GSJ: Volume 8, Issue 4, April 2020, Online: ISSN 2320-9186
www.globalscientificjournal.com

Synthesis, Characterization and Antibacterial Activities of Phenoxyl Derivatives of Imidazole

Bodunde Joseph OWOLABI[1], DasolaAiratAPATA[1], TaiwoSholagbade ADEPOJU[1*]

1: Chemistry Department, Federal University of Technology, Akure, Nigeria.

*: Corresponding Author's email address: tsadepoju@futa.edu.ng

ABSTRACT

Infections caused by bacteria have consistently emerged over the years as public health challenges due to difficulty in treatment resulting from bacterial resistance to commercial drugs. The study was conducted with the aim of discovering potential antibacterial drugs. The synthesis started with formation 1-ethyl-2-methyl-4-nitro-5-chloro imidazole as described in the literature. Then, phenol derivatives were coupled with the compound to produce 1-methyl-2-ethyl-4-nitro-5-(4-chlorophenoxyl) imidazole and 1-methyl-2-ethyl-4-nitro-5-(4-nitrophenoxyl) imidazole. Spectroscopic methods were used to characterize the synthesized compounds. The results of the antibacterial screening showed that the compounds possessed some degree of antibacterial activities against the tested bacteria including*Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis*,*Escherichia coli Shigelladysenteriae,Klebseillapneumoniae,* and*Pseudomonas aeruginosaI*.

Keywords: Bacteria, infection, drug, 1-methyl-2-ethyl-4-nitro-5-(4-chlorophenoxyl) imidazole and 1-methyl-2-ethyl-4-nitro-5-(4-nitrophenoxyl) imidazole.

1.0 INTRODUCTION

The multidrug-resistant bacteria infections have consistently emerged over the years as worrisome public health challenges [1]. The Global Risks Reports of the World Economic Forum had published in 2017 that microbial resistance to commercial drugs represents one of the greatest difficulties in health sector globally [2]. The reports have showed pathogenic bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE), vancomycin-intermediate/resistant *Staphylococcus aureus* (VISA/ VRSA), and *Pseudomonas aeruginosa*, with high number of cases of antibiotic resistance [3]. These bacteria are stubborn to treat and develop new resistance mechanism rapidly.β-lactam antibiotics used for the treatment of various bacterial infections had been rendered ineffective by β-lactamases produced by bacteria [4]. Also, cases of bacterial resistance have been recorded against first, second and third generations of cephalosporins [5]. Antibiotic resistance has significantly contributed to the rise of bacterial infections worldwide [6-8].The entire world is in need of antimicrobial drugs with new mode of action.

Imidazole is an aromatic heterocyclic compound of five-membered ring containing two atoms of nitrogen. Its structure is seen in a myriad of biological compounds such as histidine, purines, coenzymes and synthetic bioactive compounds [9]. Imidazole moiety is pivotal to drug discovery and development. Its derivatives have demonstrated activities against inflammation, cancer, tuberculosis, malaria, diabetes, viral, fungal and bacterial infections [10-15]. The aim of the research was to synthesize derivatives of imidazole as potential antibacterial agents.

2.0 MATERIALS AND METHODS

2.1 MATERIALS

All the melting points were uncorrected. Thin layer chromatography was used for purity of synthesized compounds. Fourier Transform Infrared (FTIR) spectra were recorded with

Cary model 630 spectrophotometer. Proton Nuclear Magnetic Resonance (1H NMR) spectra were obtained on Agilent NMR spectrometer (400 MHz).

2.2 Synthesis of 1-Ethyl-2-Methyl-4-Nitro-5-Chloro Imidazole (Compound A)

1-ethyl-2-methyl-5-chloro imidazole was synthesized according to the published procedure [16]. Then, nitric acid (15ml) was added to the synthesized compound and heated to dryness. Thereafter, sulfuric acid (10ml) was added and boiled for 1hr. The resulting solution was cooled and transferred into iceyielding insoluble compound A. The compound was filtered, washed with distilled water and dried. Cream crystal, M.P.: 149.5^{o}C (the melting point agreed with the literature), Yield: 76%, R_f: 0.83(DMSO and $CHCl_3$, 1:1).

2.3 General Procedure for Synthesis of PhenoxylDerivatives of Imidazole

Sodium hydroxide (144mg) was dissolved in distilled water (2 ml). Phenol derivative (500mg) was dissolved in the solution and evaporated to dryness. The resulting compound was added to compound A (500mg) in DMSO, heated for 3 hours and allowed to cool. Distilled water was added to the resulting solution. Then,it was filtered and crystallized with a mixture of water and ethanol (1:1).

2.3.1 1-Ethyl-2-Methyl-4-Nitro-5-(4-Chloro Phenoxyl) Imidazole: White crystal, M.P.: 187-183^{o}C, Yield: 43%, R_f: 0.72 (DMSO and $CHCl_3$, 1:1). δH (DMSO, ppm): 8.23 (2H, m, Ar-H), 6.83 (2H, m, Ar-H), 3.82 (3H, m, -CH_3), 1.26 (3H, m, -CH_3), 1.18 (2H, m, -CH_2). δ^{13}C ($CdCl_3$, ppm): 154.56, 137.98, 138.05, 129.58, 130.05, 115.50 (Ar-C), 38.83, 15.24, 13.62 (sp^3 C).

2.3.2 1-Ethyl-2-Methyl-4-Nitro-5-(4-Nitro Phenoxyl) Imidazole: White crystal, M.P.: 153-155^{o}C, Yield: 72%, R_f: 0.75 (DMSO and $CHCl_3$, 1:1). δH ($CdCl_3$, ppm): 8.25 (2H, m, Ar-H),

7.87 (H, s, Ar-H), 7.37 (H, d, Ar-H), 3.60 (3H, s, $-CH_3$), 2.50 (5H, m, $-CH_2CH_3$). $\delta^{13}C$ ($CdCl_3$, ppm): 160.38, 144.20, 138.51, 132.99, 126.67, 115.99 (Ar-C), 31.46 (sp^3 C).

2.4 *In vitro* Antibacterial Screening

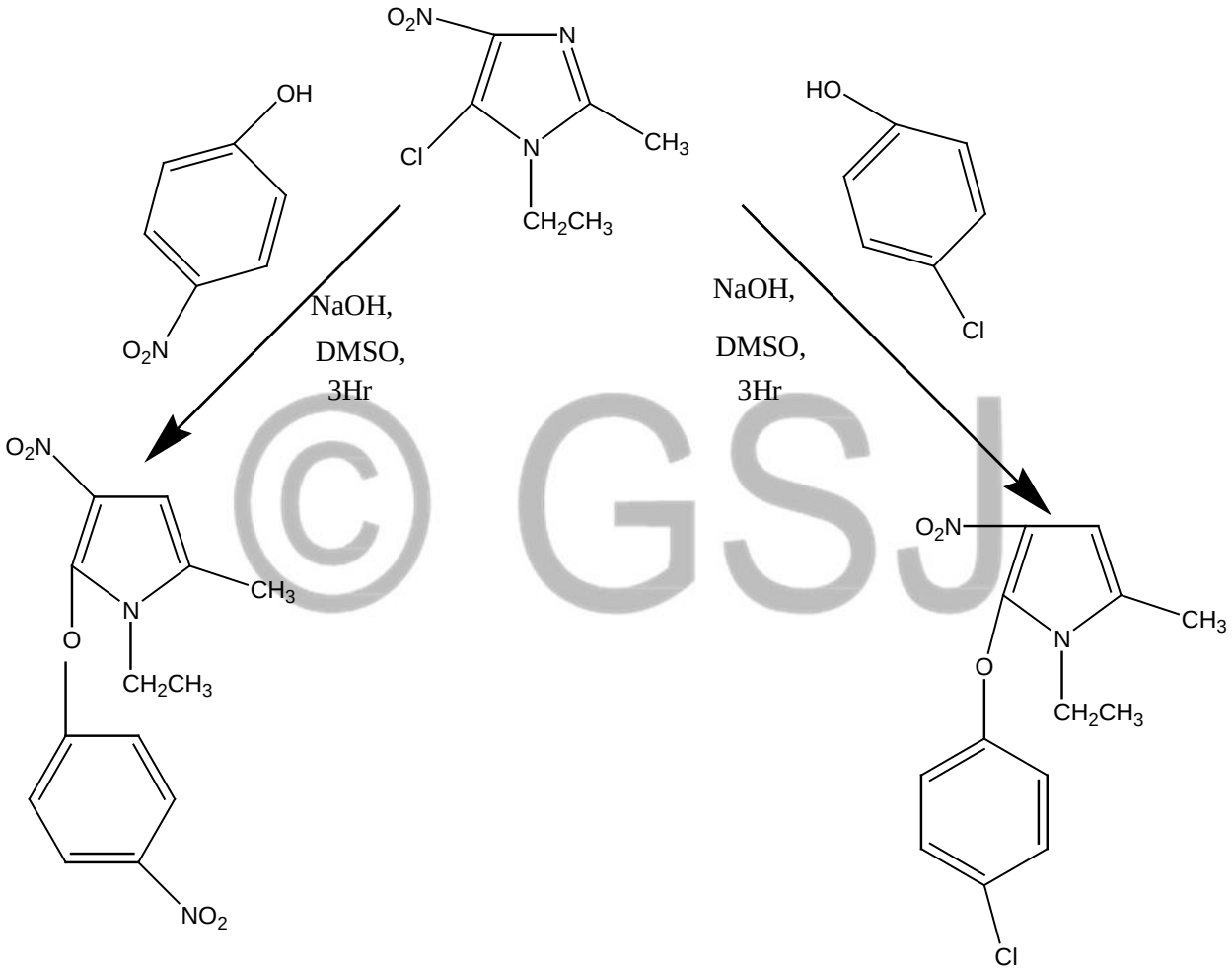
The synthesized compounds were screened for antibacterial activities against seven bacteria, include: *Enterococcus faecalis,Staphylococcus aureus*and *Staphylococcus epidermidis* were Gram-positive bacteria while*Escherichia coli Shigelladysenteriae,Klebseillapneumoniae,*and*Pseudomonas aeruginosa*were Gram-negative bacteria. Agar well diffusion method as described by Murray *et al.* (1995) [17] was applied. Cefuroxime Axetil was used as a standard drug.

3.0 RESULTS AND DISCUSSION

3.1 Synthesis of Phenoxyl Derivatives of Imidazole

1-methyl-2-ethyl-4-nitro-5-(4-chloro phenoxyl) imidazole (Compound B) and 1-methyl-2-ethyl-4-nitro-5-(4-nitro phenoxyl) imidazole (Compound C) were synthesized by coupling p-chloro phenol and p-nitro phenol respectively with 1-ethyl-2-methyl-4-nitro-5-chloro imidazole. The scheme of the reaction is shown below.The ^1H NMR spectra(Fig. 1 and 2) showed the peaks in the range of 1.18 ppm to 3.82 ppm, these confirmed the presence of methyl and methylene protonsin both compounds while the peaks in the range of 6.83 ppm to 8.25 ppm were characteristic peaks of aromatic protons present

the compounds. Furthermore, ^{13}C NMR spectra(Fig. 3 and 4) revealed the peaks between 13.62 ppm and 38.83 ppm and confirmed the presence of sp^3 carbons in the compounds. Aromatic carbons were seen between 115.50 and 160.38 in the spectra of both compounds.



C **B**

Scheme 1: Synthesis of Phenoxyl Derivatives of Imidazole. B: 1-methyl-2-ethyl-4-nitro-5-(4-chloro phenoxyl) imidazole and C: 1-methyl-2-ethyl-4-nitro-5-(4-nitro phenoxyl) imidazole.

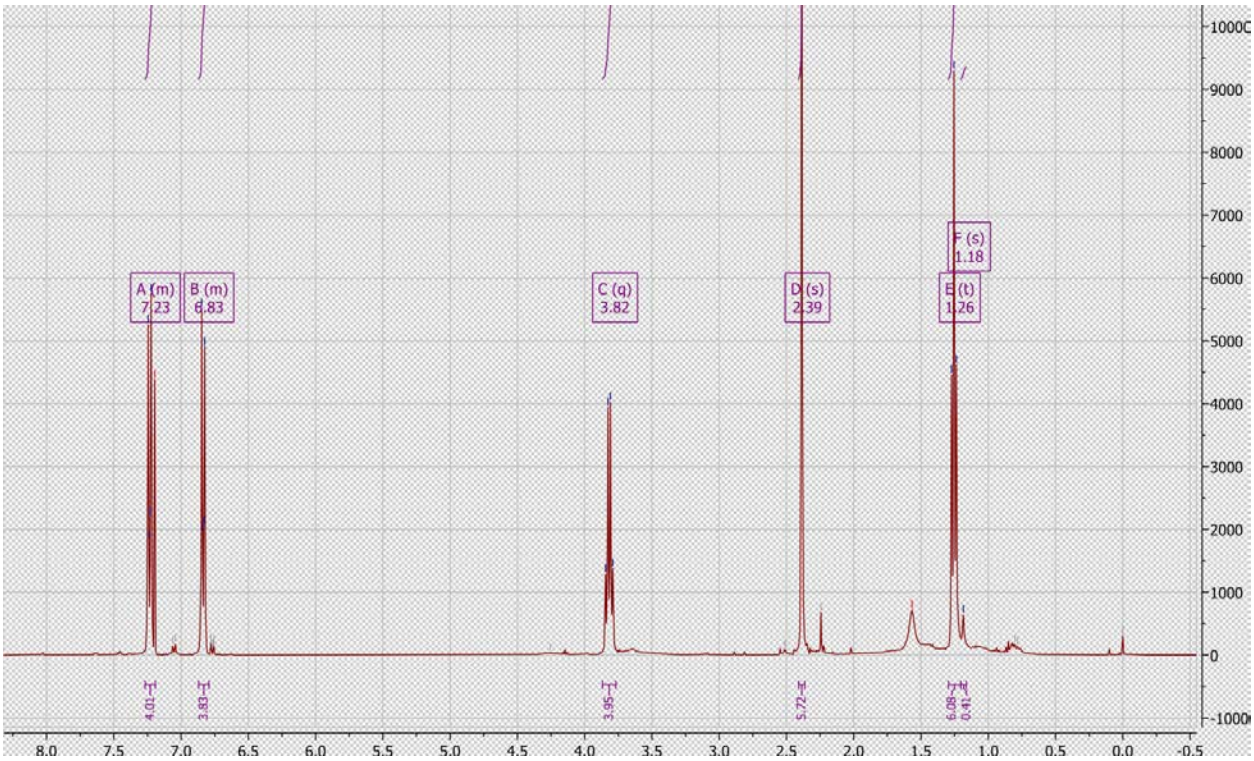


Figure 1: ^{1}H NMR spectrum of 1-methyl-2-ethyl-4-nitro-5-(4-chlorophenoxyl) imidazole.

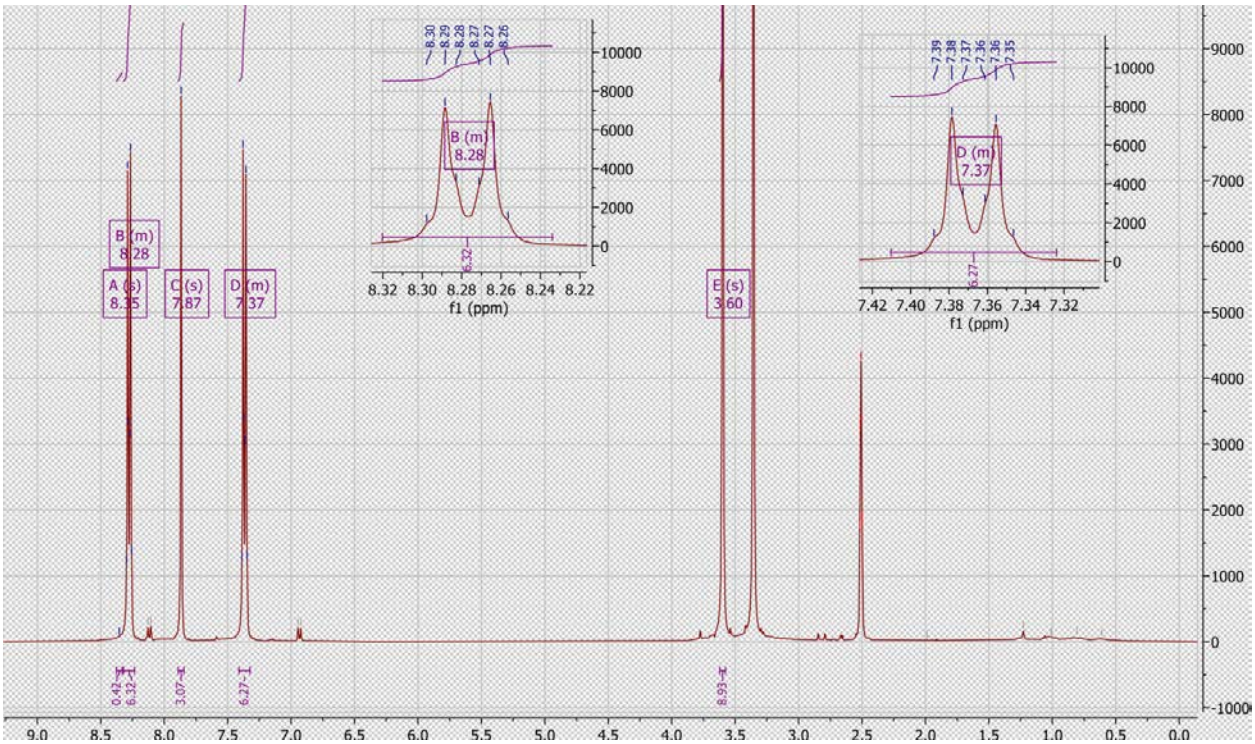


Figure 2:[1] H NMR Spectrum of 1-methyl-2-ethyl-4-nitro-5-(4-nitrophenoxyl) imidazole

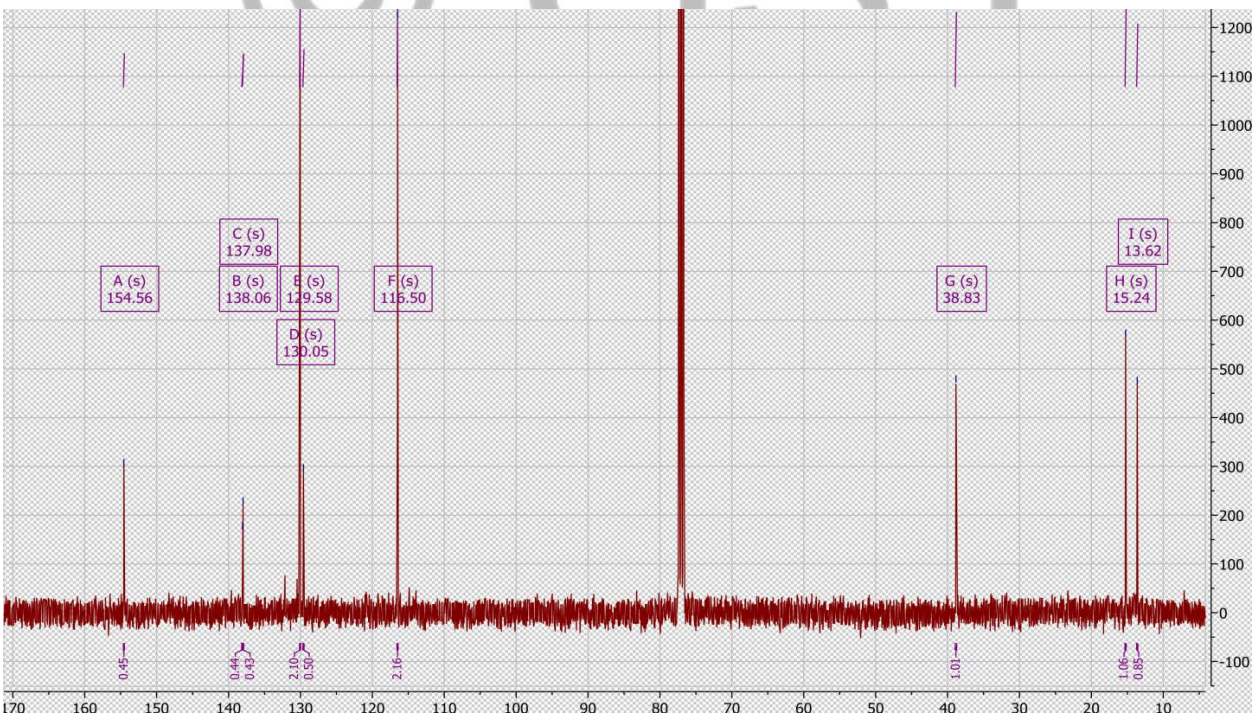


Figure. 3:[13]C NMR spectrum of 1-methyl-2-ethyl-4-nitro-5-(4-chlorophenoxyl) imidazole.

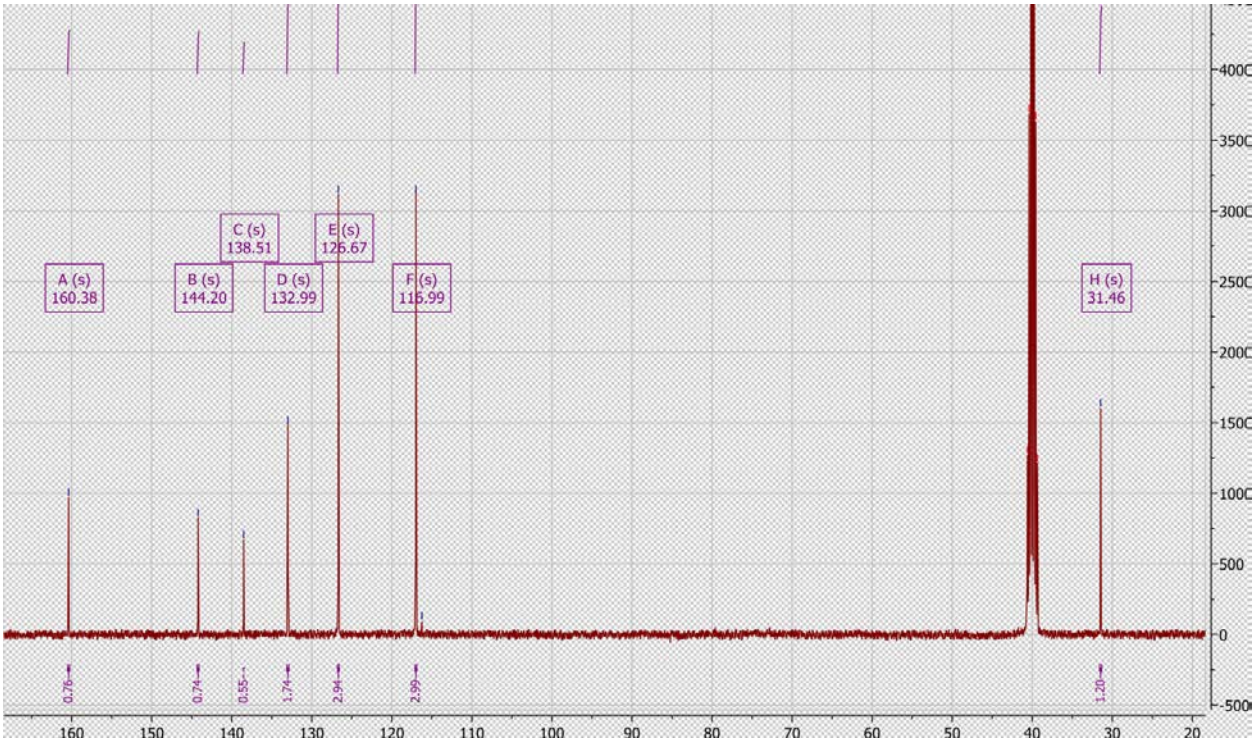


Figure 4: ^{13}C NMR Spectrum of 1-methyl-2-ethyl-4-nitro-5-(4-nitrophenoxyl) imidazole.

3.2 *In vitro* Antibacterial Screening

The inhibitory results are reported on Table 1 and the results showed both synthesized compounds exhibited certain degree of antibacterial activities.Generally, the standard drug performed better than both compounds. Compound C showed greater potency with Gram-positive bacteria than compound C. The activity of compound B against *Escherichia coli* is higher than compound C. Both compounds demonstrated similar potency against *Shigelladysenteriae*. Other Gram-negative bacteria were more inhibited using compound C and compound B. The presence of nitro group on the benzene in the

compound C might be responsible for higher antibacterial activities when compared to compound B which possessed chlorine atom on the benzene ring.

Table 1: Antibacterial activities of synthesized compounds

Bacteria	(Compound B). (mm)	(Compound C). (mm)	Cefuroxime Axetil (mm)
Escherichia coli	12.00	11.50	17.00
Pseudomonasaeruginosa	10.00	12.00	14.00
Shigelladysenteriae	10.00	10.00	20.00
Klebseillapneumonia	11.00	14.00	19.00
Enterococcus faecalis	12.00	14.00	29.00
Staphylococcus aureus	8.00	12.00	18.00
Staphylococcusepidermidis	8.00	9.00	13.00

B: 1-methyl-2-ethyl-4-nitro-5-(4-chloro phenoxyl) imidazole and C: 1-methyl-2-ethyl-4-nitro-5-(4-nitro phenoxyl) imidazole.

4.0 Conclusion

The syntheses of 1-methyl-2-ethyl-4-nitro-5-(4-chlorophenoxyl) imidazoleand 1-methyl-2-ethyl-4-nitro-5-(4-nitrophenoxyl) imidazole were successful. Both compounds demonstrated inhibition against Gram-negative and Gram-positive bacteria. The

electron-withdrawing effect of nitro group on benzene ring seemed to enhance the antibacterial activities of 1-methyl-2-ethyl-4-nitro-5-(4-nitrophenoxyl) imidazole.

5.0 Reference

1. Jain A. K., RavichandranV., Sisodiya M., Agrawal R. K. (2010). Synthesis and antibacterial evaluation of 2-substituted-4,5-diphenylN-alkyl imidazole derivatives.*Asian Pacific Journal of Tropical Medicine*471-474.

2. The Global Risks Report 2017, 12th ed.; World Economic Forum: Geneva, Switzerland, 2017; pp. 1–78. ISBN 978-1-944835-07-1.

3. Song J. H. (2008). What's new on the antimicrobial horizon? *Int J Antimicrob Agents*; 32 Suppl4:S207-13.

4. Boucher H. W., Talbot G. H., Benjamin D. K., Bradley J., Guidos R. J., Jones R. N. Murray B. E., Bonomo R. A. Gilbert D. (2013) 10×020 Progress—development of new drugs active against gram-negative bacilli: An update from the Infectious Diseases Society of America. *Clin. Infect. Dis.* 56, 1685–1694.

5. Canton R., Coque T. M. (2006) The CTX-M beta-lactamase pandemic. *Curr.Opin.Microbiol.* 9, 466–475

6. Mirjana S., Renata O., Alma R., Tomislav S., Tomica H. and Ines P. (2018) Novel Imidazole Aldoximes with Broad-Spectrum Antimicrobial Potency against Multidrug Resistant Gram-Negative Bacteria. *Molecules* 23, 1212; doi:10.3390/molecules23051212

7. Bipin K. V., Sunil K., Umesh K., Savita P. and Priti A. (2017). Synthesis of new Imidazole Derivatives as effective Antimicrobial Agents.*Indian J. Pharm. Biol. Res.* 5(1):1-9

8. Odžak R., Skocˇibušic´ M., MaravicA. (2013) Synthesis and antimicrobial profile of N substitutedimidazoliumoximes andtheirmonoquaternarysaltsagainstmultidrugresistantbacteria.*Bioorg.Med*. Chem. 21,7499–7506.

9. Zhang L., Peng, X. M., Damu G. L., Geng, R.X., Zhou, C. H. (2014). Comprehensive review in current developments of imidazole-based medicinal chemistry.*Med. Res. Rev*. 34, 340–437.

10. Nakamura T., Kakinuma H., Umemiya H., Amada H., Miyata N., *et. al* (2004) Imidazole derivatives as new potent and selective 20-HETE synthase inhibitors. *Bioorg Med ChemLett*. 14: 333-336.

11. Roman G., Riley J.G., Vlahakis J.Z., Kinobe R.T., Brien J.F., et al. (2007) Hemeoxygenase inhibition by 2-oxy-substituted 1-(1H-imidazol-1-yl)-4phenylbutanes: effect of halogen substitution in the phenyl ring. *Bioorg Med Chem*. 15: 3225-3234.

12. Bbizhayev M.A. (2006) Biological activities of the natural products. *Life Sciences* 78: 2343–2357.

13. Nantermet P.G., Barrow J.C., Lindsley S.R., Young M., Mao S. S., et al. (2004) Imidazole acetic acid TAFIa inhibitors: SAR studies centered around the basic P 1′ group. *Bioorg Med ChemLett*. 14: 2141-2145.

14. Brown E.G. (2012) Ring nitrogen and key biomolecules: The biochemistry of N-heterocycles. *Springer Science and Business Media*

15. Papadopoulou M. V., Bloomer W. D., Rosenzweig H. S., Arena A., Arrieta F., Rebolledo J. C., Smith D.K. (2014). Nitrotriazole- and imidazole-based amides and sulfonamides as antitubercular agents. *Antimicrob.Agents Chemother*.58, 6828–6836.

16. Wallach, O. Liebigs Ann. 1877, 184, 331.

17. Murray P. R., Baron E. J., Faller M. A., Terrover F. C., and Yolken H. R., (1995). Mannual of clinical microbiology. 15-18 ASM press D. C.