasini *et al*., 2013).

Halogenated imidazoles and their metal complexes have been reported to show promising use as antimicrobials (Duru *et al*., 2014, 2016; Emwanta *et al*., 2018; Anjali *et al*., 2022)

Transition metals play key roles in various aspects of human health. Manganese

possesses strong antioxidant properties (Doisy, 1973; Tripathi *et al.,* 2000). Nickel supports general human health and bodily activities (Wittsiepie *et al.,* 2009). Zinc prevents dwarfism (Prasad *et al.*, 1963; Sandstead *et al*., 1967; Nazanin *et al.*, 2013). Transition metal complexes have been shown to be of importance in the field of agriculture (Mourya and verma, 2017; Puthilibai *et al*., 2023), and have also been shown to enhance biological activities of bioactive substances (Ramesh *et al*., 2012; Revanasiddappa *et al*., 2012; Wers *et al*., 2013; Duru *et al.,* 2014).

The aim of this study is to synthesize metal complexes of halogenated imidazole and evaluate their antifungal activities.

Materials and Methods

All materials and reagents used in this study were of analytical grade and did not require further purification. Chemicals were obtained from Honeywell, Seelze, Germany and Merck, Darmstadt, Germany. The fungus used, *Candida albicans* was of analytical grade and was obtained from the Department of Microbiology, University of Port Harcourt, Choba, Nigeria. It was appropriately reidentified (Cowan and Steel, 1965)

Characterization of Synthesized compounds

The synthesized ligands and the synthesized coordination complexes were all subjected to characterization using various techniques including thin layer chromatography, melting point, ultraviolet/visible spectroscopy, and infra-red spectroscopy. The halogenated imidazoles (DCI, TBI and TII) were further characterized using gas chromatography-mass spectrometer. TLC was done using fluorescent plates (silica gel) and detected under ultraviolet lamp (DESACA) at 254nm and 366nm. Melting points were determined by using a capillary tube in GallenKamp apparatus and reported as uncorrected. Fourier-transform Infra-red spectroscopy analyses of all the synthesized compounds were done using BRUKER-ALPHA spectrometer (4000-450nm) and interpreted using BRUKER software. GCMS was done using Agilent Technologies single quadrupole 5977B GC/MSD.

Test Using Aqueous Silver Nitrate

The synthesized complexes were treated with aqueous solution of silver nitrate to determine the presence of any halide in the form of a counterion.

Fungal Toxicity Test

Collection and Identification of *Candida Albicans*

Pure clinical grade isolate of *Candida Albicans* was obtained from the department of microbiology of the University of Port-Harcourt, Nigeria. It was resuscitated using Potato Dextrose Agar (PDA) and identified by appropriate method. Subculturing was done using nutrient agar slants and incubated at 40 ^{o}C until it was used (Bhattacharyya, 2022).

Preparation of Test sample solutions

A stock solution of each sample was made by dissolving 1000 mg of the metal complex in 2 mL of DMSO equivalent to a concentration of 500 mg/mL. Serial dilution was then made to give 200, 150, 100, and 50 mg/mL concentrations and stored in a refrigerator for further use (Akujobi *et al*., 2004, Zapata-Zapata *et al*., 2022).

Antifungal Activity

The agar well diffusion method with potato dextrose agar was used. The medium was prepared in accordance with the manufacturer's standard. The Fungus was diluted with sterile water to a 0.5 McFarland solution and incubated on a fresh medium at atmospheric temperature for 72-78 hours. A cork borer (d = 4 mm) was used to bore wells in the medium and the various concentrations of the test agents were filled into the wells and incubated for 24 hours for possible inhibition to occur.

The zones of inhibition (mm) were then measured.

Synthesis of 4,5-dichloroimidazole

Sodium hydroxide (4.72 g) was added to a beaker containing 500 ml of sodium hypochlorite (3.5 % w/v). Imidazole (8g, 0.12 mol) was then added to the beaker. The resulting yellow solution was stirred for five minutes, acidified with HCl to pH 4, filtered, washed and oven dried at 50 ^{o}C overnight. The dirty brown product was recrystallized from water to afford yellow crystals tentatively identified as 4,5-dihloroimidazole ((Emwanta *et al*., (2018) adapted from Lutz and Delorenzo (1967)).

Synthesis of 2,4,5-triiodoimidazole

An aqueous solution (150 ml) of iodine (15.24 g, 0.06 mol) in potassium iodide (26.56 g, 0.16 mol) was added drop-wise over 30 minutes to a stirred aqueous solution of sodium hydroxide (2 M, 200 ml) and imidazole (1.36 g, 0.02 mol). The solution was stirred for 240 minutes allowed to stand overnight after which it was neutralized to pH 7 with 25 % ethanoic acid. The precipitate was allowed to settle and was filtered, washed with water, and kept in a vacuum oven at 50 ^{o}C. The white powdery product was recrystallized from ethanol to afford cream-coloured crystals tentatively identified as 2,4,5-triiodoimidazole (Katritzky and Rees, 1984).

Synthesis of 2,4,5-Tribromoimidazole

Imidazole (2.72 g, 0.04 mol) and anhydrous sodium acetate (40 g) were added to anhydrous acetic acid (360 ml) and stirred continuously. Bromine (6.2 ml, 0.12 mol) was mixed with anhydrous acetic acid (40 ml) and was added in a drop-wise manner to the imidazole/sodium acetate solution. Sodium acetate (10 g) was added after 20 minutes and was stirred continually for 200 minutes. Vacuum distillation technique was used to expel the acetic acid at 50 ^{o}C to almost dryness leaving a cream-coloured precipitate. The precipitate was then washed with deionised water and oven dried at 50 ^{o}C. The resulting product is a white powder tentatively identified as 2,4,5-trbromoimidazole (Emwanta *et al*., 2018 adapted from Stentio *et al*., 1973)

Synthesis of Transition Metal Complexes

The transition metal ions Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+} were all prepared by dissolving 1 mmol of their salts – Manganese II chloride ($MnCl_2$), Cobalt II chloride ($CoCl_3$), Nickel II chloride ($NiCl_2$), Copper II chloride ($CuCl_2$) and Zinc acetate ($Zn(CH_3COO)_2$) in 2 ml of distilled water. To prepare the complexes, the corresponding metal salt solution was added dropwise to a stirred solution of halogenated imidazole (2 mmol) dissolved in 30 ml of acetone over 30 minutes and allowed to stand for 24 hours. The products formed were collected, washed with cold water, filtered through sintered glass crucible and dried in vacuum oven at 50 ^{O}C overnight. The products were all subjected to recrystallization from redistilled ethanol to give the respective metal complexes (Duru *et al*., 2016, Emwanta *et al*., 2018).

Results

Halogenated Imidazoles

The products of the halogenation of imidazole are listed below.

4,5-Dichloroimidazole

The yellow crystal product obtained weighed 7.94 g corresponding to a yield of 49.33 %. It has a melting point range of 182-185 ^{o}C. Figure 1 displays the Gas Chromatography Mass Spectrum of the product 4,5-dichloroimidazole. Fragmented peaks: 109 (C_2NCl_2), 62 (CNHCl), 47 (C-Cl), 28 (CH_2N) and 12 (C).

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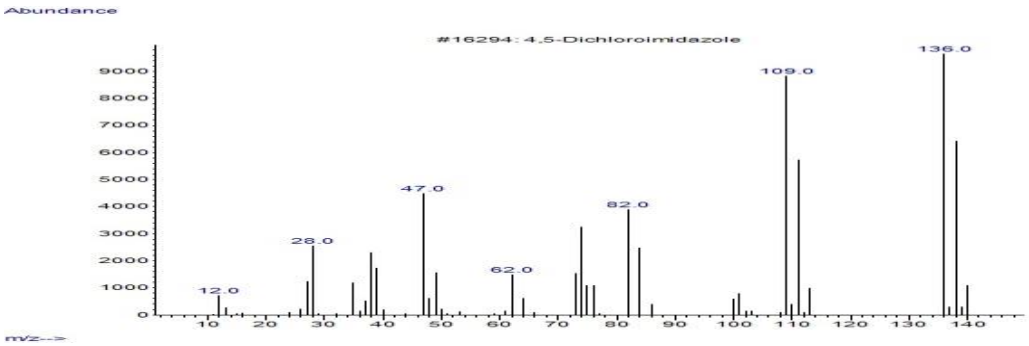


Figure 1: GCMS Spectrum of 4,5-Dichloroimidazole

2,4,5-Triiodoimidazole

The Cream-coloured crystals obtained weighed 11.03 g corresponding to a yield of 70.21 %. It has a melting point range of 188-191 ^{o}C. Figure 2 displays the Gas Chromatography Mass Spectrum of the product 2,4,5-triiodoimidazole. Fragmented peaks: 319 ($C_3N_2I_2$), 292 (C_2NI_2), 278 (C_2I_2), 192 (C_3N_2HI), 165 (C_2NI), 65 (C_3N_2H), 53 (C_2N_2H), 38 (C_2N) and 24 (C_2)

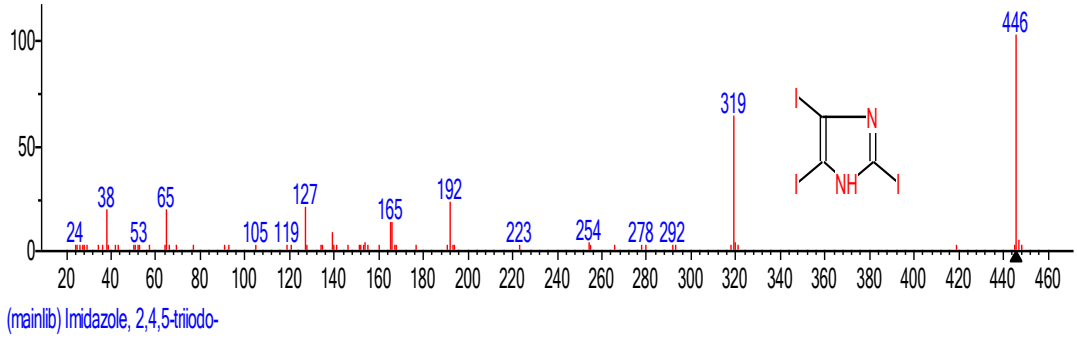


Figure 2: GCMS Spectrum of 2,4,5-Triiodoimidazole

2,4,5-Tribromoimidazole

The white powdery product obtained weighed 9.02 g corresponding to a yield of 74.18 %. It has a melting point range of 219-221^{o}C. Figure 3 displays the Gas Chromatography Mass Spectrum of the product 2,4,5-tribromoimidazole. Fragmented peaks: 277 (C_2NBr_2), 225 ($C_3N_2HBr_2$), 198 (C_2NBr_2), 144 (C_3N_2Br), 118 (C_2NBr), 106 (CNBr), 91 (CBr), 65 (C_3N_2H), 38 (C_2N), 24 (C_2) and 12 (C).

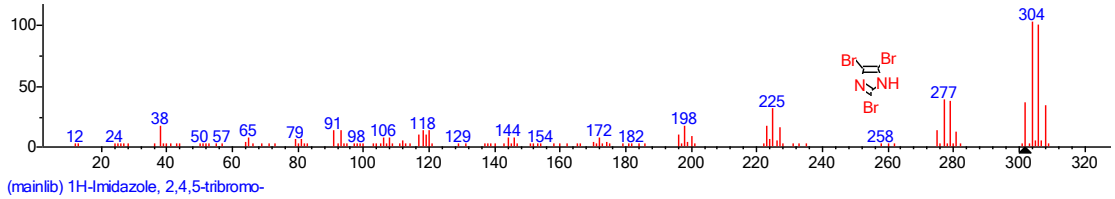


Figure 3: GCMS Spectrum of 2.4.5-Tribromoimidazole

Metal Complexes

Reaction with aqueous silver nitrate

The synthesized metal complexes were treated with aqueous silver nitrate to test for counter halogen ions. There was no observable colour change or formation of a precipitate with any of the complexes. This indicates that the complexes do not contain the counterions – Cl^{-}, Br^{-} and I^{-}. Equations 1 and 2 show the complexation reactions between the bidentate ligand and metals with a coordination number of 4 and 6 respectively.

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$M^{2+} + 2L_o \rightarrow [M(L_o)_2]$ (Equation 1)

$M^{2+} + 3L_o \rightarrow [M(L_o)_3]$ (Equation 2)

Where M^{2+} is metal ion and L_o is the ligand (Ligands are DCI, TBI and TII)

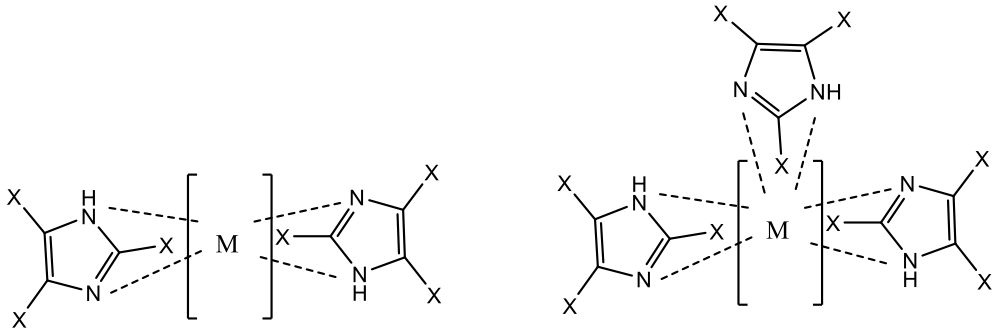


Figure 4: Schematic Diagrams for ML_2 and ML_3 Metal Complexes

The suggested molecular formulas of the complexes in line with the predominant coordination numbers of the transition metals and the bidentate nature of Imidazole (L_o) are given in Table 1

Table 1: Suggested Molecular Formula for the complexes

Metal ion	Common Coordination number	Suggested formula
Mn^{2+}	6	$[Mn(TBI)_3]$
Co^{2+}	6	$[Co(TBI)_3]$
Ni^{2+}	4	$[Ni(TBI)_2]$
Cu^{2+}	4	$[Cu(TBI)_2]$
Zn^{2+}	4	$[Zn(TBI)_2]$
Mn^{2+}	6	$[Mn(TII)_3]$
Ni^{2+}	4	$[Ni(TII)_2]$
Mn^{2+}	6	$[Mn(DCI)_3]$
Ni^{2+}	4	$[Ni(DCI)_2]$
Zn^{2+}	4	$[Zn(DCI)_2]$

Table 2 shows the physical forms and colours of the metal complexes.

Table 2: Physical Properties of the Metal Complexes

Formula	Colour	Form
$[Mn(TBI)_3]$	Cream	Flakes
$[Co(TBI)_3]$	Pink	Crystals
$[Ni(TBI)_2]$	White	Crystals
$[Cu(TBI)_2]$	Orange	Powder
$[Zn(TBI)_2]$	White	Crystals
$[Mn(TII)_3]$	Amber	Cake

$[Ni(TII)_2]$	Dirty Purple	Cake
$[Mn(DCI)_3]$	Grey	Powder
$[Ni(DCI)_2]$	Purple	Powder
$[Zn(DCI)_2]$	Yellow	Crystals

The infrared absorption analysis and the UV/Vis spectroscopy results are displayed in Table 3 and Table 4 respectively.

Table 3: Infrared Analysis Results for the Synthesized Compounds

	IR Absorption Bands (cm^{-1})				
Formula	**C-X**	**C-N**	**C=N**	**C=C**	**N-H**
TBI	661 m	1298 m	1685 w	1529 m	3069 m
$[Mn(TBI)_3]$	659 m	1297 m	1676 w	1525 m	3068 m
$[Co(TBI)_3]$	659 m	1286 m	1677 m	1526 m	3067 m
$[Ni(TBI)_2]$	659 m	1286 m	1677 w	1525 m	3067 m
$[Cu(TBI)_2]$	658 m	1286 m	1677 w	1526 m	3069 m
$[Zn(TBI)_2]$	660 m	1299 m	1677 m	1526 m	3067 m
TII	660 m	1266 m	1668 w	1503 m	3017 w
$[Mn(TII)_3]$	659 m	1266 m	1643 w	1504 w	3009 w
$[Ni(TII)_2]$	659 m	1266 m	1665 w	1503 m	3019 w
DCI	665 m	1315 m	1637 w	1573 m	3128 vw
$[Mn(DCI)_3]$	665 m	1315 m	1638 w	1574 m	3128 vw
$[Ni(DCI)_2]$	665 m	1313 m	1638 m	1573 w	3128 vw
$[Zn(DCI)_2]$	663 m	1316 m	1645 w	1555 m	3130 m

Key: vw = very weak, w = weak, m = medium, X = Br, Cl and I

Table 4: UV/VIS Analysis Results of the Synthesized Compounds

	Peak		Valley	
Formula	**Wavelength (nm)**	**Absorbance**	**Wavelength (nm)**	**Absorbance**
$[Mn(TBI)_3]$	360	1.053		
$[Co(TBI)_3]$	280	0.833	250	0.5
$[Ni(TBI)_2]$	282	0.315	836	-0.006
$[Cu(TBI)_2]$	294	0.978	262	0.547
$[Zn(TBI)_2]$	266	1.741		
$[Ni(TII)_2]$	364	0.789	384	0.355
$[Mn(DCI)_3]$	252	0.5		

$[Ni(DCI)_2]$	254	0.501
$[Zn(DCI)_2]$	254	1.021

Tables 5, 6 and 7 display the diameter of inhibition (DOI) of the ligands and their metal complexes. Griseofulvin served as a reference antifungal.

Table 5: Zones of inhibition for 4,5-dichloroimidazole and its metal complexes

	DCI			$[Mn(DCI)_3]$			$[Ni(DCI)_2]$			$[Zn(DCI)_2]$			Griseofulvin		
Conc. (mg/mL)	200	100	50	200	100	50	200	100	50	200	100	50	200	100	50
DOI (mm)	12	9	7.2	14	11	10	16	12	9.8	12	7	5.3	13	8.4	7.5

*DOI – Diameter of inhibition

Table 6: Zones of inhibition for 2,4,5-triiodoimidazole and its metal complexes

	TII			$[Mn(TII)_3]$			$[Ni(TII)_2]$			Griseofulvin		
Conc. (mg/mL)	200	100	50	200	100	50	200	100	50	200	100	50
DOI (mm)	10	8.2	7	10.5	9	8	10.7	9	8.4	13	8.4	7.5

Table 7: Zones of inhibition for 2,4,5-tribromoimidazole and its metal complexes

	TBI			$[Mn(TBI)_3]$			$[Co(TBI)_3]$			$[Zn(TBI)_2]$			Griseofulvin		
Conc. (mg/mL)	200	100	50	200	100	50	200	100	50	200	100	50	200	100	50
DOI (mm)	14	12	10	13	8	5.5	14	9	7.8	14	10	6.6	13	8.4	7.5

Discussion

The mass spectra of the ligands (Figures 1, 2 and 3), show various fragmentation peaks corresponding to masses of possible fragments leading to the structures of each molecule. Table 3 shows the infrared absorptions of the ligand and their complexes. Some of the infrared absorption bands of the ligands (TII, TBI and DCI) were altered after complexation. In triiodoimidazole, the C=N band was reduced from 1668 to 1643 cm^{-1}, while the C=C and N-H bands were reduced from 1529 to 1525 and 3017 to 3009 cm^{-1} respectively. The C=N band was reduced from 1685 in tribromoimidazole to 1676 cm^{-1} in Mn^{2+} and 1677 cm^{-1} in the Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} complexes. The C=C, C=N and C-X bands in dichloroimidazole were altered from 1573 to 1555, 1637 to 1645 and 665 to 663 cm^{-1} respectively.

Table 4 shows the highest UV/Vis absorption values of the metal complexes with their corresponding absorbances.

Table 5 shows the zones of inhibition of the metal complexes of 4,5-dichloroimidazole. It is observed that the Zn (II) complex showed no remarkable difference from the ligand itself despite being toxic to *Candida albicans*. It is also observed that the sensitivity increased with the Mn (II) and Ni (II) complexes.

Table 6 shows the zones of inhibition of the metal complexes of 2,4,5-triiodoimidazole. It is observed that *Candida albicans* showed less toxicity to both the ligand and the metal complexes when compared to the reference antifungal.

Table 7 shows the zone of inhibition of the metal complexes of 2,4,5-tribromoimidazole. The tribromoimidazole ligand is observed to be relatively more toxic to the fungus than it metal complexes. However, the Co (II), Mn (II) and Zn (II)

complexes show good toxicity to the fungus. The Ni (II) and Cu (II) complexes were not sensitive to the fungus at any concentration.

Conclusion

Halogenated imidazole (TII, TBI and DCI) have been synthesized and characterized using spectroscopic methods. Their metal complexes were successfully synthesized using various metal salts and characterized using spectral methods. The observed changes in absorption bands of the C-N, C=N and C=C bands upon complexation indicates new compounds different from the starting materials. This effect is observed more with the C–N and C=N bonds which are at the donor points of the ligand. The trend in sensitivity of the ligands is TBI > DCI > TII. This trend changed with Mn^{2+} to DCI > TBI > TII and with Ni^{2+} to DCI > TII > TBI. The toxicity levels of the metal complexes do not correlate with the trend in atomic masses but could be related to the interaction between ligand and metal ions.

The study showed that the synthesized metal complexes were effective as antifungals and provides data for further research in drug development.

Conflict of Interest

The authors declare that there is no conflict of interest as far as this publication in concerned

References

Aboagye, C. I., Ampomah, G. B., Mensah, J. O., Mensah, C. N., Nartey, D, Gasu, E. M., and Borquaye, L. S. (2023). N-benzylimidazoles as potential antimicrobial and antibiofilm agents – syntheses, bioactivity and molecular docking studies. Scientific African. 19: e01529. https://doi.org/10.1016/j.sciaf.2022.e01529

Ahmed, S.K., Hussein, S., Qurbani, K., Ibrahim, R.H., Fareeq, A., Mahmood, K.A., Mohamed, M.G. (2024). Antimicrobial resistance: Impacts, challenges, and future prospects. Journal of medicine, surgery, and public health. 2: 100081. https://doi.org/10.1016/j.glmedi.2024.100081

Akujobi, C., Anyanwu, B.N., Onyeze, C. and Ibekwe, V.I. (2004). Antibacterial Activities and Preliminary Phytochemical Screening of Four Medicinal Plants. Journal of Applied Sciences. 7(3): 4328 – 4338.

Anjali Krishna, G., Dhanya, T. M., Shanty, A. A., Raghu, K.G., and Mohanan, P.V. (2023). Transition metal complexes of imidazole derived Schiff bases: Antioxidant/anti-inflammatory/antimicrobial/enzyme inhibition and cytotoxicity properties. Journal of molecular structure. 1274: 134384. https://doi.org/10.1016/j.molstruc.2022.134384

Bhattacharyya, S. (2023). Laboratory diagnostic methods for medically important Fungi. IP international journal of medical microbiology and tropical diseases. 8(3): 79-182. https://doi.org/j/ijmmtd.2022.038

Chidambaranathan, V., Mahalakshmi, C.M., Karthick, M. and Shanmugam, M. (2015). Synthesis, spectral characterization and antimicrobial studies of novel imidazole derivatives. Der Pharma Chemica. 7(1): 14-19. DOI: https://dx.doi.org/10.4314/base.v37i5.6

Cowan, S. T. and Steel, K. J. (1993). Medical Technology: Manual for the identification of Medical Bacteria. 3rd Edition, Cambridge University Press, New York. 1-40

Doisy, E.A. Jr. (1973). Micronutrient controls on biosynthesis of clotting proteins and cholesterol. In: Hemphill, D.D. (Ed). Trace substances in environmental health

VI. Columbia, MO: University of Missouri. 193-199

Duru, I. A., Duru, C. E., Ngochindo, R., and Ukiwe, L. (2016). Synthesis and antimicrobial activity of triiodoimidazole and its transition metal complexes. Journal of Chemical Society of Nigerian. 41 Retrieved from https://journals.chemsociety.org.ng/index.php/jcsn/article/view/37

Duru, I.A., Ngochindo, R.I. and Duru, C.E. (2014). Enhancement of the bioactivity of 4,5-dibromoimidazole by its Co(II) complex. International Organization of Scientific Research Journal of Applied Chemistry. 7(9): 28– 32

Emwanta, D. O., Ngochindo, R. I., Odokuma, L. O and Eruteya, C. O. (2018). Evaluation of the Microbial toxicities of 4,5-dichloroimidazole and its Mn (II), Ni (II) and Zn (II) complexes. International Journal of biological and pharmaceutical science. 4: 1-6

Emwanta, D. O., Ngochindo, R. I., Odokuma, L. O and Eruteya, C. O. (2018). Synthesis and Evaluation of the antiicrobial activities of halogenated imidazoles and their Mn (II), Ni (II) and Zn (II) complexes. International Journal of biological and pharmaceutical science. 4: 14-21

Faleye, O. S., Boya, B. R., Lee, J., Choi, I., and Lee, J. (2024). Halogenated Antimicrobial Agents to Combat Drug-Resistant Pathogens. Pharmacological reviews. 76: 90-141. https://doi.org/10.1124/pharmrev.123.000863

Guengerich, F.P. (2011). Mechanisms of Drug Toxicity and Relevance to Pharmaceutical Development. Drug Metabolism and Pharmacokinetics. 26(1): 3-14

Haryadi, W and Pranowo, H. D. (2023). Molecular docking and dynamics analysis of halogenated imidazole chalcone as anticancer compounds. Pharmacia. 70(2): 323-329. https://doi.org/10.3897/pharmacia.70.e101989

Hassan, A. Y., El-Sebaey, S. A., El Deeb, M. A. and Elzoghbi, M. S. (2021). Potential antiviral and anticancer effect of imidazoles and bridgehead imidazoles generated by HPV-Induced cervical carcinomas via reactivating the P53/ pRb pathway and inhibition of CA IX. Journal of molecular structure. 1230: 129865. **https://doi.org/10.1016/j.molstruc.2020.129865**

Katritzky A.R. and Rees C.W. (1984). Comprehensive Heterocyclic Chemistry. 5th Edition, Pergamon press, New York. 469-498

Lutz, A.W. and Delorenzo, S. (1967). Novel halogenated imidazoles, Chloroimidazoles. Journal of Heterocyclic Chemistry. 4(3): 400-401.

Mourya, U. and Verma, R. (2017). Synthesis and characterization of some transition metal complexes with Schiff base ligand and their application in agriculture. International journal of scientific and engineering research. 8(5): 1121-1129

Nazanin, R., Richard, H., Roya K. and Rainer S. (2013). Zinc and its importance for human health: An integrative review. Journal of Research in Medical Sciences. 18: 144-57

Prasad, A.S., Miale, A. Jr., Farid, Z., Sandstead, H.H. and Schulert, A.R. (1963). Zinc metabolism in patients with the syndrome of iron deficiency anemia, hepatosplenomegaly, dwarfism, and hypogonadism. Journal of Laboratory and Clinical Medicine. 61: 537–49.

Puthilibai, G., Devatarika, V., Haewon, B., Behura, S. S., Lautre, H. K., Subha, V., Sangwan, P., and Sunil, J. (2023).

Synthesized and hypothesized Schiff-base ligand and its metal (II) complexes DNA binding mode. Bulletin of chemical society of Ethiopia. 37(5): 1133-1139

Ramesh, G.N., Rao, Y.S., Prathima, B., Sravani, V. and Reddy A.V. (2012). Synthesis, Characterization and Biological Activities of Manganese (II) Complex: Molecular Modeling of DNA Interactions. Der Pharmacia Lettre. 4(4), 1299-1307.

Revanasiddappa, H.D., Shivakumar, L., Prasad, K.S. Vijay, B. and Jayalakshmi, B. (2012). Synthesis, Structural Characterization and Antimicrobial Activity Evaluation of Manganese (II) Complexes with Biologically Important Drugs. Chemical Sciences Journal. 3: 64-73

Sandstead, H.H., Prasad, A.S., Schulert, A.R., Farid, Z., Miale, A. Jr. and Bassilly, S. (1967). Human zinc deficiency, endocrine manifestations and response to treatment. The American Journal of Clinical Nutrition. 20: 422–42.

Stensio, D.A., Wahlberg, K. and Wharen, R. (1973). Synthesis of brominated imidazoles, Acta Chemica Scandinavica. 27: 2179-2183.

Suhasini, G.E., Nirmala, M., Archanagiri, D.R., Varalaksmi, V. and Raj, B.S.S. (2013). Antidiabetic Activity Of New Imidazole Derivative (2-(2-benzylidenehydrazinyl)-5,5-diphenyl-1,5-dihydro-4H-imidazol-4-one) ($C_{22}H_{17}N_4OCl$). International Journal of Pharmaceutical, Chemical and Biological Sciences. 3(4): 1293-1304.

Tripathi, R.M., Mahapatra, S., Raghunath, R., Sastry, V.N. and Krishnamoorthy, T.M. (2000). Daily intake of manganese by the adult population of Mumbai. Science of the Total Environment. 250(1-3): 43-50

Wers, E., Bunetel, L., Oudadesse, H., Lefeuvre, B., Lucas-Girot, A., Mostafa, A. and Pellen, P. (2013). Effect of Copper and Zinc on the Bioactivity and Cells Viability of Bioactive Glasses. Bioceramics Development and Application. 1: 1-3.

Wittsiepie, J., Schne, K., Hilbig, A., Schrey, P., Kersting. M. and Wilhem, M. (2009) Dietary intake of nickel and zinc by young children—results from food duplicate portion measurements in comparison to data calculated from dietary records and available data on levels in food groups. Journal of Trace Elements in Medicine and Biology. 23(3): 183-194

Zapata-Zapata, C., Loaiza-Oliva, M., Martinez-Pabon, M. C., Stashenko, E. E., and Mesa-Arango, A. C. (2022). In Vitro activity of Essential Oils distilled from Colombian plants against Candida auris and other Candida species with different antifungal susceptibility profiles. Molecules. 27(20): 6837. https://doi.org/10.3390/molcules27206837