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Bioassay of 2-[(4H-[1,2,4]Triazol-3-ylimino)-methyl]-phenol Chelates

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ABSTRACT

New bioactive compounds designed and synthesized through condensation reaction of equimolar ratio of 2-Hydroxycarbaldehyde and 1H-1,2,4-Triazole-3-amine by reflux via acid catalysis, yielded 2-[(4H-[1,2,4]Triazol-3-ylimino)-methyl]-phenol ligand (L). The chelates were synthesized by the reaction of the synthesized L with the corresponding metal chloride salts. The synthesized compounds were characterized based on the available physical, analytical and spectroscopic techniques. The compounds were obtained in good yields (70-77.6 %), stable, non-hygroscopic at room temperature with distinctive color intensities and high melting and decomposition temperatures (180-275 ℃). The ligand was soluble in acetone, DMF and DMSO while it chelates were soluble in DMF and DMSO. Conductivity measurement data obtained in the range of 17.4-23.2 $\Omega^{-1}cm^2mol^{-1}$ revealed non-conducting nature of the synthesized chelates. The FT-IR data obtained revealed the presence of significant bands that supported the formation of the synthesized compounds. Magnetic susceptibility carried out revealed the magnetic behavior (paramagnetic and diamagnetic) and indicated hexa-coordinated structure of the synthesized chelates. The CHN microanalysis data obtained were consistent with the theoretical data and the stoichiometric ratio of the compounds. The electronic spectra obtained revealed transitions suitable for chelation and formation of the compounds. Antimicrobial sensitivity test carried out against two bacterial and two fungal strains (*Staphylococcus aureus, Escherichia coli* and *Aspergillus fumigatus, Candida albican)* respectively, through agar well diffusion method showed that the synthesized compounds were biologically active in dose dependent manner. Some of the compounds showed comparable activity as Gentamycin and Ketoconazole with 25 and 24 mm zones of inhibition for bacterial and fungal strains respectively.

Keywords:
Synthesis
Chelates and
Bioactivity

INTRODUCTION

Infectious diseases have increasingly become alarming to public health with the rise of antibiotic resistance (Regiel-Futyra, *et al.*, 2017). To overhaul this constrain, new chemical pharmacophores with enhanced and different mode of activity are essential to overcome the menace of resistance of the conventional drugs (Alaghaz, 2014). Triazoles are one of the most important pharmacologically active molecules that possess various therapeutic activities against drug resistant as well as drug sensitive pathogens (Ghanaat, *et al.*, 2020).

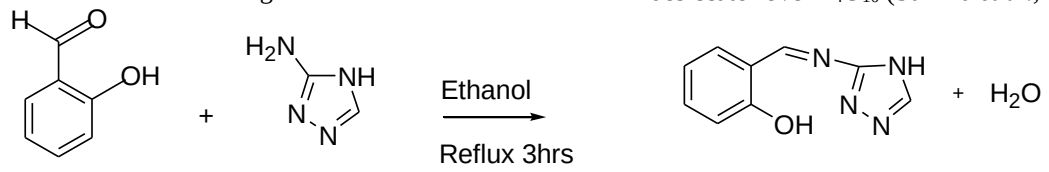
The presence of three nitrogen atoms in their structure make them electron rich systems and allow them to interact with the biological systems (Holm and Straub, 2011). The derivatives of 1,2,4-triazole are well known for their extensive range of therapeutic properties (Nair, *et al.,* 2016). 1,2,4-Triazole derivatives are highly efficient and possess vast range of biological activities such as antiviral Chohan and Hanif (2010), analgesic (Vijesh, *et al.,* 2013), anticancer (Kulabas, *et al.,* 2016), anti-hypertensive (Liu, *et al.,* 2013), anti-microbial (Popiołek, *et al.,* 2013), anti-inflammatory (Paprocka, *et al.,* 2015) and antitumor (Salerno, *et al.,* 2013). The chemistry of imines and their derivatives occupy a significant place due to their well-established biological properties and their ability to form stable chelates with most of the transition metals (Gupta, *et al.,* 2020), 1H-1,2,4-Triazole-3,5-diamine metal chelates have been explored for anticancer (Amer, *et al.,* 2013), antifungal, antibacterial as well as cytotoxic activities (Chohan and Sumrra, 2012). In continuation to explore more metal-based bioactive compounds, we report the efficient synthesis of 2-[(4H-[1,2,4]Triazol-3-ylimino)-methyl]-phenol ligand (L) and it metal chelates in 1:2 (M:L) stoichiometric ratio.

MATERIAL AND METHOD

All the reagents used are of analytical grade and were used without further purification. They were obtained from Sigma-Aldrich (>95 % purity). The glass ware used in this experiment were soaked in concentrated HNO_3 and washed with detergent then rinsed with distilled water and dried in an oven at 120 ℃. Mettler balance model AB54 was used for weighing. Infrared spectral analysis was conducted using Agilent technologies Cary 630 Fourier transform infrared spectrophotometer, conductivity measurement was carried out using Jenway 4010 conductivity meter, melting point and decomposition temperature was carried out using Gallenkamp melting point apparatus MPD 350 series, magnetic susceptibility measurement was conducted using magnetic susceptibility balance MK1 model and electronic spectra was obtained from Perkin Elmer LAMBDA 365 UV-Visible spectrophotometer. Atomic absorption spectroscopy was carried out using Perkin Elmer PinAAcle 900H and CHN micro analysis was obtained using Perkin Elmer series II 2400 elemental analyzer. The test organisms (*Staphylococcus aureus, Escherichia coli, Aspergillus fumigatus* and *Candida albican)* were obtained from Aminu Kano Teaching Hospital (AKTH) and identified at the Department of Microbiology, Bayero University, Kano.

Synthesis of 2-[(4H-[1,2,4]Triazol-3-ylimino)-methyl]-phenol (L)

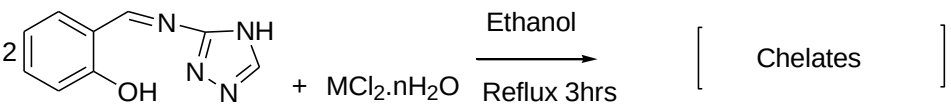
A 2-hydroxycarbaldehyde (0.12212 g, 1 mmol) was dissolved in 25 cm^3 ethanol, few drops of acetic acid was added and heated at 80 ℃ for 15 minutes. An ethanolic solution of 1H-1,2,4-Triazole-3-amine (0.08408 g, 1 mmol) was added and the mixture was refluxed with continuous stirring for 3 hours as shown in Scheme 1. The resulted product was obtained after cooling, then filtered, recrystallized in ethanol and dried in a desiccator over P_4O_{10} (Sumrra *et al.,* 2021).



Scheme 1: Synthetic Reaction of 2-[(4H-[1,2,4]Triazol-3-ylimino)-methyl]-phenol (L)

Synthesis of 2-[(4H-[1,2,4]Triazol-3-ylimino)-methyl]-phenol Chelates

The chelates were synthesized from the reaction of corresponding metal salts $MCl_2.nH_2O$ 1 mmol in 25 cm^3 ethanol and a stirred solution of the synthesized 2-[(4H-[1,2,4]Triazol-3-ylimino)-methyl]-phenol (0.3764 g, 2 mmol) also in 25 cm^3 ethanol as shown in Scheme 2. The mixtures were refluxed at 80 ℃ with continuous stirring for 4 hours, the resulted products were filtered after cooling, then recrystallized in ethanol and dried over P_4O_{10} in a desiccator (Sumrra *et al.,* 2021).



Scheme 2: Synthetic Reaction of 2-[(4H-[1,2,4]Triazol-3-ylimino)-methyl]-phenol Chelates

Bioassay

Antibacterial potency of the synthesized compounds was evaluated through agar well diffusion method and McFarland solution was used as reference for adjusting the bacterial suspension. They were inoculated on the solidified agar plate, wells of 6mm in diameter were dug

on the media using sterile metallic borer and concentration of the test samples were introduced in to the respective wells. The petri dishes containing Nutrient Agar (NA) media with the strains were then incubated at 37 °C for 24 hours. The antibacterial potential of the tested compounds was determined by measuring the diameter of the zone of inhibition around the wells in millimeters (Essawi and Srour, 2000; Valgas *et al.,* 2007).

Agar well diffusion method was also employed to access the antifungal potency of the synthesized compounds with McFarland solution as reference for adjusting the fungal suspension. They were inoculated on the solidified agar plate, wells of 6 mm in diameter were dug on the media using sterile metallic borer and concentration of the test samples were introduced in to the respective wells. The petri dishes containing Potato Dextrose Agar (PDA) media with the fungal strains were then incubated at 37 °C for 48 hours. The antifungal potential of the tested compounds was determined by measuring the diameter of the zone of inhibition around the wells in millimeters (Essawi and Srour, 2000; Valgas *et al.,* 2007).

RESULTS AND DISCUSSION

Table 1: Physical Properties of L and its Chelates

Compound	Colour	Yield(%)	M. Point (℃)	D. Temp.(℃)
L	Yellow	77.60	180	-
$[Ni(L)_2].3H_2O$	Green	71.90	-	275
$[Cu(L)_2].2H_2O$	Green	75.80	-	260
$[Zn(L)_2].2H_2O$	Cream	70.00	-	250

Key: L = $C_9H_8N_4O$, M. Point = Melting point temperature, D. Temp. = Decomposition temperature.

As shown in Table 1 the synthesized compounds were obtained in good yields 70-77.6 % which reflected the maximum conversion of the reactants to products. Different color intensities were observed for the compounds and this may be due to the presence of imine chromophore in the case of the ligand and transitions probably charge transfer in the case of the chelates. The melting point value of the ligand (180 ℃) and the decomposition temperatures of the chelates in the range 250-275 ℃ indicated significant thermal stability of the synthesized compounds. The increase in temperature above that of the ligand and the decomposition of the chelates without melting supported the formation of the chelates.

Table 2: Solubility Test of L and its Chelates in Some Common Solvents

Compound	nhexane	Benzene	D.Ether	$CHCl_3$	Acetone	Ethanol	Methanol	DMF	DMSO	H_2O
L	IS	IS	IS	IS	S	SS	SS	S	S	SS
$[Ni(L)_2].3H_2O$	IS	IS	IS	IS	IS	IS	IS	S	S	IS
$[Cu(L)2].2H_2O$	IS	IS	IS	IS	IS	IS	IS	S	S	IS
$[Zn(L)2].H_2O$	IS	IS	IS	IS	IS	IS	IS	S	S	IS

Key: L = $C_9H_8N_4O$, S = Soluble, SS = Slightly soluble, IS = Insoluble.

The data of the solution chemistry of the synthesized compound in this work were carried out in the following solvents; n-hexane, benzene, diethyl ether, carbontrichloride, acetone, ethanol, methanol, DMF, DMSO and water. The ligand was found to be soluble in acetone, DMF and DMSO while slightly soluble in ethanol, methanol and H_2O but insoluble in the rest of the solvents. The chelates however, were found to be soluble in only DMF and DMSO. It is noteworthy to mention that the ligand was found to be soluble in ethanol at elevated temperature. The data indicated that the synthesized compounds are likely mixed polar and non-polar substances. Furthermore, the decrease in solubility of the chelates may be associated with chelation phenomenon according to Tweedy chelation theory. The data were presented in Table 2.

Table 3: Water of Hydration Analysis of L Chelates

Compound	Hydration Temp.	Weight Loss(g) Observed (Calculated)	%H_2O	Water of Hydration
$[Ni(L)_2].3H_2O$	110℃	0.0540 (0.05434)	11.09	3
$[Cu(L)_2].2H_2O$	110℃	0.0359 (0.0360)	7.596	2
$[Zn(L)_2].H_2O$	110℃	0.0180 (0.0180)	3.930	1

Key: L = $C_9H_8N_4O$

Water of hydration determination was carried out by heating the measured sample in an oven at 110 ℃ until a constant weight was attained. The weight of the anhydrous sample was deducted from the weight of the original sample, the difference was considered as the mass of water lost which is in turn used to calculate the percentage and number of water of hydration present is each chelate. The data (Table 3) revealed the presence of water of hydration in all the synthesized chelates.

Table 4: Molar Conductance Measurement of L Chelates

Compound	Concentration ($moldm^{-3}$)	Specific Conductance ($\Omega^{-1}cm^{-1}$)	Molar Conductance ($\Omega^{-1}cm^2mol^{-1}$)
$[Ni(L)_2].3H_2O$	$1x10^{-3}$	$17.4\ x10^{-6}$	17.4
$[Cu(L)_2].2H_2O$	$1x10^{-3}$	$23.2\ x10^{-6}$	23.2
$[Zn(L)_2].H_2O$	$1x10^{-3}$	$21.7\ x10^{-6}$	21.7

Key: L = $C_9H_8N_4O$

Chelates compounds dissociate in solutions to ions and counters ions, upon which there molar conductance can be measured using mathematical relations. This provides the charge type and structural information of the compounds. The molar conductance values of the synthesized chelates in DMSO solvent at room temperature were presented in Table 4. The values were obtained below 50 $\Omega^{-1}cm^2mol^{-1}$ (17.4-23.2 $\Omega^{-1}cm^2mol^{-1}$) which suggested that the synthesized chelates were non-conducting, similar data were reported in the work of Sadiq *et al.*, 2025.

Table 5: Infrared Spectral Data of L and its Chelates

Compound	$v(C=N)_{azomethine}$	$v(C=N)_{triazole}$	v(M-N)	v(M-O)	v(C-O)	$v(H_2O)$
L	1611	1577	-	-	1276	3100
$[Ni(L)_2].3H_2O$	1629	1551	607	459	1238	3134
$[Cu(L)_2].2H_2O$	1637	1547	629	490	1220	3152
$[Zn(L)_2].H_2O$	1622	1559	652	422	1231	3324

Key: L = $C_9H_8N_4O$

The FT-IR spectra of L and its chelates were compared. The intense band due to azomethine ν(C=N) stretch was observed at 1611 cm^{-1} in the spectrum of L. The IR spectra of the chelates displayed absorption bands in the range of 1622-1637 cm^{-1} characteristic of ν(C=N) stretching frequencies. The absorption bands for ν(C=N) stretch were shifted to higher wave numbers, indicating their participation in the coordination with the metal ions. A peak at 1577 cm^{-1} due to the presence of C=N group of the triazole ring which shifted to lower frequencies (1547-1559 cm^{-1}) in the spectra of the chelates suggested their participation in the coordination with the metal ions, Sumrra *et al.,* 2021 reported a similar data. The metal-ligand bond was further substantiated by the appearance of absorption bands in the range of 607-652 cm^{-1} assigned to ν(M-N) which were absent in the spectrum of the ligand . A broad band at 3100 cm^{-1} confirmed the presence of O-H group in the spectrum of the ligand, whereas the broader bands in the range of 3123-3324 cm^{-1} in the spectra of the chelates were due to the presence of water of hydration outside the coordination sphere of the chelates. A band at 1276 cm^{-1} assigned to C-O in the spectrum of the ligand which has considerably shifted to the range of 1208-1259 cm^{-1} in the spectra of the chelates indicated the involvement of deprotonated phenolic-O in the chelates formation, this has been further supported by the presence of bands in the range of 422-459 cm^{-1} assigned to ν(M-O) stretching vibrations, which were absent in the spectrum of the ligand. The overall data suggested the ligand-metal interaction through azomethine-N, triazole-N and phenolic-O of the ligand. The FT-IR data were presented in Table 5.

Table 6: Magnetic Susceptibility Measurement of L Chelates

Compound	Xg ($ergG^{-2}g^{-1}$)	Xm ($ergG^{-2}mol^{-1}$)	μeff (BM)	Number of unpaired electros
$[Ni(L)_2].3H_2O$	8.6950×10^{-6}	3.765×10^{-3}	3.00	2
$[Cu(L)_2].2H_2O$	3.0340×10^{-6}	1.329×10^{-3}	1.78	1
$[Zn(L)_2].H_2O$	-4.4200×10^{-7}	-1.900×10^{-4}	-	0

Key: L = $C_9H_8N_4O$

The presence or absence of unpaired electrons in the orbital of a metal in a chelate compound determines whether a chelate is paramagnetic or diamagnetic and therefore its magnetic properties. The data obtained were presented in Tables 6. The values of the magnetic moment obtained for the L chelates were 3.00, 1.78, 0 BM and the number of unpaired electrons were 2, 1 and 0 for the synthesized Ni(II), Cu(II) and Zn(II) chelates respectively, as reported in the work of Abdullahi *et al.,* 2026. These therefore indicated that all the chelates are paramagnetic in nature with the exception of Zn chelate as its data substantiated diamagnetic nature. The magnetic moment of a chelate compound directly indicates its number of unpaired electrons and helps determine its spatial geometry and crystal field splitting (Jha and Indradeo, 2000). The magnetic moment values (Table 6) obtained also falls within the ranges of values observed for hexa-coordinated chelates, therefore octahedral geometry were suggested for all the synthesized chelates in this work.

Table 7: CHN Elemental Microanalysis of L and its Chelates

Compound	%C Found (Calculated)	%H Found (Calculated)	%N Found (Calculated)
L	57.401 (57.440)	4.259 (4.280)	29.501 (29.770)
$[Ni(L)_2].3H_2O$	44.196 (44.380)	4.310 (4.4140)	22.901 (23.000)
$[Cu(L)_2].2H_2O$	45.490 (45.620)	3.801 (3.830)	23.490 (23.640)
$[Zn(L)_2].H_2O$	47.189 (47.230)	3.430 (3.520)	24.401 (24.480)

Key: L = $C_9H_8N_4O$

The micro-analytical data of the ligand L and its chelates were reported in Table 7. The data varies in the range of 0.021–0.269 % with the theoretical data. The micro analytical data obtained for the synthesized compounds were in good agreement with the theoretical data. It is therefore in good consistency with the proposed stoichiometry (1:2) metal-ligand ratio of the chelates compounds and further substantiated the compounds purity.

Table 8: Atomic Absorption Spectroscopy (Metal Content L of Chelates)

Compound	$Mass(g)_{Metal}$	% Metal	$Number_{Metal}$
$[Ni(L)_2].3H_2O$	0.0587	12.05	1
$[Cu(L)_2].2H_2O$	0.0636	13.41	1
$[Zn(L)_2].H_2O$	0.0657	14.28	1

Key: L = $C_9H_8N_4O$

The metals were determined by analyzing the corresponding samples of the chelates solutions in atomic absorption spectrometer. The values obtained (Table 8) confirmed the presence of metal ions in all the synthesized chelates and were used to calculate the number of metal ions present in the compounds.

Table 9: Electronic Spectral Data of L and its Chelates

Compound	π-π*(nm)	π-$\pi^*_{Benzene}$ (nm)	n-π*(nm)	C-T
L	246	255	332	
$[Ni(L)_2].3H_2O$	208	280	358	380
$[Cu(L)_2].2H_2O$	231	249	344	425
$[Zn(L)_2].H_2O$	254	294	375	446

Key: L = $C_9H_8N_4O$

The electronic absorption spectra of the ligand showed intra ligand π→π* transitions in the region of (246–255 nm) and also displayed n→π* inter ligand transitions band at 332 nm which may be due to the presence of C=N chromophores and auxochromes in the compound. Moreover, the bands of both π→π* and n→π* were shifted in the distinctive wavelength regions of 208-294 nm and 344-375 nm respectively, in the spectra of the chelates indicating metal-ligand chelation. Furthermore, new bands in the range of 380-446 nm assigned to charge transfer transitions were observed in the spectra of the synthesized chelates which further substantiated the formation of the chelates, similar data were reported by Sumrra *et al.*, 2021. The values were reported in Table 9.

Table 10: Antibacterial Sensitivity Data of L and its Chelates (Zone of Inhibition in mm)

Compound	*Staphylococcus aureus*			*Salmonella typhi*		
	60 mg/ml	30 mg/ml	15 mg/ml	60 mg/ml	30 mg/ml	15 mg/ml
Gentamycin (Standard)	25	-	-	31	-	-
DMSO (Control)	06	06	06	06	06	06
L	16	14	12	14	12	10
$[Ni(L)_2].3H_2O$	23	15	14	20	14	10
$[Cu(L)_2].2H_2O$	25	20	18	23	19	17
$[Zn(L)_2].H_2O$	20	15	14	21	17	15

Key: L = $C_9H_8N_4O$

The *in-vitro* antimicrobial activity of the synthesized compounds together with Gentamycin as the reference drug were evaluated against two pathogens (*Staphylococcus aureus* and *Salmonella typhi*). In each anti-bacterial susceptibility experiment, the inoculum controls presented clear detectable growth after the incubation period, indicating that all of the isolates were viable and that the conditions were suitable for bacterial growth. The results revealed that all of the compounds exhibited antibacterial activity in different degrees (as shown in Table 10) for the analysed pathogens. The compounds displayed moderate to good activities against *Staphylococcus aureus* with copper chelate exhibiting the highest activity (25 mm) comparable to Gentamycin (the standard drug used).

Table 11: Antifungal Sensitivity Data of L and its Chelates (Zone of Inhibition in mm)

Compound	*Aspergillus fumigatus*			*Candida albican*		
	60 mg/ml	30 mg/ml	15mg/ml	60 mg/ml	30 mg/ml	15 mg/ml
Ketoconazole (Standard)	27	-	-	24	-	-
DMSO (Control)	06	06	06	06	06	06
L	12	08	06	15	13	09
$[Ni(L)_2].3H_2O$	23	17	16	22	16	15
$[Cu(L)_2].2H_2O$	22	18	16	23	19	17
$[Zn(L)_2].H_2O$	22	17	15	24	20	18

Key: L = $C_9H_8N_4O$

The synthesized compounds were analyzed for anti-fungal activity against two fungal strains (*Aspergillus fumigatus* and *Candida albican*). The findings of the *in-vitro* anti-fungal activity enlisted in Table 11 displayed the comparison of the synthesized ligand and its derived chelates against the tested pathogens. The activity results of both compounds were measured by taking their zones of inhibition. Ketoconazole was used as the positive control while DMSO as the solvent and negative control as it showed no activity against the fungal strains. The ligand and its chelates showed varying degree of inhibitory growth. Comparable activities were seen for the L chelates with respect to *Aspergillus fumigatus* and *Candida albican*, though zinc chelate recorded the highest activity of 24 mm inhibition zone comparable to the standard drug used (Ketoconazole).

Taken together both the antibacterial and antifungal data, the chelates exhibited superior activity than their ligand. The enhanced activity of the chelates compounds were explained by Tweedy chelation theory and Overtone's concept of cell permeability. During the formation of the chelate ring between metal and ligand, the positive charge of the metal ion are slightly shared by the ligands which resulted in the decrease in polar character of the metal ion. Due to chelation, the π-electrons gets delocalized over the complete chelate ring, thus enhancing the lipophilic character of the chelate. The increase in lipophilic character of the chelate resulted in

their increased penetration through the organism's cell membrane, thus supporting their bio-distribution across the organism and improving their bioactivity.

Based on the physical, analytical and spectroscopic data obtained, the following structures were proposed for the synthesized chelates.

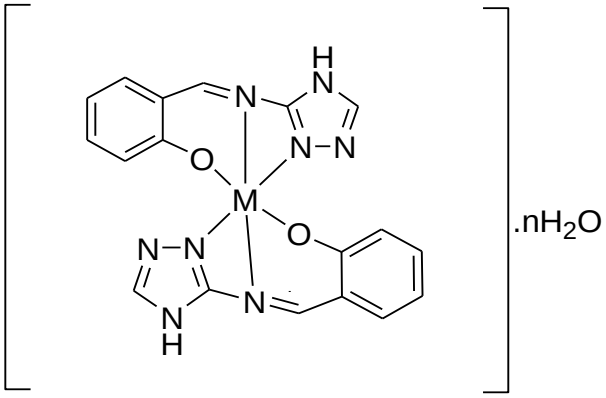


Figure 1: Proposed Structure of the synthesized Chelates
Where M = Metal (Ni(II), Cu(II) and Zn(II)) n=Stoichiometric number

CONCLUSION

Four new bioactive compounds were successfully synthesized and characterized. The compounds were obtained in good yields, stable, non-hygroscopic at room temperature with distinctive color intensities and high melting and decomposition temperatures. All the synthesized compounds were soluble in DMF and DMSO. The chelates were non-conducting, hydrated, hexa-coordinated paramagnetic with the exception of zinc chelate and in 1:2 metal-ligand ratio. The synthesized compounds were biologically active against the tested strains in dose dependent manner. Though the compounds did not showed increased activity than the standard drugs used in this work, they could still compliment the conventional drugs and more importantly, metal-based therapeutics could be the solution to the menace of multi-drug resistance seeing how they offer different mode of action.

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Declaration of Competing Interest

The authors report no conflict of interest.

Credit Authorship Contribution Statement

Bashir Umar Sambo: Conceptualization, Data curation, Investigation, Writing, Funding, Writing-original Draft and editing.
Ibrahim Tajo Siraj: Project administration, Supervision and Review.
Ibrahim Abubakar Sadiq: Methodology and Formal analysis.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found through the corresponding author: *busambo.bus@gmail.com*

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