Tanzania Journal of Science 45(3): 518-526, 2019 ISSN 0856-1761, e-ISSN 2507-7961

An Investigation of the Potentials of 2-[(2-Hydroxyphenyl) Methylidene] Hydrazine-1-Carbothioamide and its Mn(II) and Zn(II) Complexes as Antimicrobial Agents

Umar Sani[1]*, Musbahu Yahaya[2] and Dailami S Adam[3]
[1]*Department of Pure and Industrial Chemistry, Bayero University, Kano, Nigeria*
**Corresponding author: E-mail: sumar.chm@buk.edu.ng*
[2]*Department of Chemistry, Sule Lamido University Kafin Hausa, Jigawa, Nigeria*
E-mail: musbahu.yahaya@yahoo.com
[3]*Department of Chemistry, Federal University Lokoja, Kogi, Nigeria*
E-mail: copydailami@yahoo.com

Abstract

Antibiotic resistance as a result of misuse, overuse or abuse of drugs is an issue of serious concern world over. The quest for more active and robust antimicrobial agents remains a scientific challenge and requires multimillion-dollar investment in the area of drug design and development. Here in, we report the synthesis and characterisation of a tridentate thiosemicarbazone (2-[(2-hydroxyphenyl)methylidene]hydrazine-1-carbothioamide) (HL) from salicylaldehyde and thiosemicarbazide. Its complexes with Mn(II) and Zn(II) were prepared following similar technique and characterised by melting point, FT-IR, UV –visible spectrophotometry, and elemental analysis. The Mn(II) complex showed paramagnetism with a magnetic moment value of 5.80 BM while the Zn(II) complex was diamagnetic. Both complexes were nonelectrolyte with molar conductivities below 2 $ohm^{-1}cm^2mol^{-1}$. The potentials of the compounds as antibacterial and antifungal agents were investigated against three bacterial: *Staphylococcus aureus, Escherichia coli and Salmonella typhi*, and two fungal: *Aspergillus flavus and Mucor indicus* isolates. Interestingly, all the compounds showed medium to high activities against the tested isolates (except for the *Mucor indicus* which resisted all the compounds) and hence their potential as antimicrobial agents.

Keywords: Thiosemicarbazone, Mn(II) and Zn(II) Complexes, Antibacterial, Antifungal, Antibiotic resistance

Introduction

The past few decades have witnessed growing interests in the chemistry of chelating ligands particularly those bearing sulphur, nitrogen and oxygen moieties (Rana et al. 2009, Makki et al. 2011, Fatondji 2018). Sulphur containing compounds are of particular special interests in drug design due to their variety of biological activities. Multi-donor ligands are widely studied in coordination and organometallic chemistry because of their chelating ability, flexibility and hemilability (Fliedel and Braunstein 2014).

Among the various organic ligands studied in the literature, Schiff bases are by far and wide the most investigated, owing to their ease of preparation and functionalization, tunability and stability. A class of compounds containing both the imine (C=N) and thio (C=S) functionality are termed as thiosemicarbazones, with general structure as shown in (Figure 1).

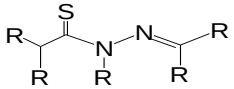


Figure 1: General structure of a thiosemicarbazone (R = H, alkyl or aryl group).

These compounds and their transition metal complexes enjoy great interests of many researchers in the field of drug design and discovery. They have been reported to show antibacterial (Vasanthakumar and Suma 2009, Gujarathi et al. 2013, Kumar and Kumar 2013), antifungal (Kumar and Kumar 2013, Kovač et al. 2017), antiviral (Terzioğlu et al. 2006, Padmanabhan et al. 2017), anticancer (Hu et al. 2006, Fatondji et al. 2018) and tyrosinase inhibitory activities (Soares et al. 2017).Thiosemicarbazones are poorly soluble in water, but their complexes are highly soluble enhancing their values in pharmacological applications.

In a typical thiosemicarbazone, both the nitrogen and sulphur functionalities are considered as soft donor sites, enabling hemilability to the metal in complexes during biological activity (Pahontu et al. 2015). When oxygen is introduced as an additional donor site, the chemistry becomes even more interesting, enhancing the stability of the complexes due to the hard donor nature of the oxygen site by forming a stable covalent bond with the coordinating metal.

For example, Pahontu and co-workers reported the antibacterial, antifungal and *in vitro* antileukemia activities of a series of M(II) complexes with a tridentate (1-phenyl-3-methyl-4-benzoyl-5-pyrazolone 4-ethyl-thiosemicarbazone) ligand, and fully characterise them including single crystal structures (Pahontu et al. 2015).Antibacterial and antifungal activities were found to be higher in the M(II) complexes than for the free ligand. The effect of the free ligand and its metal complexes on the proliferation of HL-60 cells was also tested. The higher activities recorded were attributed to the hemilability of the N and S functionalities as well as the formation of highly stable complexes with the tridentate ligand.

A series of semicarbazones and thiosemicarbazones were prepared by chemical modification of Lapachol (Souza et al. 2013). These compounds were tested for antimicrobial activities against several bacteria and fungi by the broth microdilution method. The thiosemicarbazone derivatives were active against 11 clinical isolates of *Paracoccidioides brasiliensis*, with Minimum Inhibitory Concentrations (MICs) ranging from 0.01 - 0.10 µmol/ml. From the MICs obtained for the lapachol-derived thiosemicarbazones against *S. aureus, E. faecalis, C. gattii* and several isolates of *P. brasiliensis*, it was shown that the compounds have the potential to be developed into novel drugs to treat infections caused by the tested microbes.

The synthesis of 1-[(2′-hydroxy-4′-isopropoxy-5′- nitrophenyl)-ethanone]-4-(aryl)-3-thiosemicarbazones was reported by Parekh and co-researcher (Parekh and Desai 2006). All the compounds were screened for their antibacterial activities against gram positive bacteria: *Bacillus subtilis* and *Staphylococcus aureus,* and gram negative bacteria: *Escherichia coli* and *Salmonella typhi*. Preliminary screening of the compounds revealed their activities against the all the tested isolates.

Melha reported the synthesis, spectroscopic and biological studies of Cu(II), Ni(II), Zn(II), Co(II), Mn(II), Fe(III) and Cr(III) complexes of N^4-(7′-chloroquinoline-4′-ylamino)-N^1-(2-hydroxy-benzylidene)thiosemicarbazone by the reaction of N^4-(7′-chloroquinolin-4′-ylamino)thiosemicarbazide with 2-hydroxybenzaldehyde (Melha 2008). Results from the *in vitro* antimicrobial studies on the synthesised compounds against some bacterial and fungal isolates revealed interesting and significant activities (Melha 2008).

Hundreds of articles can be found in the literature on the biological activities of thiosemicarbazones and their transition metal complexes. These numbers are still on the increase as a result of the increasing trends in microbial resistance against the commercially available antibiotics (WHO 2018). These increasing trends in resistance result in the continuous decline in the number of patented antibacterial drugs as shown (Figure 2).

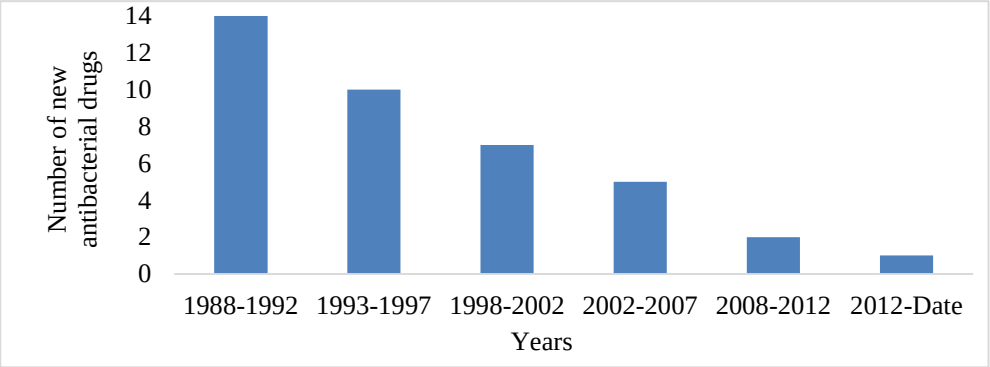


Figure 2: Dwindling nature of antibiotics development.

In the present contribution, we wish to add to the global quest for better and robust antibiotics by investigating the potentials of 2 - [(2 - hydroxyphenyl) methylidene] hydrazine-1-carbothioamide and its Mn(II) and Zn(II) complexes as antimicrobial agents.

Materials and Methods

Chemicals, materials and equipment

All the reagents used in this study were of analytical grade. Glassware were washed thoroughly with detergent and rinsed with distilled water, and then dried in an oven at 110 °C before use. Melting point and decomposition temperature were determined on Guoming RY-2 melting point apparatus. FT-IR spectra were recorded using Shimadzu FTIR-8400S spectrophotometer. Electrical conductivities were measured using Jenway 4010 model conductivity meter while the Perkin Elmer Lambda 35 model of spectrophotometer was used for the UV-visible study. Magnetic susceptibilities of complexes were determined on MBS MK1 Magnetic susceptibility balance at STP. Elemental analysis was done using Perkin Elmer Series 11 (CHNS) Analyser 2400 at the Micro Analytical Laboratory, King Fahd University of Petroleum and Minerals, Kingdom of Saudi Arabia. The clinical isolates used in this study were obtained from Aminu Kano Teaching Hospital (AKTH), Kano and identified at the Department of Microbiology, Bayero University, Kano.

Synthesis of the ligand

Conventional solvent reflux method was used to synthesise the ligand. Thiosemicarbazide (1.822 g, 20 mmol) dissolved in 15 ml of ethanol was mixed with salicylaldehyde (2.1 ml, 20 mmol) in a round bottom flask and stirred for 10 min. Few drops of acetic acid were then added to the mixture and refluxed at 80 °C for 2 h. The mixture was then allowed to settle, cooled in an ice bath to recover the product as a white precipitate. The solids obtained were filtered, washed with ethanol, recrystallized from diethyl ether and dried in a desiccator over $CaCl_2$ (Chandra et al. 2012).

$$C_7H_6O_2 + CH_5N_3S \longrightarrow C_8H_9N_3OS + H_2O \quad ....(1)$$

Synthesis of the complexes

Job's method of continuous variation was employed to understand the coordination behaviour of the metal ions under study (Sani and Yahaya 2016). In a typical procedure, 3 mM solution of the ligand and the metal salt in methanol were prepared. Various ratios of the metal salt to ligand (M:HL) (v/v) solutions were prepared as follows: 1:15, 3:13, 5:11, 7:9, 9:7, 5:11, 3:13 and 15:1 so that the total volume of the mixture is 16 ml. The solutions (3 mM) containing 100% of the respective

metal acetate in methanol were scanned (as blank) to find the wavelength of maximum absorption (λ_{max}) for each metal ion which was used in the analysis (Sani and Yahaya 2016). The absorbance values obtained were plotted against mole fractions (M/HL) of the mixtures. Average number of coordinated ligands to the metal ion was obtained from the plots (Figure 3).

To the hot methanol solution of the ligand (10 mmol) was added hot methanol solution of the appropriate mass of the corresponding metal(II) acetate (5 mmol) dropwise and with constant stirring. The mixture was then refluxed for four hours at 80 °C. On cooling, coloured precipitates were obtained, recovered by filtration, purified with methanol and diethyl ether, and dried in a desiccator over $CaCl_2$ (Chandra et al. 2012).

$$2C_8H_9N_3OS + M(C_2H_3O_2)_2 \longrightarrow M(C_8H_8NOS)_2 + 2C_2H_3O_2H \quad ....(2)$$

M = Mn or Zn

Antimicrobial screening

The synthesised ligand and M(II) complexes were screened *in vitro* against three bacteria, viz: *Staphylococcus aureus*, *Escherichia coli* and *Salmonella typhi*, and two fungi: *Aspergillus flavus* and *Mucor indicus*, by employing the disc diffusion method according to the literature procedure (Sharma et al. 2009). Nutrient agar and Potato dextrose agar were used as culture media for the bacterial and fungal isolates, respectively. These were prepared under sterile conditions, poured into clean petri dishes and allowed to solidify at room temperature (Figure 3a). Suspension of the microorganisms was then rubbed onto the surface of the solidified media using sterile swabs. Three concentrations (250, 500 and 1000 µg/disc) of the test compounds in DMSO were prepared by serial dilution. Small discs of clean filter paper (6 mm in diameter) were dipped into the prepared solutions of the test compounds and allowed to be completely soaked. These small discs were then placed on the already prepared plates and incubated at 37 °C for 24 hours (Figure 3b). Activities were determined by measuring (in mm) the diameter of the zone showing complete inhibition (equation 3) and values obtained were compared with the activity of some standard antimicrobial drugs.

Zone of inhibition (mm) = Total diameter of inhibition (mm) – Disc diameter (mm) ….. (3)

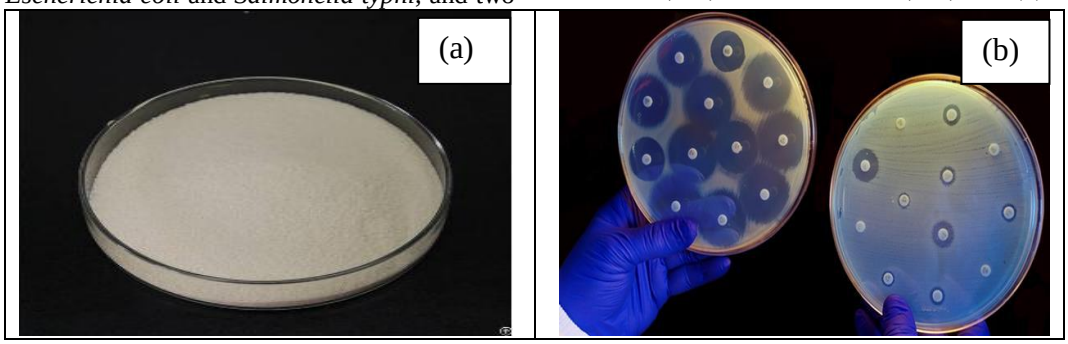


Figure 3: Prepared media plates before incubation (a) and after incubation (b).

Results and Discussion

A tridentate SNO donor type thiosemicarbazone ligand was successfully prepared by the condensation of salicylaldehyde and thiosemicarbazide according to the reported procedure (Chandra et al. 2012) as white solid. Sharp melting temperature of 217 °C indicated the formation of the ligand in pure form. The manganese(II) and zinc(II) Schiff base complexes of the ligand were obtained as green and yellow precipitates with melting temperatures of 266 and 255 °C, respectively (Table 1). All the compounds were soluble in protic solvents.

The ligand was slightly soluble in water while the complexes were readily soluble in water and DMSO. Therefore, most of the studies were carried out in methanol and DMSO solvents. From the obtained molar conductance values of the complexes (Table 1), it can be said that both complexes are non-electrolyte. Magnetic calculations gave a negative value for the Zn(II) complex indicating diamagnetism which is not surprising since most Zn complexes are reported to be diamagnetic (Sharma and Chaturvedi 2014).

Table 1: Physical properties of the compounds

Compound	Colour	Yield (%)	Melting temp. (°C)	Molar conductance ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff} (BM)	Magnetic Property
HL	White	90	217	N.D.	N.D.	N.D.
$[MnL_2]$	Green	96	266	1.82	5.80	Paramagnetic
$[ZnL_2]$	Yellow	79	255	1.00	-	Diamagnetic

L= 2-[(2-hydroxyphenyl)methylidene]hydrazine-1-carbothioamido, N.D. = Not determined.

To understand the coordination behaviour of the ligand, preliminary study was carried out using the Job's method of continuous variation (Sani and Yahaya 2016). The trend in absorbance values indicated that the ligand coordinates to both the metal ions in a 1:2 (metal to ligand) stoichiometry (Figure 4).

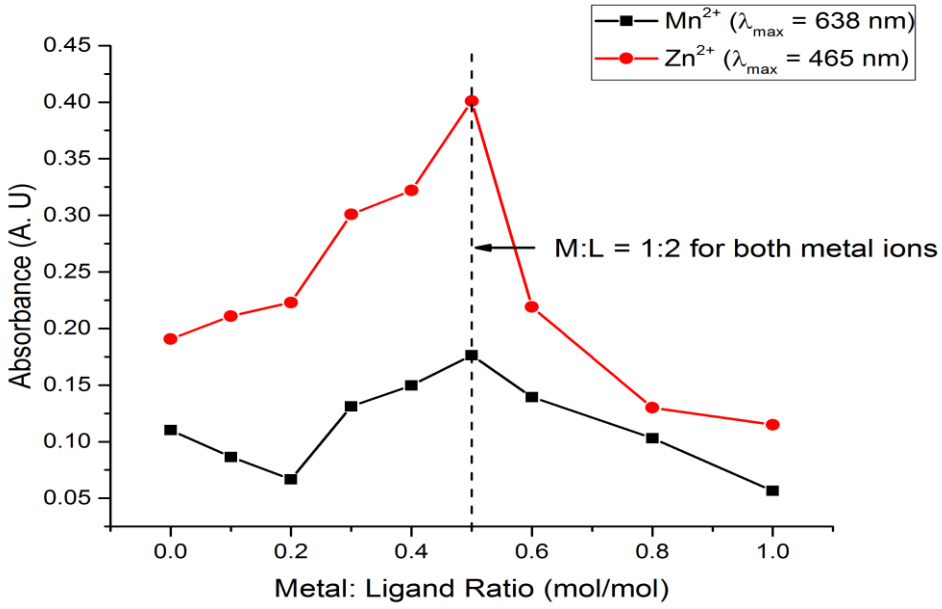


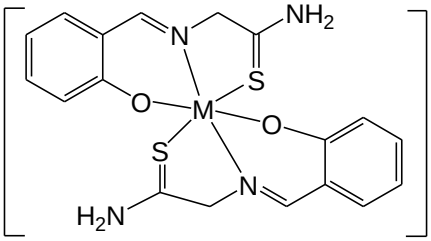
Figure 4: Metal to Ligand stoichiometry for Mn^{2+} and Zn^{2+} ions.

The functional groups in the ligand and its coordination behaviour to the metal ions were determined by using FT-IR spectroscopy. The spectrum of the ligand showed a broad peak at 3429 cm^{-1} characteristic of the hydroxyl (OH) of phenolic group. The absence of this band in the spectra of the complexes indicated deprotonation and covalent bond formation between the metal ions and the phenolic oxygen (Shaikh 2014). Absorption band at 833

cm^{-1} is assigned to C=S bond in the thiosemicarbazone ligand. This band shifted slightly to lower absorption frequencies of 816 and 828 cm^{-1}in the spectra of the Mn(II) and Zn(II) complexes, respectively, which is an indication of coordination to the metal ions (Tyagi and Chandra 2012). Strong and sharp peak at 1616 cm^{-1} in the spectrum of the free ligand is characteristic of C=N bond of the imine group. This peak shifted to lower frequencies (1523 and 1612 cm^{-1}) in the spectra of the Mn(II) and Zn(II) complexes, respectively. These shifts resulted from coordinate bond formation between the nitrogen of the imine group in the ligand to the respective metal ions (Mounika et al. 2010). New bands appeared at lower frequency (615-623 cm^{-1} and 447-455 cm^{-1}) in the spectra of the Mn(II) and Zn(II) complexes corresponding to M-O and M-N stretching vibration modes, respectively (Table 3). The appearance of these bands supported our argument that the ligand coordinated to the metal ions through the thio-S, imino-N and phenolic-O atoms, similar to the observation by Mounika and co-researchers (Mounika et al. 2010).

The exact elemental composition of C, H, N and S in the ligand and the complexes was determined using Perkin Elmer Series 11 (CHNS) Elemental Analyser 2400 model (Table 2). The values obtained for the respective elements agreed well with the theoretical calculations from the balanced stoichiometric equations for the reactions (Table 2).

The magnetic properties of the complexes were reported in (Table 1). The Mn(II) complex showed paramagnetism with a magnetic moment value of 5.8 BM which falls within the range of 5.7–6.0 B.M for octahedral Mn(II) complexes as reported in the literature (Revanasiddappa et al. 2012). The Zn (II) complex however showed a negative magnetic moment value which is an indication of diamagnetism. We proposed octahedral geometry (Figure 5) for the Mn(II) and Zn(II) complexes as well in line with the FT-IR and elemental analysis results (Tables 2 and 3) as well as the literature report by Mounika et al. (2010) as a supporting evidence.



M = Mn^{2+} or Zn^{2+}

Figure 5: Proposed general structure of the metal complexes.

Table 2: Elemental composition of the compounds

Compound	Elemental composition (%); Calculated (Found)			
	%C	%H	%N	%S
HL	49.21 (49.74)	4.65 (4.71)	21.52 (21.45)	16.42 (14.80)
$[MnL_2]$	43.32 (42.44)	3.64 (3.37)	18.95 (17.97)	14.46 (14.39)
$[ZnL_2]$	42.34 (42.27)	3.55 (2.74)	18.52 (18.12)	14.13 (12.15)

L = 2-[(2-hydroxyphenyl)methylidene]hydrazine-1-carbothioamido

Table 3: Selected vibration frequencies of the compounds

Compound	υ(O-H) cm^{-1}	υ(C=N) cm^{-1}	υ(C=S) cm^{-1}	υ(M-O) cm^{-1}	υ(M-N) cm^{-1}
HL	3429	1616	833	-	-
$[MnL_2]$	-	1523	816	663	486
$[ZnL_2]$	-	1612	828	623	455

L = 2-[(2-hydroxyphenyl)methylidene]hydrazine-1-carbothioamido

Tanzania Journal of Science 45(3): 518-526, 2019 ISSN 0856-1761, e-ISSN 2507-7961

The *in vitro* antibacterial and antifungal activities of the ligand and the M(II) complexes are presented in Tables 4 and 5, respectively. A close look at the values of the zones of inhibition showed that the metal complexes exhibited higher activities compared to the free ligand. This can be explained by the greater lipophilicity of the complexes than the free ligand. During bioactivity, the metal complexes tend to bind strongly to the lipids of the cell membrane of the micro-organism, making it easier to diffuse into the cell quicker and destroy the cells' nucleus. This concept is best explained by the Overton's concept and Tweedy's chelation theory (Thangadurai and Natarajan 2001).

Table 4: Antibacterial activity of the compounds

Compound	Concentration (µg/ml)								
	250	500	1000	250	500	1000	250	500	1000
	Zone of inhibition (mm)								
	Staphyloccocus aureus			*Escherichia coli*			*Salmonella typhi*		
HL	10	12	14	08	10	12	11	14	20
$[MnL_2]$	11	14	24	11	16	20	12	16	22
$[ZnL_2]$	10	12	16	08	10	14	13	16	24
Standard (5 mg/ml)	Gentamicin 30			Gentamicin 28			Gentamicin 26		

L = 2-[(2-hydroxyphenyl)methylidene]hydrazine-1-carbothioamido

Table 5: Antifungal activity of the compounds

Compound	Concentration (µg/ml)					
	250	500	1000	250	500	1000
	Zone of inhibition (mm)					
	Aspergillus flavus			*Mucor indicus*		
HL	08	09	12	0	0	0
$[MnL_2]$	10	12	14	0	0	0
$[ZnL_2]$	10	11	16	0	0	0
Standard (5 mg/ml)	Ketoconazole 33			Ketoconazole 38		

L = 2-[(2-hydroxyphenyl)methylidene]hydrazine-1-carbothioamido

The highest antibacterial activities were recorded for the Mn(II) complex against *Staphylococcus aureus* and *Escherichia coli* (Table 4). All the test compounds were inactive against *Mucor indicus* fungus at the working concentrations. This inactivity may be attributed to the ability of the microbe to build a stronger shell around its cell membrane, making it difficult for the compounds to penetrate the cell. Although all test compounds showed lower activities compared to the standards (5 mg/ml) used, the results can be considered promising at the working concentrations and improvements are possible by upgrading the concentration above 1 mg/ml.

Conclusion

A thiosemicarbazone (SNO donor type) ligand and its metal complexes of Mn(II) and Zn(II) have been successfully synthesised and characterised. Elemental analysis was used to ascertain the chemical composition of both the ligand and the complexes. From the FTIR (Table 3) data, the presence of absorption bands corresponding to the coordination of the metals to the nitrogen of the azomethine,

thiocarbonyl sulphur and oxygen of the hydroxyl groups of the ligand informed the proposed structure of the complexes as shown in Figure 5. These were further supported by the elemental analysis results (Table 2).

Antimicrobial screening of the compounds revealed the superior activity of the complexes over the free ligand. These observations are better understood based on the Overton's concept and Tweedy's chelation theory as explained by Thangadurai and Natarajan (2001). The highest antibacterial activities were recorded on Mn(II) complex against *Staphylococcus aureus* and *Escherichia coli*. Similar antifungal activities were observed against the *Aspergillus flavus* isolate while all the test compounds were inactive against *Mucor indicus* at the working concentrations. However, we recommend that higher concentrations (above 1 mg/ml) of the test compounds should be tried against the notorious *Mucor indicus* isolate. All the test compounds are promising antimicrobial agents subject to *in vivo* and cytotoxicity studies.

Acknowledgement

The authors wish to thank the Departments of Pure and Industrial Chemistry and Microbiology, Bayero University Kano for providing the enabling environment to carry out this research work. M. Yahaya thanks Sule Lamido University Kafin Hausa for the MSc. study fellowship.

References

Chandra S, Raizada S, and Verma R 2012 Synthesis, characterisation and biological activities of copper(II) complexes with semicarbazones and thiosemicarbazones. *J. Chem. Pharm. Res.* 4(3): 1612–1618.

Fatondji RH, Kpoviessi S, Gbaguidi F, Sika KC, Gbenou J, Accrombessi GC, Moudachirou M and Poupaert J 2018 Synthesis, Characterization and antimicrobial properties of some 1,3,4-thiadiazolines. *Am. J. Appl. Chem.* 6(2): 64–70.

Fliedel C, and Braunstein P 2014 Recent advances in S-functionalized N-heterocyclic carbene ligands: From the synthesis of azolium salts and metal complexes to applications. *J. Organometal. Chem.* 751: 286–300.

Gujarathi JR, Pawar NS and Bendre RS 2013 Synthesis, spectral and biological study of four and five co-ordinate copper (II) complexes derived from 5-chloro-2-hydroxy acetophenone N(4)-methyl thiosemicarbazone *Schol. Res. Libr. Pharm. Chem.* 5(2): 111–117.

Hu, WX, Zhou W, Xia CN and Wen X 2006 Synthesis and anticancer activity of thiosemicarbazones. *Bioorg. Medicin. Chem. Lett.* 16(8): 2213–2218.

Kovač T, Kovač M, Strelec I, Nevistić A and Molnar M 2017 Antifungal and antiaflatoxigenic activities of coumarinyl thiosemicarbazides against *Aspergillus flavus* NRRL 3251. *Arch. Industr. Hyg. Toxicol.* 68(1): 9–15.

Kumar S and Kumar N 2013 Synthesis, characterization and antimicrobial studies on some transition metal complexes of thiosemicarbazone. *Int. J. Res. Pharm. Biomed. Sci.* 4(1): 305–311.

Makki MST, Abdel-Rahman RM and El-Shahawi MS 2011 Synthesis of new bioactive sulfur compounds bearing heterocyclic moiety and their analytical applications. *Int. J. Chem.* 3(1): 181–192.

Melha KSA 2008 In-vitro antibacterial, antifungal activity of some transition metal complexes of thiosemicarbazone Schiff base (HL) derived from N4-(7′-chloroquinolin-4′-ylamino) thiosemicarbazide. *J. Enzyme Inhibit. Medicin. Chem.* 23(4): 493–503.

Mounika K, Pragathi A and Gyanakumari C 2010 Synthesis¸ Characterization and biological activity of a Schiff base derived from 3-ethoxy salicylaldehyde and 2-amino benzoic acid and its transition metal complexes. *J. Sci. Res.* 2(3): 513–524.

Padmanabhan P, Khaleefathullah S, Kaveri K, Palani G, Ramanathan G, Thennarasu S and Tirichurapalli Sivagnanam U 2017

Antiviral activity of thiosemicarbazones derived from α-amino acids against Dengue virus. *J. Med. Virol.* 89(3): 546–552.

Pahontu E, Julea F, Rosu T, Purcarea V, Chumakov Y, Petrenco P and Gulea A 2015 Antibacterial, antifungal and in vitro antileukaemia activity of metal complexes with thiosemicarbazones. *J. Cell. Molec. Med.* 19(4): 865–878.

Parekh AK and Desai KK 2006 Synthesis and antibacterial activity of thiosemicarbazones. *India J. Chem.* 45B: 1072–1075.

Rana A, Sutradhar M, Mandal SS and Ghosh S 2009 Synthesis, chemical and electrochemical studies of complexes of a tridentate ONS chelating ligand built around the elusive $[Mo^{VI}\ OS]^{2+}$ core. *J. Coordin. Chem.* 62(21): 3522–3531.

Revanasiddappa HD, Shivakumar L, Prasad KS, Vijay B and Jayalakshmi B 2012 Synthesis, structural characterization and antimicrobial activity evaluation of manganese(II) complexes with biologically important drugs. *Chem. Sci. J.* 2012: 1–9.

Sani U and Yahaya M 2016 Synthesis, Characterisation and antimicrobial studies on 2-[(2-hydroxyphenyl) methylidene] hydrazine-1-carbothioamide and its Ni(II) and Cu(II) complexes. *Chem. Search J.* 7(2): 57–63.

Shaikh JA 2014 Synthesis, Spectral characterization and X-ray diffraction studies of some Pd(II) complexes with Schiff bases. *Int. Lett. Chem. Phys. Astron.* 17: 272–280.

Sharma K, Biyala MK, Swami M, Fahmi N and Singh RV 2009 Coordination chemistry of palladium(II) and platinum(II) complexes with bioactive Schiff bases: Synthetic, spectral and biocidal aspects. *Russ' J. Coordin. Chem.* 35(2): 142–148.

Sharma N and Chaturvedi K 2014 Iron(II), nickel(II), copper(II) and zinc(II) complexes of 2,4-dinitro-6(pyridine-2-ylmethylamino) methylphenolate: Synthesis, characterization and antimicrobial activities. *Int. J. Curr. Microbiol. Appl. Sci.* 3(4): 65–74.

Soares MA, Almeida MA, Marins-Goulart C, Chaves OA, Echevarria A and de Oliveira MCC 2017 Thiosemicarbazones as inhibitors of tyrosinase enzyme. *Bioorg. Medicin. Chem. Lett.* 27(15): 3546–3550.

Souza MA, Johann S, Rodrigues LA, Lima S, Campos FF, Mendes IC, Beraldo H, Souza-Fagundes EM, Cisalpino PS, Rosa CA, Alves TA, Pereira de Sá N, and Zani CL 2013 The antimicrobial activity of lapachol and its thiosemicarbazone and semicarbazone derivatives. *Mem. Inst. Oswaldo Cruz.* 108(3): 342–351.

Terzioğlu N, Karalı N, Gürsoy A, Pannecouque C, Leysen P, Paeshuyse J, Neyts J and De Clercq E 2006 Synthesis and primary antiviral activity evaluation of 3-hydrazono-5-nitro-2-indolinone derivatives. *Arkivoc* 1: 109–118.

Thangadurai TD and Natarajan K 2001 Mixed ligand complexes of ruthenium(II) containing α, β -unsaturated-β-ketoamines and their antibacterial activity. *Trans. Metal Chem.* 26: 500–504.

Tyagi M and Chandra S 2012 Synthesis, characterization and biocidal properties of platinum metal complexes derived from 2,6-diacetylpyridine (bis thiosemicarbazone). *Open J. Inorg. Chem.* 2(03): 41–48.

Vasanthakumar M and Suma S 2009 Synthesis and characterisation of metal momplexes of orthovanillin thiosemicarbazone. *Orient. J. Chem.* 25(3): 515–522.

WHO (World Health Organization) 2018 World Health Statistics: Monitoring Health for the SDGs, Sustainable Development Goals, WHO, Geneva. http://apps.who.int/iris