FUDMA Journal of Sciences (FJS)
ISSN online: 2616-1370
ISSN print: 2645 - 2944
Vol. 8 No. 2, April, 2024, pp 235 - 240
DOI: https://doi.org/10.33003/fjs-2024-0802-2314

ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF SOME HYDRAZONES SYNTHESIZED FROM NICOTINIC ACID HYDRAZIDE

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ABSTRACT

N'-(2-pyridinylmethylene)nicotinohydrazide **A**, N'-(4-pyridinylmethylene)nicotinohydrazide **B**, N'-(2-ethoxybenzylidene)nicotinohydrazide **C**, N'-(4- ethoxybenzyldene)nicotinohydrazide **D** and N'-(2-hydroxyl-5-methoxybenzylidene)nicotinohydrazide **E**, was prepared by refluxing the ethanolic solution of nictonic acid hydrazide and ethanolic solutions of 2-pyridinrcarboxaldehyde, 4-pyridinecarboxaldehyde, 2-ethoxybenzaldehyde, 4-ethoxybenzaldehyde and 2-hydroxy-5-methoxybenzaldehyde in 1:1 mole ratio for 4 hours in a separate reactions. The compounds obtained had a melting point between (120-236 ^{o}C) and a percentage yield between (52.38-77.70 %). They were crystalline solids. The compounds' solubility were assessed in water, ethanol, methanol, acetone, hexane, diethyl ether, dimethyl sulfoxide (DMSO), ethyl acetate, and chloroform. The substances were discovered to be fully soluble in DMSO and methanol. FT-IR, ^{1}H-NMR and ^{13}C-NMR were used for the characterization of the compounds. The antibacterial and antifungal properties were tested against *Methicillin-resistant Staphylococcus Aureus, Vancomycin-resistant Enterococci, S. aureus, S. typhi, P. aeruginosa, A. nigre, A. flavus,* and *C. albicans.* The zones of inhibitions ranged from 22 to 28 mm and the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) were found to be 0.063 mg/mL, 0.125 mg/mL and 0.125 mg/mL respectively. These indicated that the compounds might be good potential drug candidates.

Keywords: Hydrazones, Drug, Nicotinic acid hydrazide, Ethanol

INTRODUCTION

For a very long time, it was understood that fungi and bacteria are among the microbes that cause a wide range of illnesses. These bacteria reside on the body's surface and were once thought to be detrimental to various body systems, but studies have since shown that they have both beneficial and negative impacts (Kruger *et al.,* 2019). These microbes have been constantly surviving in the living systems for decades, which has been attributed to the development of adaptation mechanisms to withstand the prescribed antibiotics when given repeatedly over an extended period (Galvao *et al.,* 2019). In order to counteract the consequences of these germs' well-known resistance to current medications, alternative antibiotics need to be developed concurrently. Because of their numerous pharmacological properties, hydrazones are well-known physiologically active compounds that have drawn the interest of numerous synthetic medicinal chemists. Several studies have shown that the azomethine functional group (-NH-N=CH-) is what underpins the biological activities of this class of compounds (Amrata *et al.,* 2014).

Hydrazones were known to possess anti-tubercular activity (Vidya and Rachana, 2015), anti-oxidant activity (Cinar and Topal, 2022), anti-inflammatory activity (Hussain and Ali, 2017), antimicrobial activity (Popiolek, 2021) and as well as anticorrosion activity (Chafiq *et al.,* 2020).

This paper presents the synthesis, characterization and antibacterial and antifungal activities of hydrazones derived from the reaction of nicotinic acid hydrazide with 2-pyridinrcarboxaldehyde, 4-pyridinecarboxaldehyde, 2-ethoxybenzaldehyde, 4-ethoxybenzaldehyde and 2-hydroxy-5-methoxybenzaldehyde.

MATERIALS AND METHODS

Chemicals and Reagents

The chemicals used in this work are nicotinic acid hydrazide, 2-pyridinrcarboxaldehyde, 4-pyridinecarboxaldehyde, 2-ethoxybenzaldehyde, 4-ethoxybenzaldehyde and 2-hydroxy-5-methoxybenzaldehyde purchased from Sigma-Aldrich and are of analytical grades. Other reagents used are ethanol, glacial acetic acid, methanol, ethyl acetate, DMF, chloroform, diethyl ether and water.

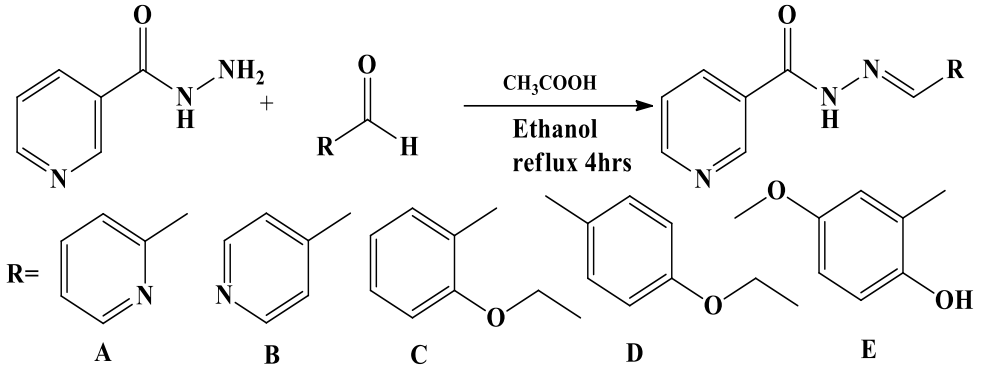
Instrumentations

The instruments used are an automated digital melting point apparatus for the melting point determination, Bruker Tensor-27 platinum ATR-FTIR spectrometer for the infrared spectroscopy analysis and Bruker NMR-400 MHz spectrometer was used for the proton and carbon-13 spectroscopy analysis study.

MATERIALS AND METHODS

Synthesis of the compounds

The five compounds (**A–E**) were synthesized as reported by Pisk et al., (2020). To the ethanolic solutions of nicotinic acid hydrazide, 2-pyridinrcarboxaldehyde, 4-pyridinecarboxaldehyde, 2-ethoxybenzaldehyde, 4-ethoxybenzaldehyde, and 2-hydroxy-5methoxybenzaldehyde were added in separate reactions in a 1:1 mole ratio while being constantly stirred for a few minutes. Afterwards, a small amount of glacial acetic acid was added in a few drops, and the solutions were placed under reflux for four (4) hours. Using pre-coated thin-layer chromatographic plate with a single spot visible, the reaction's completion was observed. After allowing the solutions to cool and crystallize for one to four days, the resulting crystals were separated from the ethanol, dried over silica gel in a desiccator, and weighed.



Scheme 1: synthesis of the hydrazones.

Antimicrobial activity

Test microorganisms

The antimicrobial activities of compounds **A-E** were determined using pathogenic microbes, the microbes were obtained from the department of medical microbiology Ahmadu Bello University teaching hospital Zaria. The pathogens are: *Methicillin Resistant Staphylococcus Aureus*, *Vancomycin Resistant Enterococci*, *Staphylococcus aureus*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Candida albicans*, *Aspergillus nigre* and *Aspergillus flavus*.

Culture media preparations

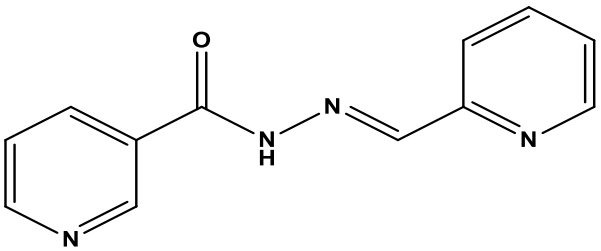
Agar well diffusion method was the method used for the screening of the compounds, the medium utilized as the microorganisms' growth media were Mueller Hinton agar and Sabouraud dextrose agar. After sterilizing the medium for 15 minutes at 121 ^{o}C per the manufacturer's recommendations, they were put onto sterile petri dishes and let to cool and solidify. This was to ensure that no undesirable bacteria came into contact with the agar while it was being prepared. 0.10 mL of the test microorganisms, was seeded onto the sterilized media and evenly distributed throughout its surface using a sterile swap. Each inoculation medium had a well cut out of its center using a standard cork borer with a 6 mm diameter (Uttu *et al.,* 2023).

Antimicrobial assay

About 0.10 mL of the solution of each compound (**A-E**) of the concentration 0.500 mg/mL was introduced into the well on the inoculated medium. After the bacteria and fungi were incubated for 24 hours at 37 °C and 1–7 days at 30 °C, respectively, the medium plates were examined for the zone of growth inhibitions, which were measured using a clear ruler and the results were noted in millimeters. As reference drugs, ciprofloxacin, fulcin, fluconazole, and sparfloxacin were utilized. The minimal inhibitory concentrations were determined using Mueller Hinton and Sabouraud dextrose broth. The compounds were prepared as two-fold serial dilutions at concentrations of 0.500 mg/mL, 0.250 mg/mL, 0.125 mg/mL, 0.063 mg/mL, and 0.031 mg/mL for the MIC determination. The contents were also utilized for the determination of the minimum bactericidal and fungicidal concentrations, as described by Uttu *et al.,* (2023).

RESULTS AND DISCUSSION

Compound A



(*E*)-*N*'-(2-pyridinylmethylene)nicotinohydrazide

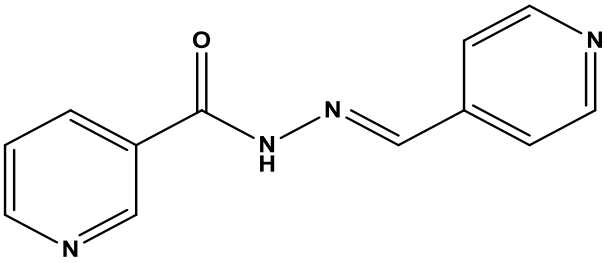
The compound produced was crystalline white solid, with yield of 58.52 % and a melting point of 120 ^{o}C.

FT-IR: 3471, 3146, 2990, 2841, 2361, 1652, 1565, 1462, 1431 and 1282 cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-d$_6$): 12.50 ppm (s, 1H), 9.10 ppm (s, 1H), 8.80 ppm (d, 1H), 8.64 ppm (d, 1H), 8.50 ppm (s, 1H), 8.30 ppm (d, 1H), 8.00 ppm (d, 1H), 7.00 ppm (t, 1H), 7.60 ppm (dd, 1H) and 7.45 ppm (t, 1H).

^{13}C-NMR (400 MHz, DMSO-d^6):162.44, 153.54, 152.94, 150.04, 149.15, 149.11, 137.40, 136.02, 129.46, 125.04, 124.12, and 120.53 ppm respectively.

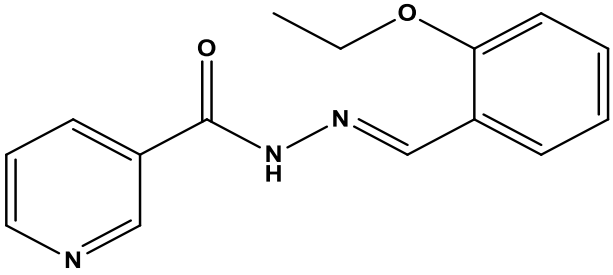
Compound B



(*E*)-*N*'-(4-pyridinylmethylene)nicotinohydrazide

The compound was crystalline milky solid, the yield was 54.64% with a melting point of 199 ^{o}C.
FT-IR: 3495, 3395, 3208, 3056, 2859, 1645, 1562, 1479, 1417 and 1299 cm^{-1}.
^{1}H-NMR (400 MHz, DMSO-d$_6$): 12.25 ppm (s, 1H), 9.10 ppm (S, 1H), 8.80 ppm (d, 1H), 8.65 ppm (d, 2H), 8.45 ppm (s, 1H), 8.28 ppm (d, 1H), 7.70 ppm (d, 2H) and 7.57 ppm (dd, 1H).
^{13}C-NMR (400MHz, DMSO-d$_6$): 162.53, 152.98, 150.48, 149.14, 146.50, 141.76, 136.03, 129.36, 123.58 and 121.54 ppm.

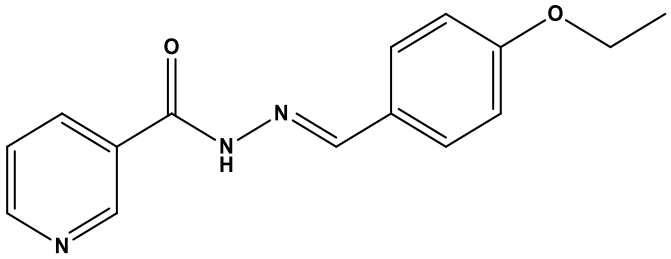
Compound C



(*E*)-*N*'-(2-ethoxybenzylidene)nicotinohydrazide

The compound was crystalline white solid, 77.70 % of yield and has a melting point of 173 ^{o}C.
FT-IR: 3184, 3018, 2924, 2869, 1645, 1562, 1455, 1354 and 1296 cm^{-1}.
^{1}H-NMR (400 MHz, DMSO-d$_6$): 12.00 ppm (s, 1H), 9.10 ppm (s. 1H), 8.82 ppm (s, 1H), 8.76 ppm (d, 1H), 8.30 ppm (d, 1H),7.90 ppm (d, 1H), 7.55 ppm (dd, 1H), 7.40 ppm (t, 1H), 7.10 ppm (d, 1H), 7.03 ppm (t, 1H), 4.15 ppm (q, 2H) and 1.28 ppm (t, 3H).
^{13}C-NMR (400 MHz, DMSO-d$_6$): 162.03, 157.69, 152.68, 149.08, 144.41, 135.89, 132.19, 129.69, 126.11, 124.00, 122.76, 121.17, 113.30, 64.33 and 15.15 ppm.

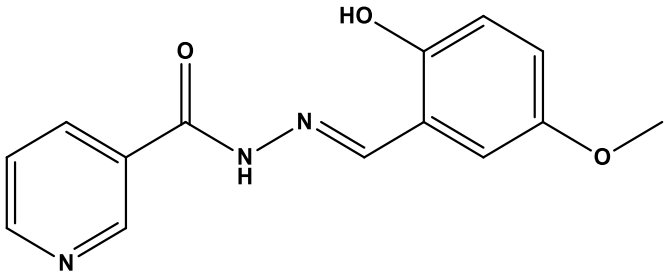
Compound D



(*E*)-*N*'-(4-ethoxybenzylidene)nicotinohydrazide

The compound was crystalline white solid, 66.48 % yield and 236 ^{o}C melting point.
FT-IR: 3184, 3066, 2980, 2831, 1662, 1597, 1505, 1424, 1351 and 1247 cm^{-1}.
^{1}H-NMR (400MHz, DMSO-d$_6$): 11.88 ppm (s, 1H), 9.08 ppm (s, 1H), 8.76 ppm (d, 1H), 8.40 ppm (s, 1H), 8.25 ppm (d, 1H), 7.70 ppm (d, 2H), 7.55 ppm (dd, 1H), 7.00 ppm (d, 2H), 4.15 ppm (q, 2H) and 1.28 ppm (t, 3H).
^{13}C-NMR (400 MHz, DMSO-d$_6$): 161.96, 160.77, 152.63, 149.00, 135.83, 129.80, 129.31, 128.84, 127.00, 124.04, 115.26, 63.76 and 15.08 ppm.

Compound E



(*E*)-*N*'-(2-hydroxy-5-methoxybenzylidene)nicotinohydrazide

The compound was crystalline yellow solid, percentage yield of 52.38 % and melting point of 161 ºC.
FT-IR: 3384, 3056, 2990, 2841, 2357, 1648, 1565, 1489, 1330, 1282 and 1161 cm^{-1}.
^{1}H-NMR (400 MHz, DMSO-d_6):12.25 ppm (s, 1H), 10.50 ppm (s, 1H), 9.10 ppm (s, 1H), 8.78 ppm (d, 1H), 8.65 ppm (s, 1H), 8.28 ppm (d, 1H), 7.60 ppm (dd, 1H), 7.18 ppm (s, 1H), 6.80-7.00 ppm (m, 2H), 4.00 ppm (s, 3H).
^{13}C-NMR (400 MHz, DMSO-d_6):161.99, 152.88, 152.63, 151.95, 149.06, 148.31, 135.96, 129.25, 124.13, 119.43, 118.99, 117.79, 112.36 and 55.98 ppm.

Antibacterial and Antifungal result

Zone of inhibitions of the compounds against the tested microorganisms

Table 1: Zone of inhibitions results (mm)

Test Organism	Compounds (0.50 mg/mL)					Standard drugs (10 µg/mL)			
	A	B	C	D	E	Sparfloxacin	Ciprofloxacin	Fluconazole	Fulcin
MRSA	0	0	25	23	27	35	0	-	-
VRE	26	28	28	25	0	0	28	-	-
S. aureus	23	25	0	0	26	31	0	-	-
S. typhi	0	0	0	0	0	0	40	-	-
P. aeruginosa	27	24	26	23	25	34	0	-	-
C. Albicans	26	28	24	26	24	-	-	36	0
A. nigre	0	0	24	28	0	-	-	0	30
A. flavus	22	24	24	25	24	-	-	0	28

Methicillin Resistant Staphylococcus Aureus; MRSA, *Vancomycin Resistant Enterococci;* VRE, Not Determined; -.

Minimum inhibitory concentration (MIC)

Table 2: Minimum inhibitory concentration results (mg/mL)

Test Organisms	Compounds (mg/mL)				
	A	B	C	D	E
MRSA	-	-	0.125	0.125	0.063
VRE	0.125	0.063	0.063	0.125	-
S. aureus	0.125	0.125	-	-	0.125
S. typhi	-	-	-	-	-
P. aeruginosa	0.063	0.125	0.125	0.125	0.125
C. albicans	0.125	0.063	0.125	0.125	0.125
A. nigre	-	-	0.125	0.063	-
A. flavus	0.125	0.125	0.125	0.125	0.125

Methicillin Resistant Staphylococcus Aureus; MRSA, *Vancomycin Resistant Enterococci;* VRE.

Minimum bactericidal and fungicidal (MBC/MFC) concentration

Table 3: Minimum bactericidal and fungicidal concentrations (mg/mL)

Test Organism	Compounds (mg/mL)				
	A	B	C	D	E
MRSA	-	-	0.250	0.500	0.250
VRE	0.250	0.125	0.125	0.250	-
S. aureus	0.500	0.250	-	-	0.250
S. typhi	-	-	-	-	-
P. aeruginosa	0.250	0.250	0.250	0.500	0.250
C. albicans	0.250	0.125	0.250	0.250	0.250
A. nigre	-	-	0.250	0.125	-
A. flavus	0.500	0.250	0.250	0.250	0.250

Methicillin Resistant Staphylococcus Aureus; MRSA, *Vancomycin Resistant Enterococci;* VRE.

Discussion

The yields obtained are average (52.38 – 77.7 %), this could be as a result of overheating or errors encountered during the recrystallization process. The complete solubility of the compounds in methanol and DMSO demonstrates their polarity.

The FTIR analysis of the compounds identified key bands responsible for functional group vibrations. The carbonyl *v*(C=O), azomethine *v*(C=N) and *v*(N-H) vibrations are assigned to bands at 1662-1645 cm^{-1} and 1597-1562 cm^{-1} and 3495-3056 cm^{-1} respectively (Idris *et al.,* 2020; Abubakar and Eke, 2021). Particularly, the strong *v*(C=N) vibrations in all compounds is a confirmation of the successful condensation reaction (imine bond formation) that lead to the hydrazones formation. This is in agreement with previous reports (Mainsah *et al;* 2019, Ntum *et al;* 2020, Moustafa *et al;* 2022). The singlet proton resonances observed in all the compounds at the extreme downfield were caused by deshielded (-NH-N-) protons in the regions 12.50, 12.25, 12.00, 11.88, and 10.50 ppm. Because there were less deshielded azomethine protons (-N=CH-), there were additional singlet protons that peaked in all of the compounds at 8.50, 8.45, 8.82, 8.40, and 8.65 ppm. Since none of these protons had any neighbors, they all appeared as singlet. The carbon-13 resonance signals of all hydrazones **A – E,** studied resonate strongly at 162.44, 162.53, 162.03, 161.96, and 161.99 ppm respectively and were attributed to their respective carbonyl carbons. A similar set of peaks attributed to azomethine carbon resonances at 149.15, 146.50, 144.41, 135.83, and 148.31 ppm in the compounds. Each synthesized compound's spectrum revealed the presence of only one carbonyl carbon, which supports the FTIR result and further suggested the successful synthesis compounds.

The *in vitro* antibacterial and antifungal studies showed good activity of all the compounds against the tested microorganisms compared to standard drugs (Table 1). The compounds **A** and **B** revealed similar antimicrobial activities which is not surprising since they are isomeric pairs. The compound **A** showed the highest zone of inhibition of 27 mm against *P. aeruginosa* while compound **B** has its highest zone of inhibitions of 28 mm against *VRE* and *C. albicans*. The compounds also have minimum inhibitory concentrations of 0.063 mg/mL respectively against *P. aeruginosa* and *VRE* (Table 1&2). They also have the minimum bactericidal concentrations of 0.250 mg/mL and 0.125 mg/mL against *VRE* and *P. aeruginosa* and minimum fungicidal concentrations of 0.250 mg/mL and 0.125 mg/mL against *C. albicans* (Table 3). Their good activity might also be accounted as results of heteroatoms present in both the aromatics rings of the compounds and the azomethine functional groups (Popiolek, 2021). Similarly, compound **C** and **D** showed similar antimicrobial activity which is also accounted as a result of being an isomers. The compound **C** has highest zone of inhibition of 28 mm against *VRE* and compound **D** has its highest zone of inhibition of 28 mm against *A. nigre* (Table 1&2). The minimum inhibitory concentrations of 0.063 mg/mL were recorded also for the compounds against *VRE* and *A. nigre* (Table 1&2). The compounds also revealed minimum bactericidal concentrations of 0.125 mg/mL and 0.250 mg/mL against *VRE* and minimum fungicidal concentrations of 0.250 mg/mL and 0.125 mg/mL against *C. albicans*, *A. nigre* and *A. flavus* (Table 3). The remarkable activity might also be due to the presence of electron donating group (CH_3-CH_2-O-) in the structures of the compounds as reported in some literatures (He and Xue, 2021; Popiolek, 2021). The last compound which is compound **E** revealed its highest zone of inhibition of 27 mm and minimum inhibitory concentrations of 0.063 mg/mL against *MRSA* (Table 1&2). The compound also showed minimum bactericidal and fungicidal concentration of 0.250mg/mL against *MRSA, S. aureus*, *P. aeruginosa*, *A. nigre* and *A. flavus* (Table 3). The strong activity might also be related to the presence of hydroxyl (-OH) group at the ortho position and methoxy (CH_3-O-) group at the meta position of the phenyl ring which are all electron donating groups (Popiolek, 2021; Zhou *et al.,* 2023).

Generally, the improved activities of these compounds are likely due to the chemical relationship between the carbonyl O, NH, alkoxy groups and the aromatic structures of these compounds. These engender a structure activity relationship leading to improved antimicrobial activity. The activity may also be linked to the heteroatoms present in the compounds that interact with the targeted microorganisms' proteins, cell walls, or DNA enzymes through hydrogen bonding or similar interactions, thereby inhibiting the functions of the enzymes in synthesis of proteins, cell walls, or DNA replications, among other processes (Abubakar & Eke; 2019, Popiolek, 2021; Uddin *et al.,* 2021; Kenny, 2022).

The compounds activities against the examined microorganisms have shown that they may make ideal candidates for use in the development of medications to treat infections or illnesses brought on by these germs. However the compounds exhibited no efficacy against *S. typhi*. This is either due to low concentrations of the compounds or because the microbes has become resistant to these class of hydrazones. Compared to standard drugs used as control, the compounds exhibited good efficiency and might serve as potential drugs candidates.

CONCLUSION

Five asymmetric hydrazones were produced by the reaction of nicotinic acid hydrazide with 2-pyridinrcarboxaldehyde, 4-pyridinecarboxaldehyde, 2-ethoxybenzaldehyde, 4-ethoxybenzaldehyde, and 2-hydroxy-5methoxybenzaldehyde. The compounds had a yield of and were solids that were soluble in DMSO. Through the use of FTIR, ^{1}H-NMR, and ^{13}C-NMR analysis, the compounds synthesis were confirmed. When compared to the common medications employed as standard control, the compounds good activity was demonstrated by their *in vitro* antibacterial and antifungal activity.

ACKNOWLEDGEMENT

The authors wish to thank the Department of Chemistry, Ahmadu Bello University Zaria, for providing a bench space for the work, Dr. Minka'ilu from the department of microbiology, Nigeria Institute of Leather and Science Technology, NILEST, Samaru, Zaria, for his tremendous effort in antimicrobial studies and all others that helped directly or indirectly in this work.

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