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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SUBSTITUTED PHENYL OXAZOLE -2,4-DIAMINE DERIVATIVES

Ashitha P.V.*, Nivea Cleo and Dr. Minu B. Pattasseril

Assistant Professor, KMCT College of Pharmaceutical Sciences, Kallanthode, 673601 Kozhikode, Kerala.

***Corresponding Author: Ashitha P.V.**
Assistant Professor, KMCT College of Pharmaceutical Sciences, Kallanthode, 673601 Kozhikode, Kerala.

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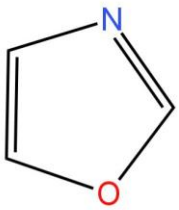
ABSTRACT
The present study deals in the reaction of aniline with chloroacetyl chloride to produce an intermediate, which undergoes condensation with urea under reflux in the presence of ethanol to produce oxazole derivatives. The synthesized compounds were characterized by IR spectral data. The Compounds were screened for antimicrobial activity against strains of gram positive and negative bacteria. The synthesized compounds displayed interesting antimicrobial activity. Compounds 3b was the most potent in this study and displayed higher activity compared to the reference drugs. All the other compounds showed good to moderate antibacterial activity.

KEYWORDS: Oxazole, *Staphylococcus aureus*, chloroacetylchloride, antimicrobial.

INTRODUCTION

Oxazole is the parent compound for vast class of heterocyclic aromatic organic compounds. These are azoles with an oxygen and nitrogen separated by one carbon. Substitution in oxazole derivatives provides marked biological activities like antibacterial, antifungal, anti-inflammatory etc. In focus of above observations demand for a new class of antibacterial agents is substantially high in the last decade due to increased resistance towards various available antibiotics. An attempt has been made to synthesise new oxazole derivatives with the hope to get better antibacterial agents. Synthesised compounds were characterised by IR spectrum and screened for antimicrobial activity against gram negative bacteria E.coli and gram positive bacteria Staphylococcus aureus by disc diffusion method.



Structure of oxazole

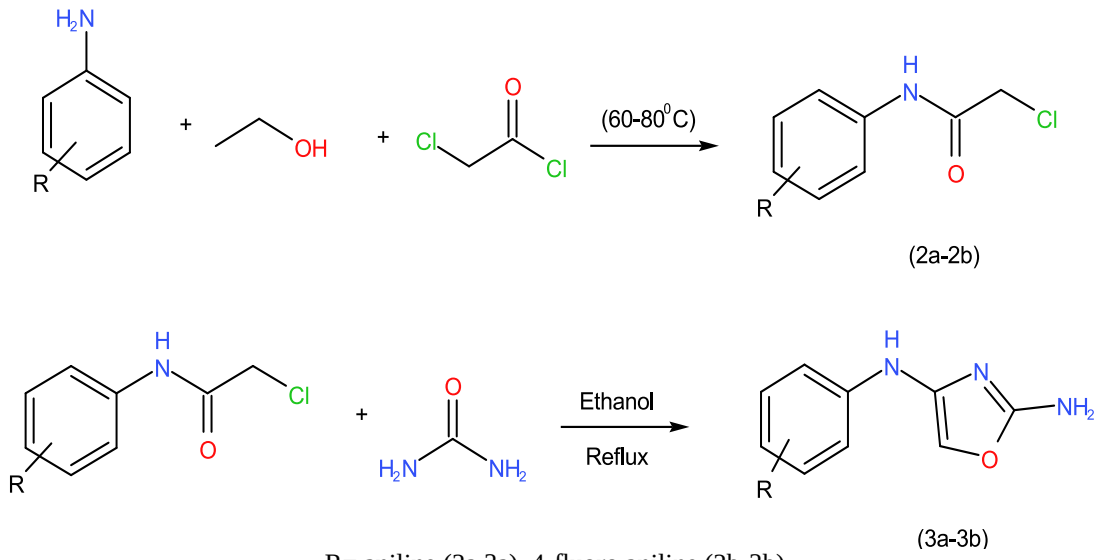
MATERIALS AND METHODS

All the chemicals and reagents were obtained from Isochem laboratories (Angamaly, Kochi), and TCI chemicals, Chennai and used without further purification. The reactions were monitored by preparative TLC and visualization on TLC was achieved by iodine chamber. The melting points of the synthesized compounds were determined by open capillary method using melting point apparatus.

The characterisations of synthesized compounds were confirmed by IR spectra. The infrared spectra were recorded on FTIR spectrophotometer (Shimadzu CORP 00271) KMCT College of pharmaceutical sciences, Kallanthode.

General method for synthesis of substituted 2-chloro N-phenyl acetamide and its derivative (2a-2b)

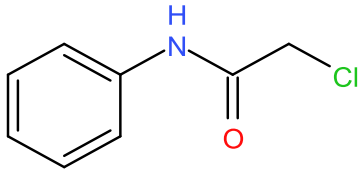
5ml substituted aniline is mixed with 7 ml of ethanol were shaken in a magnetic stirrer for half an hour.4 ml chloroacetylchloride was added drop by drop to the above mixture. The mixture was then stirred for half an hour with heating. The stirred mixture was then poured into ice cold water. The mass obtained was filtered and recrystallized from ethanol.



R= aniline (2a,3a), 4-fluoro aniline (2b-3b)

Scheme 1: The synthetic route of substituted N^4-phenyl oxazole 2, 4-diamine derivatives.

2-chloro N-phenyl acetamide (2a)



Greyish brown; 80 % yield, Mp: 136-139^0 C, IR (cm^{-1}): 3350 cm^{-1} (NH stretch), 1550 cm^{-1} (C=O stretch), 3050 cm^{-1} (aromatic CH stretch), 1610 cm^{-1} (C=C stretch), 557 cm^{-1} (C-Cl stretch).

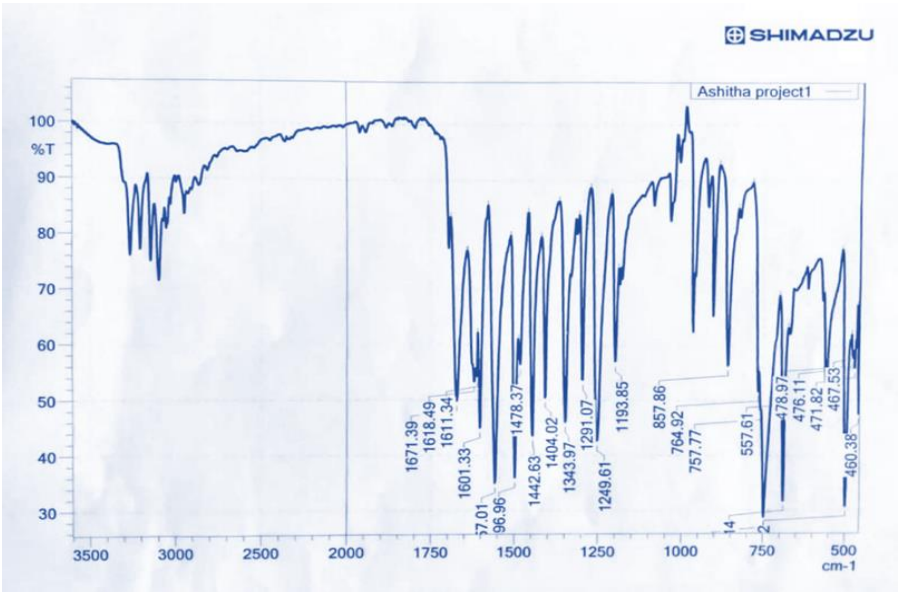
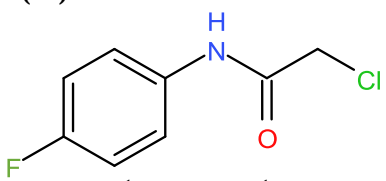


Figure1: IR spectra of 2-chloro N –phenyl acetamide (2a).

2-chloro N - (4- fluorophenyl) acetamide (2b)



Pale yellow; 85 % yield, Mp: 110-119^0 C, IR (cm^{-1}): 3350 cm^{-1} (NH stretch), 1550 cm^{-1} (C=O stretch), 3050 cm^{-1} (aromatic CH stretch), 1610 cm^{-1} (C=C stretch), 557 cm^{-1} (C-Cl stretch), 1211 cm^{-1} (C-F stretch).

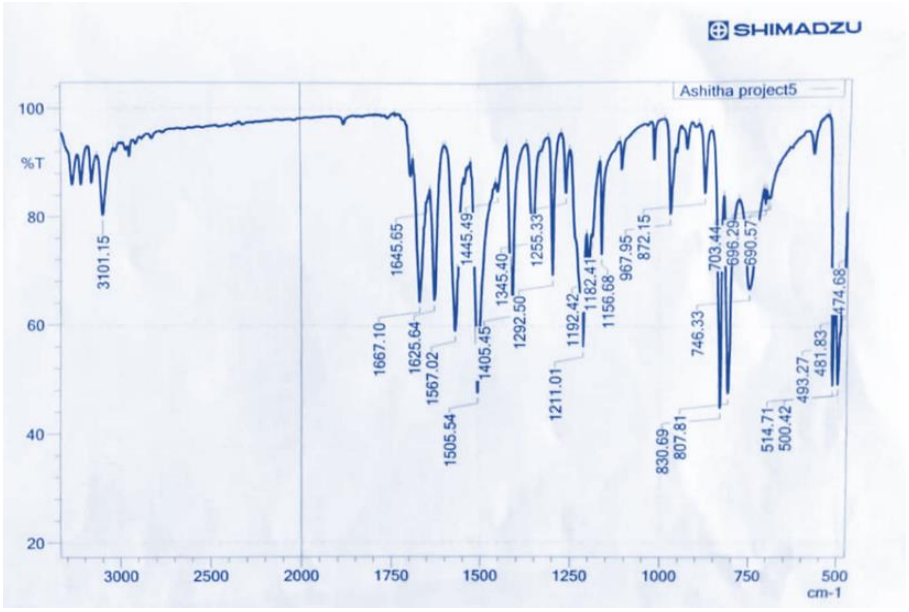
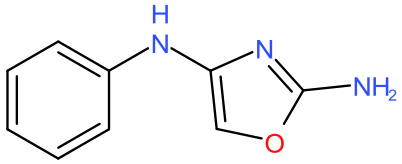


Figure 2: IR spectra of 2-chloro N - (4- fluorophenyl) acetamide (2b).

General method for synthesis of substituted N^4-phenyl oxazole 2, 4-diamine and its derivative (3a-3b):
A mixture of substituted 2-chloro N-phenylacetamide (1.6g) and urea (0.6 g) were dissolved in 10 ml ethanol and the reaction mixture stirred at reflux for 2 hours and poured in to ice cold water and filtered.

N^4-phenyl oxazole 2, 4-diamine (3a)



N^4-phenyl oxazole 2,4-diamine

Off white; 60% yield, Mp: 210-214^0 C, IR (cm^{-1}): 3300 cm^{-1} (NH stretch), 1671 cm^{-1} (C=N stretch), 3430 cm^{-1} (aromatic CH stretch), 1610 cm^{-1} (C=C stretch), 557 cm^{-1} (C-Cl stretch), 1211 cm^{-1} (C-F stretch), 1193 cm^{-1} (C-O stretch).

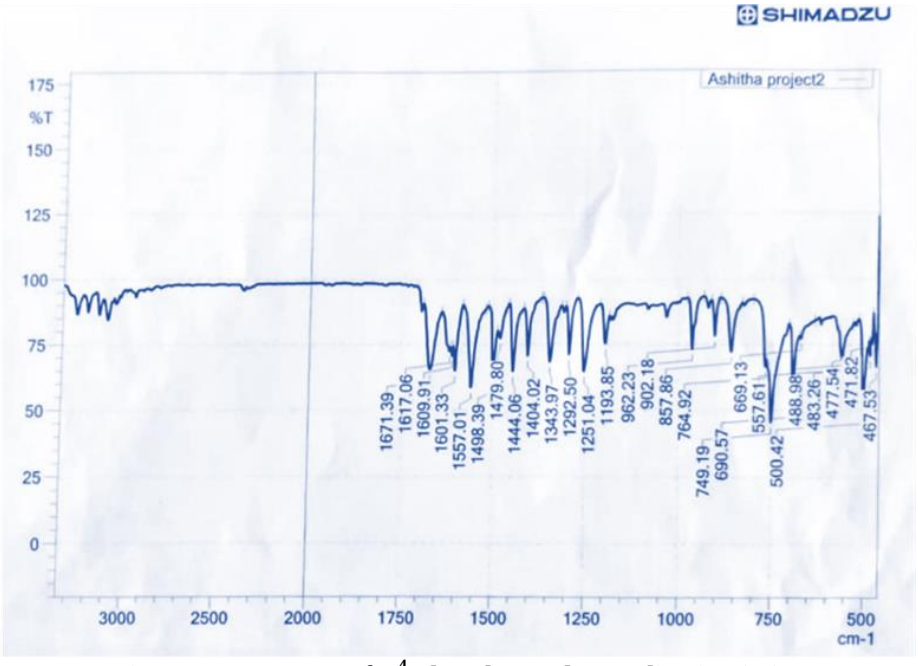
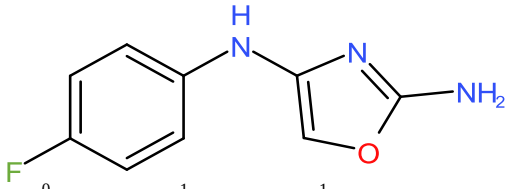


Figure 3: IR spectra of N^4-phenyl oxazole 2, 4-diamine (3a).

N^4 – (4-fluoro phenyl) oxazole 2, 4-diamine (3b)



Pale brown; 63% yield, Mp: 198-205^0 C, IR (cm^{-1}): 3350 cm^{-1} (NH stretch), 1667 cm^{-1} (C=N stretch), 3050 cm^{-1} (aromatic CH stretch), 1610 cm^{-1} (C=C stretch), 557 cm^{-1} (C-Cl stretch), 1211 cm^{-1} (C-F stretch) 1182 cm^{-1} (C-O stretch).

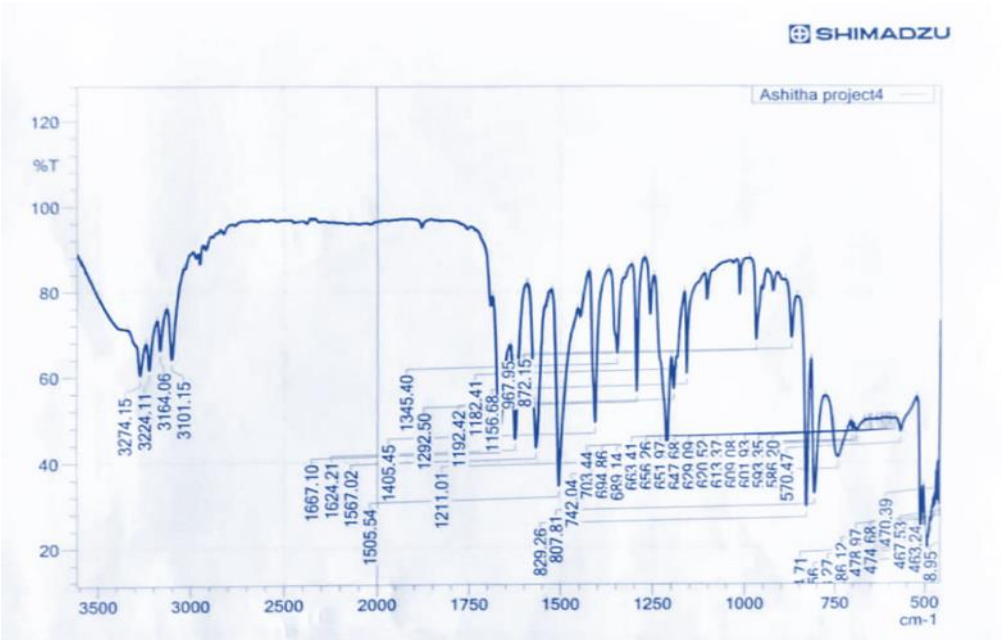


Figure 4: N^4 - (4-fluoro phenyl) oxazole 2, 4-diamine (3b).

Anti-microbial activity

All the synthesized compounds were screened for their antimicrobial properties against *Staphylococcus aureus*, (gram positive) *E.coli* (gram negative bacteria).The antimicrobial activities of the synthesized compounds done by disc diffusion method .Bacterial inoculums were spread on nutrient agar. After the inoculums dried, 6mm diameter wells were made in the agar plate with a sterile cork borer. The synthesized compounds were taken in the concentration of 20µg/ml. Ciprofloxacin 50µg/ml was used as standard for the antimicrobial activity. The petridish were incubated at 37◦C for 24 hours. The zone of inhibition was measured in mm to estimate the potency of the test compounds.

RESULT AND DISCUSSION

Oxazole and halogenated oxazole show wide spectrum of pharmacological applications. The synthesis of all compounds was carried out as depicted in scheme-1. The resulting compounds were purified by recrystallization using ethanol. All the synthesized compounds were characterized by FT-IR. The IR spectrum of synthesized compound showed characteristic absorption bands of C=N in the range of1660-1750 cm^{-1} and C-O stretching in the range of 1180-1200 cm^{-1} confirms the formation of synthesized compounds.

Table No 1: Physical data of oxazole derivatives.

Compound	Molecular formula	Molecular weight	Melting point	% Yield
3a	$C_9H_9N_3O$	175.19	210-214^0	60
3b	$C_9H_8FN_3O$	193.18	198-205^0	63

Antimicrobial Activity

The synthesized compounds were screened for antimicrobial activity against strains of gram positive *Staphylococcus aureus* and negative bacteria *E.coli*. All synthesized compounds are showed better activity when compared to standard ciprofloxacin. The compound 3b shows excellent activity against *Staphylococcus aureus and E.coli*. The compound 3b may cause higher antimicrobial activity due to the presence of fluorine.

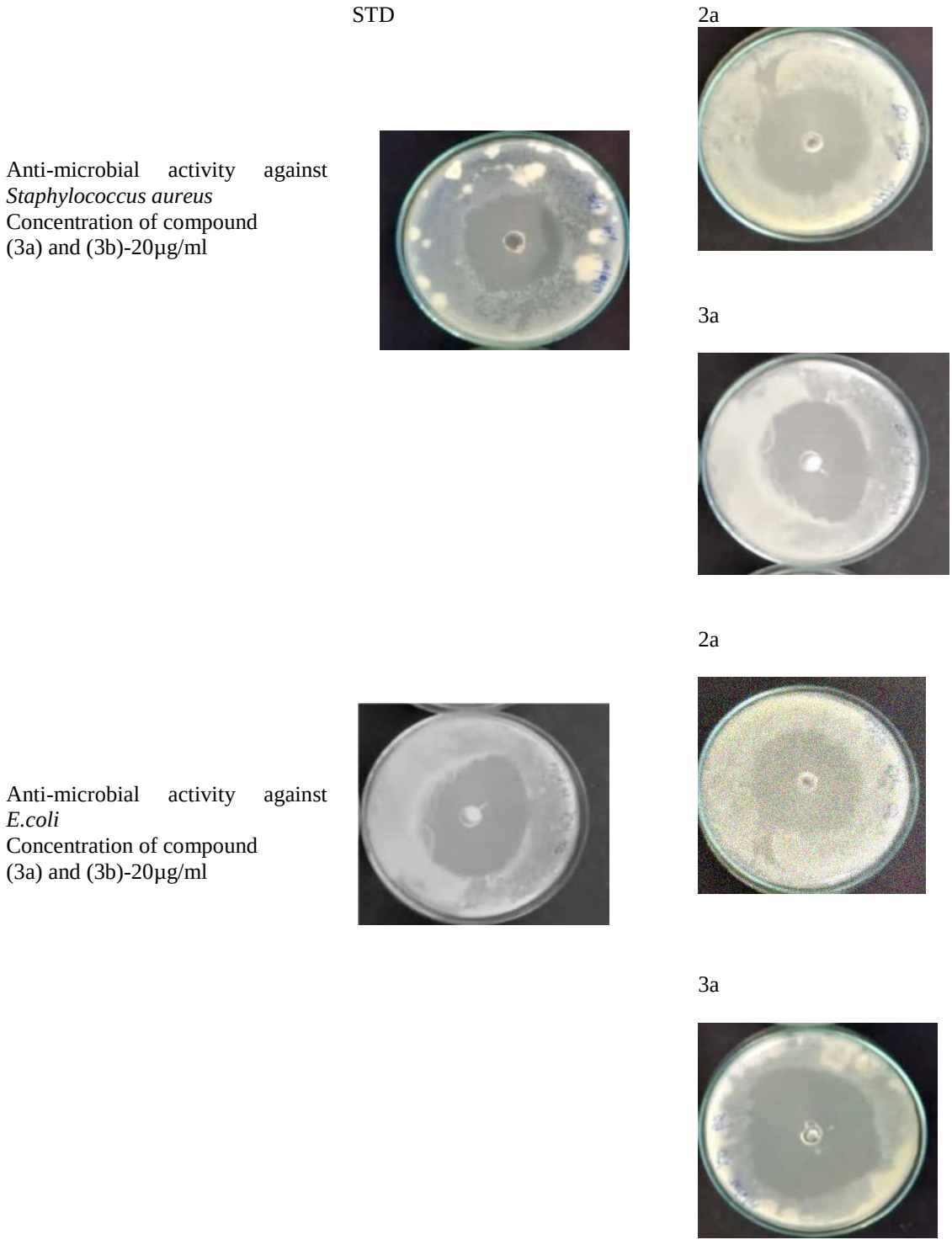


Figure 5: Zone of inhibition of synthesized compounds against *Staphylococcus aureus* and *E.coli* strains.

Table No. 2: Zone of inhibition of synthesized compounds.

Compounds	Concentration (µg/ml)	Zone of inhibition (mm) Staphylococcus aureus	Zone of inhibition (mm) E.coli
3a	20	31	30
3b	20	34	38
Ciprofloxacin	50	26	33

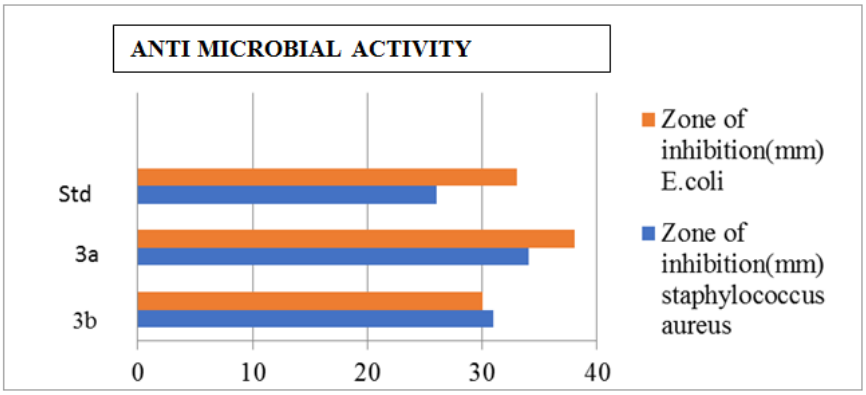


Figure 6: Graphical representation of antimicrobial activity of synthesized compounds.

SUMMARY AND CONCLUSION

In the study we have synthesized new derivatives of oxazole using aniline and 4-fluoro aniline by conventional method. The IR spectrum of synthesized compound showed characteristic absorption bands of C=N in the range of1660-1750 cm^{-1} and C-O stretching in the range of 1180-1200 cm^{-1} confirms the formation of synthesized compounds. These were screened for its antimicrobial activity against ciprofloxacin. Both the compounds showed better activity against gram positive and gram negative bacterial strains. But the compound 3b showed better activity (34 mm and 38 mm), this may because of presence of the highly electro negative atom like fluorine. So further studies can be done by using this compound as a lead molecule for the development of further antibacterial agent.

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