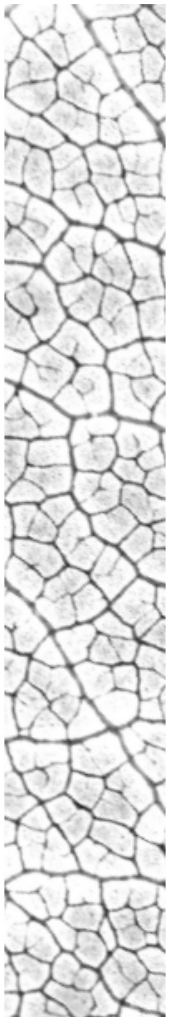

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Synthesis of some new 1,3,4-oxadiazole compounds derived from 1H-imidazole and study their biological activity

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Abstract
Ethyl 2-(1H-imidazol-1-yl)acetate (A_1) was synthesized by the reaction of ethylchloroacetate with imidazol, Then refluxed with hydrazine hydrate to obtain 2-(1H-imidazol-1-yl)acidhydrazid (A_2) . (A_2) was reaction with various substituted benzyldehyd to gain 6 novel compounds shiffe bases(A_{3-8}).and 5-(1H-imidazol-1-yl)methyl)3-N-acetyl-2-(aryl)-1,3,4-(2H)-Oxadiazol (A_{9-14}) were synthesized by the reaction of shiffe bases(A_{3-8})with acetic anhydride .In order to show the antibacterial activity of prepared compounds are evaluated against four types of common bacteria (***Proteus spp,S.pyogenes***, *Escherichia coli,p.aeruginosa*). The result of biological study are compared with standered antibiotic (**Ciprofloxacin** & **Tetracycline**). The structure of the synthesized compounds are confirmed by I.R, ^{1}H-NMR &^{13}C-NMR spectra and Some chemical physical data.

Keywords: imidiazole , oxadiazole, biological activity, shiffe base

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INTRODUCTION

Heterocyclic compounds have received considerable attention from researchers because of their important role in the medical and pharmaceutical fields. Several studies have shown that amidazole metabolites act as antibiotic against antibacterial (Moghadam et al. 2017, Skocibusic et al. 2018, Zavada et al. 2018), antifungal (Bae et al. 2018, Verma et al. 2017), and anticancer (Kumar et al. 2017, Ramanathan 2017, Tabassum et al. 2018), as well as ant inflammatory (Ali et al. 2017, Faisal and Jihad 2018, Tahlan et al. 2019, Veeraragavan et al. 2017). It has also been used in the industrial field as an antioxidant (Maruthamuthu et al. 2016).

1,3,4-Oxadiazole is a heterocyclic compounds containing an oxygen atom and two nitrogen atoms in a five-membered ring. More widely studied by researchers because of their many important chemical and biological activity. Such as anthelmintic activity against (Srinivas and Kumar 2010), antibacterial (Majed et al. 2018), anticonvulsant (Khatoon et al. 2017), anticancer (Amer et al. 2018), antioxidant (Alp et al. 2015), etc.

In this study, we considered the preparation of a number of derivatives of oxadiazole derived from amidazole as in the scheme (I) and study its biological effect on a number of negative bacteria and positive chromium dye.

MATERIALS AND METHODS

Chemicals and Instruments

Melting points are uncorrected and were recorded in an open capillary tube on Stuart melting point apparatus. Infrared spectra have been recorded on a ShimadzoFTIR-8100 spectrophotometer using KBr discs–and. the NMR spectrometer (H ^{1} -NMR, C^{13} -NMR) was measured at (Al-Bayt University | Water Research Center, Kingdom of Jordan Hashemite University. Using a device (Ultra shield 300 MHz.Bruker2003) And solvent was used DMSO -d_6. All solvents and chemical reagents have been purchased from Aldrich, alfaaesar, sigma. Reaction monitoring and verification of the purity of the compounds were done by TLC on silica gel-percolated alumni sheets (type 60 F254 Merck, Darmstadt, Germany) using appropriate element.

Synthesis of Ethyl 2-(1H-imidazol-1-yl)acetate (A_1): (Kharb et al. 2012) (A_1)

A mixtuer of amidazole (0.014 Mol) with ethyl chloroacetate (0.014 Mol) in 20 ml of dry acetone in presence of potassium carbonate (1.932 gm) was reflex for (6) hr. with stirring at (80) C°. The solvent evaporates

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Table 1. The physical properties of compounds

Comp .No	R	M.P (C^0)	Yield %	color	Molecular Formula
A_3	4-OH	146-148	53	Red	$C_{12}H_{12}N_4O_2$
A_4	4-N$(CH_3)_2$	162-164	66	yellow	$C_{14}H_{17}N_5O$
A_5	4-NO_2	118-120	25	Brown	$C_{12}H_{11}N_5O_3$
A_6	4-OCH_3	149-151	73	yellow	$C_{13}H_{14}N_4O_2$
A_7	3-NO_2	159-160	58	yellow	$C_{12}H_{11}N_5O_3$
A_8	H	213-215	78	yellow	$C_{12}H_{12}N_4O$

Table 2. The physical properties of compounds

Comp .No	R	M.P (c^0)	Yield %	Molecular Formula
A_9	4-OH	100-102	75	$C_{14}H_{13}N_4O_3$
A_{10}	4-N$(CH_3)_2$	88-91	55	$C_{16}H_{18}N_5O_2$
A_{11}	4-NO_2	157-158	42	$C_{14}H_{12}N_5O_4$
A_{12}	4-OCH_3	168-169	21	$C_{15}H_{15}N_4O_3$
A_{13}	3-NO_2	186-188	80	$C_{14}H_{12}N_5O_4$
A_{14}	H	96-98	66	$C_{14}H_{13}N_4O_2$

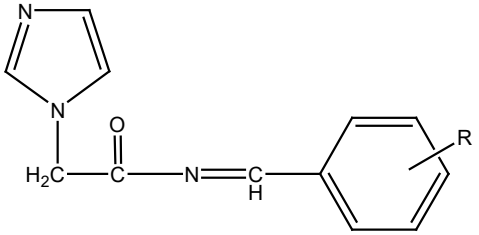
under the pressure and the solution is filtered and the separated product has been recrystallized from ethanol to give crystals of white color 86% melting point (48-50°).

Synthesis of 2 –(1H – imidazol -1 –yl) aced hydrazide: (Frank et al. 2007) (A_2)

A mixture of (0.004 mol \ 0.6178 gm) of A_1 with (0.04 mol \ 2 gm) of Hydrazine hydrate (80% in 20ml of Ethanol Absolute were reflex for (3) hr., concentrate the remaining solution and cooled The result was separated by filtration and re-crystallized from ethanol to get On Crystals of brown color (90%) Melting Point (61-62 M).

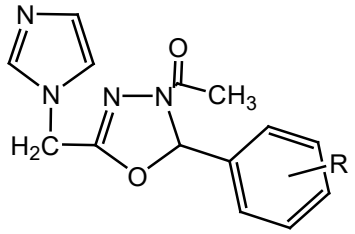
Synthesis of N-(aryldine)-2-(1H-imidazol – 1-yl) acetamide: (de Oliveiral et al. 2013) (A_{3-8})

A mixture of (0.0014 mol, 0.2 gm) of A_2 and aromatic Benzyldehyde (0.0014 mol) in (20ml) of absolute ethanolethe mixture were reflex for 4 hours concentrates the solution cools. The result was separated by filtration and re-crystallized from ethanol. Physical properties for synthesized compounds in a **Table 1**.



Synthesis of 5-(1H-imidazol-1-yl)methyl)3-N-acetyl-2-(aryl)-1,3,4-(2H)-Oxadiazole: (de Oliveiral et al. 2013) (A_{9-14})

A mixture of (0.01mol) from shiff base (A_{3-8}) with (10ml) of Acetic Anhydride, was reflexed for (6) hr., then the solvent evaporated by distillation. The residue was added to the crash ice. The result was separated by filtration and re-crystallized from Dioxins. Physical properties for synthesized compounds in a **Table 2**.



EVALUATION OF BIOLOGICAL ACTIVITY

The antimicrobial activities of the synthesized compounds were determined in vitro against several pathogenic representative microorganism (*Escherichia coli* and *Proteusspp),* using Agar well-diffusion method (Sharshira and Hamada 2011). Ciprofloxacin were used as standard drugs for studying the potential activities of these compounds. All the compounds were tested at different concentration level (0.01, 0.001, 0.0001 mg / ml), DMSO was used as solvent and as control. The inhibition zone diameter in mm (IZD) was used as a criterion for the antimicrobial activity. The lowest concentration required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC, µg/mL), was determined for all the compounds and compared with the control. The investigation of antibacterial screening data revealed that OXADIAZOLE derivatives (A_{9-14}). Compounds (A_{9-14}) exhibited good antibacterial activity towards the both gram negative bacteria (*Escherichia coli, p.aeruginosa*). Compounds (A_{9-14}) have also exhibited good antibacterial activity towards gram positive bacteria (***Proteus spp***, ***S.pyogenes***), showed high activity against all the microorganisms employed in contrast with the **Ciprofloxacin** & **Tetracycline**. The maximum activity (MIC = 12 µg/mL & MIC = 20µg/mL) was indicated for compounds. The results are summarized in figures.

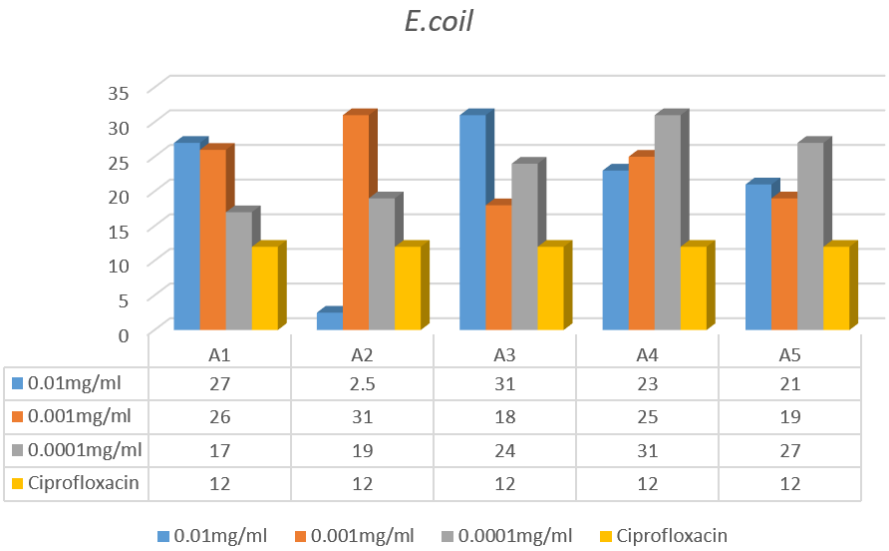


Fig. 1. Differential effect and different concentrations of compounds (A_{9-14}) studied against bacteria (*E.Coli*)

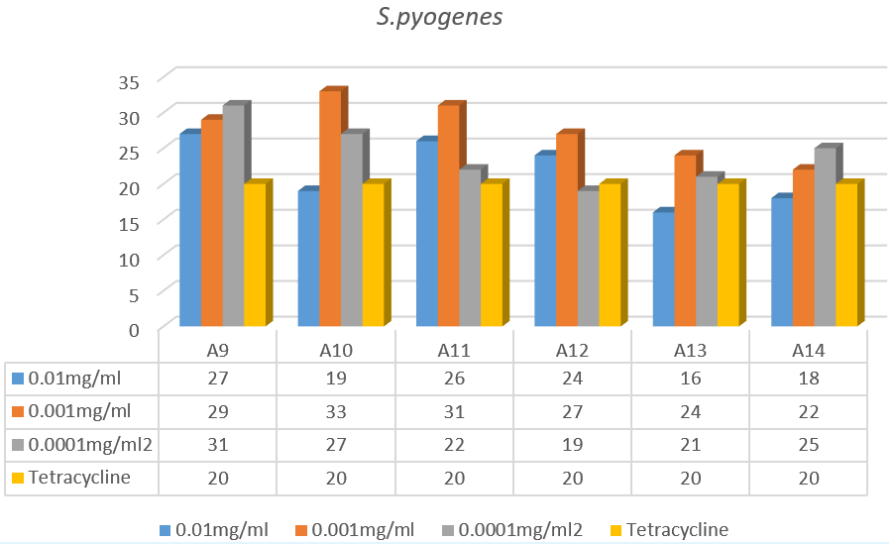


Fig. 2. Differential effect and different concentrations of compounds (W_{9-16}) studied against bacteria (*S.pyogenes*)

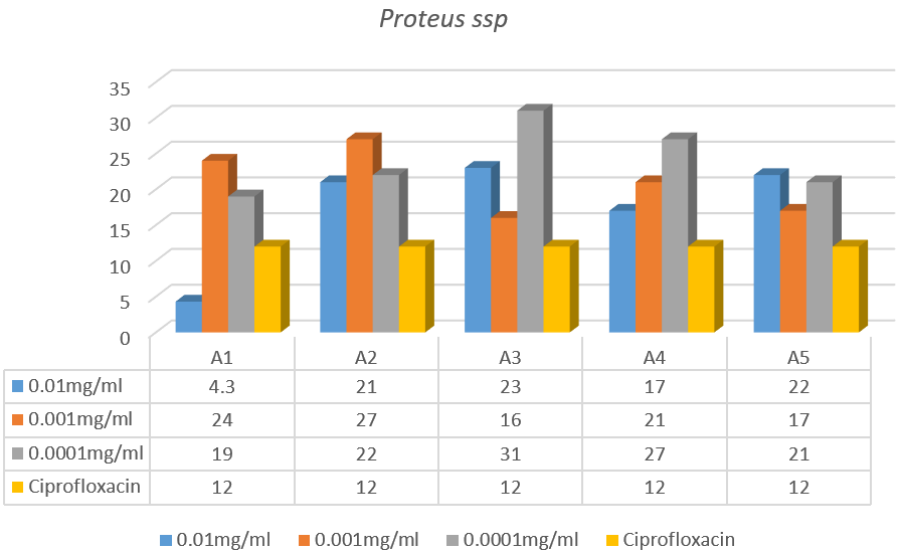


Fig. 3. Differential effect and different concentrations of compounds (A_{9-14}) studied against bacteria (*protussp*)

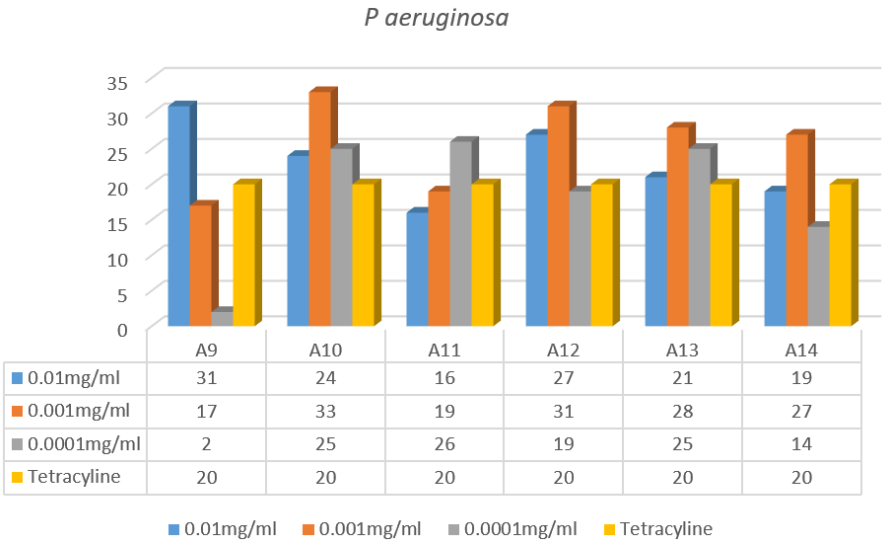


Fig. 4. Differential effect and different concentrations of compounds (W_{9-16}) studied against bacteria (*p.aeruinosa*)

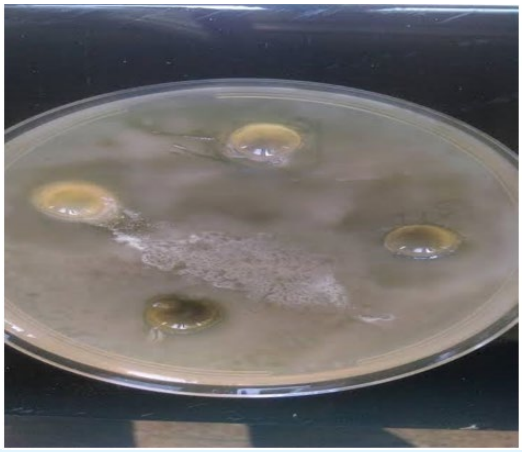


Fig. 5. Compound (A4) inhibits growth of bacteria E.Coli

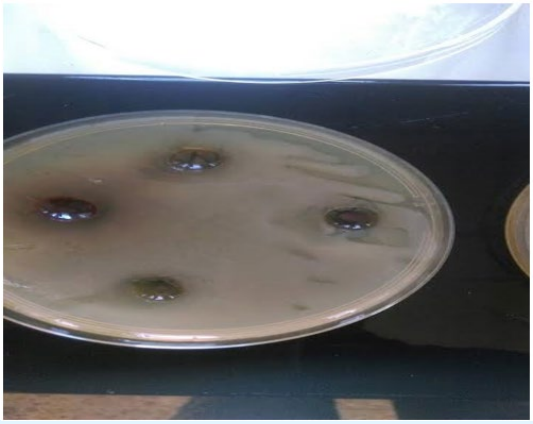


Fig. 7. Compound (A9) inhibits growth of bacteria P.areuginosa

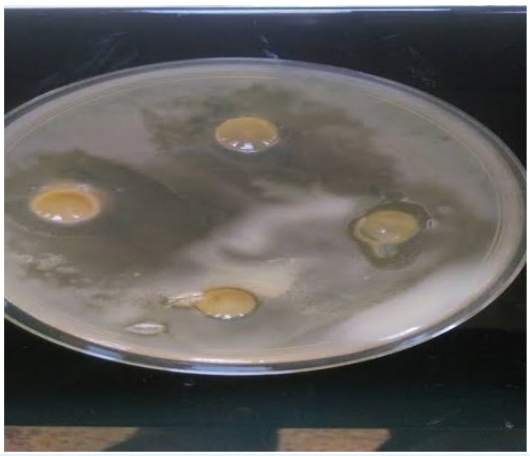


Fig. 6. Compound (A4) inhibits growth of bacteria E.Coli

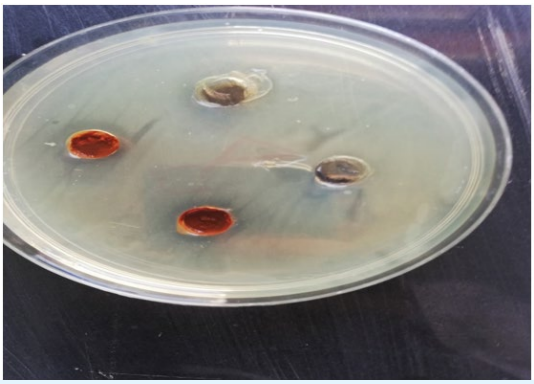


Fig. 8. Compound (A9) inhibits growth of bacteria P.areuginosa

RESULTS AND DISCUSSION

Ethyl 2-(1H-imidazol-1-yl)acetate (A_1) was synthesized from the reaction between ethyl chloro acetate and imidazole. The IR spectrum of this compound (A_1) is showed a band at (1750 cm^{-1}) which was assigned to the typical carbonyl group for ester. More over this compound exhibited significant bands in the region at (3080, 1450) belong to C-H Ar., and the band at (1150 cm^{-1}) due to the C-O-C for the ester. The H^1-NMR spectrum of (A_1) also showed a signal at the frequency (δ1.3ppm) to (3H, CH3) and a signal at

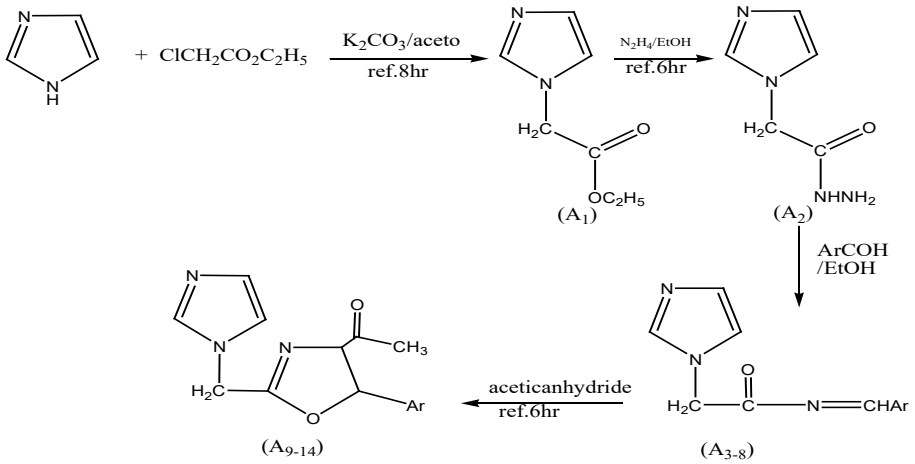


Fig. 9. Synthesis of title compound (A_{1-14})

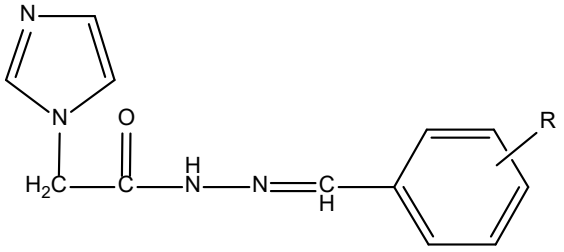


Table 3. IR –spectral data of Compounds (A_{3-8})

Compd. No.	R	IR υ cm^{-1}(KBr)				
		O ‖ C—N	C=C	C-N	C=N	others
A_3	4-OH	1677	1450,1556	1210	1604	3450 for OH
A_4	4-N(CH_3)$_2$	1690	1456,1558	1227	1598	2800-2900forC-H aliphatic
A_5	4-NO_2	1687	1450,1555	1202	1636	1250 As(C-O-C),1100 Sy(C-O-C)
A_6	4-OCH_3	1699	1456-1556	1227	1602	2800-2900for C-H aliphatic
A_7	3-NO_2	1679	1450-1550	1120	1606	1250 As(C-O-C),1100 Sy(C-O-C)
A_8	H	1684	1438,1510	1169	1606	

frequency (δ3.6ppm) to (2H, CH2) for the ethyl group, and a signal at frequency (δ 4.6ppm) due to (2H, CH2) of the methyl group, as well as a signal at the range (δ 6.5-7.6 ppm) to (3H imidazole). C^{13}-NMR showed a signal at δ 616 ppm related to (C, CH3) and a signal at δ 60 ppm regarding to (C, CH2, ethyl) and a signal at frequency (δ 60ppm) concerning the carbonyl) as well as a signal at (δ 120, 135, 145 ppm) referring to C2, C3, C5, imidazole. The 2 –(1H – imidazol -1 –yl) acid hydrazide was synthesized from Ethyl 2-(1H-imidazol-1-yl)acetate and hydrazine hydrate as it was stated in the experimental part. The IR –spectrum of this compound showed (KBr cm^{-1}) stretching bands at (3300, 3190 and 3041) cm^{-1} which assigned to the asymmetrical and symmetrical band stretch bands of (NH2) and (NH) group and band at 1690 cm^{1-} which was assigned to the carbonyl group for acid hydrizid. A number of N-(aryldine)-2-(1H-imidazol – 1-yl) acetamide (A_{3-8}) were synthesized through the reaction of 2 –(1H – imidazol -1 –yl) acid hydrazide with aromatic benzeyldehyd in presence of ethanol (**Scheme 1**). The structure of the synthesized compounds were confirmed by their melting point and IR-spectroscopy H-NMR & C^{13}-NMR. The characteristic absorption bands (KBr cm^{-1}) are shown in **Tables 3**-**6**. The reaction of synthesized compound (A3-8) With acetic anhydride give 5-(1H-imidazol-1-yl)methyl)3-N-acetyl-2-(aryl)-1,3,4-(2H)-Oxadiazole. The structure of the synthesized compounds were confirmed by their melting point and IR-spectroscopy H-NMR & C^{13}-NMR. The characteristic absorption bands (KBr cm^{-1}) are shown in **Tables 4**, **7** and **8**. It was worth to say here that the synthesized compounds will be studied in the nearest future to show their expected biological activity.

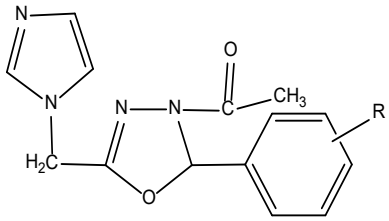


Table 4. IR –spectral data of Compounds (A_{9-14})

Compd. No.	R	IR υ cm^{-1}(KBr)					
		O ‖ C—N	C=C	C-N	C=N	C-O-C	Others
A_9	4-OH	1710	1450,1556	1210	1604	1100	3450 for OH
A_{10}	4-N(CH_3)$_2$	1700	1456,1558	1227	1598	1125	2800-2900 for C-H aliphatic
A_{11}	4-NO_2	1709	1450,1555	1202	1636	1120	1250 As(C-O-C),1100 Sy(C-O-C)
A_{12}	4-OCH_3	1710	1456-1556	1227	1602	1120	2800-2900 for C-H aliphatic
A_{13}	3-NO_2	1702	1450-1550	1120	1606	1125	1250 As(C-O-C),1100 Sy(C-O-C)
A_{14}	H	1708	1438,1510	1169	1606	1100	

Table 5. ^{1}HNMR of Compounds (A_{5-6})

Comp. No.	R	^{1}HNMR chemical shift in ppm
A_5	O-CH_3	4.0 (H,NH) 8.3 N=CH, Ar – H (7.05 –8.2),2.35 CH_3
A_6	NO_2	4.6 H,NH, 8.1 N=CH, Ar – H (6.00 –8.0)

Table 6. ^{13}C-NMR of Compounds (A_{5-6})

Comp. No.	R	C-NMR chemical shift in ppm^{13}
A_5	O-CH_3	165(C=O) 143(N=CH), 60CH_3
A_6	NO_2	160(C=O) 145(N=CH), (120,135,125) imidazole rang

Table 7. ^{1}HNMR of Compounds (A_{11-12})

Comp. No.	R	^{1}HNMR chemical shift in ppm
A_{11}	O-CH_3	2.6 for CH_3,acetyl, 2.0 (H,C3),3.6(H,C2)oxadiazole range,3.2(O-CH3)
A_{12}	NO_2	2.6 for CH_3,acetyl, 2.0 (H,C3),3.6(H,C2)oxadiazole range

Table 8. ^{13}C-NMRof Compounds (A_{11-12})

Comp. No.	R	C-NMR chemical shift in ppm^{13}
A_{11}	O-CH_3	20for CH_3,acetyl, 85 (C3),65(H,C2)oxadiazole range,45(O-CH3)
A_{12}	NO_2	20for CH_3,acetyl, 85 (C3),65(H,C2)oxadiazole range

CONCLUSIONS

This work describes new derivatives for the heterocyclic imidazole & oxadiazole. The antimicrobial activity of these compounds was evaluated against Gram-positive, Gram-negative bacteria. Most of the compounds showed moderate antimicrobial activity.

REFERENCES

Ali I, Lone MN, Aboul-Enein HY (2017) Imidazoles as potential anticancer agents. Med Chem Comm, (9): 1742-1773. https://doi.org/10.1039/C7MD00067G

Alp AS, Kılcıgil G, Özdamar ED, Çoban T, Eke B (2015) Synthesis and evaluation of antioxidant activities of novel 1,3,4-oxadiazole and imine containing 1H-benzimidazoles, Turkish Journal of Chemistry, 39: 42-53. https://doi.org/10.3906/kim-1403-44

Amer HH, Ali OM, Salama AA, El-gendy MS, Houssin OK (2018) Synthesis of some new 1,3,4-oxadiazole derivatives bearing sugars and Î±-aminophosphonate derived from 4-nitrophenol as anticancer agents. National Journal of Physiology, Pharmacy and Pharmacology, 8(9): 1275-86.

Bae SH, Park JH, Choi HG, Kim H, Kim SH (2018) Imidazole Antifungal Drugs Inhibit the Cell Proliferation and Invasion of Human Breast Cancer Cells. Biomol ther, 26(5): 494-502. https://doi.org/10.4062/biomolther.2018.042

de Oliveiral CS, Liral BF, Barbosa-Filholl JM, Lorenzoll JGF, de Menezesll CP, dos Santosll JMCG, et al. (2013) Synthesis and Testing of 3-Acetyl-2,5-Disubstituted-2,3-Dihydro-1,3,4-oxadiazole Derivatives for Antifungal

Activity Against Selected *Candida* Species. J. Braz. Chem. Soc., 24(1): 115-20. https://doi.org/10.1590/S0103-50532013000100016

Faisal M, Jihad MI (2018) Synthesis, Characterization and Anti-Inflammatory Activity Assessment of New Ibuprofen Analogues Containing Imidazole-4- One Derivatives. Journal of Global pharma Technology, 10(03): 134-41.

Frank PV, Girish KS, Kalluraya B (2007) Solvent-free microwave-assisted synthesis of oxadiazoles containing imidazole moiety. J. Chem. Sci., 119(1): 41-6. https://doi.org/10.1007/s12039-007-0007-7

Kharb R, Sharma PC, Bhandari A, Yar MS (2012) Synthesis, spectral characterization and anthelmintic evaluation of some novel imidazole bearing triazole derivatives. Der Pharmacia Lettre, 4(2): 652-7.

Khatoon Y, Shaquiquzzaman M, Singh V, Sarafroz M (2017) Synthesis, anticonvulsant and neurotoxicity screening of some novel 2, 5-Disubstituted - 1, 3, 4 – Oxadiazole derivatives. International Journal of Pharmaceutical Sciences and Drug Research, 9(1): 22-9. https://doi.org/10.25004/IJPSDR.2017.090104

Kumar M, Kumar D, Raj V (2017) Studies on Imidazole and its Derivatives with Particular Emphasis on Their Chemical/biological Applications as Bioactive Molecules/Intermediated to Bioactive Molecule. Curr Synthetic Systems Biology, 5(1). https://doi.org/10.4172/2332-0737.1000135

Majed N, Majid R, Majed R (2018) Synthesis of some new heterocyclic compounds derived from β-Lactam derivatives and Their Biological Activity Study. J. Pharm. Sci. & Res., 10(11), 2964-8. https://doi.org/10.22159/ajpcr.2018.v11i10.29048

Maruthamuthu, Rajam S, Stella PCR, et al. (2016) The chemistry and biological significance of imidazole, benzimidazole, benzoxazole, tetrazole and quinazolinone nucleus. Journal of Chemical and pharmaceutical Research, 8(5): 505-26.

Moghadam ME, Divsalar A, Zara MS, et al. (2017) Anticancer, antibacterial and antifungal activity of new ni (ii) and cu (ii) complexes of imidazole-phenanthroline derivatives. Journal Nucleosides, Nucleotides and Nucleic acids, 36(1): 667-75. https://doi.org/10.1080/15257770.2017.1388393

Ramanathan P (2017) Synthesis, Spectral Characterization and Biological Studies of 2-(4-Methoxynaphthalen-1-Yl)-1-(4- Methoxyphenyl)-1H-Phenanthro[9,10-D] Imidazole. Mod Chem Appl, 5: 242. https://doi.org/10.4172/2329-6798.1000242

Sharshira EM, Hamada NMM (2011) Synthesis and *in Vitro* Antimicrobial Activity of Some Pyrazolyl-1-carboxamide Derivatives Molecules, 16(9): 7736-45. https://doi.org/10.3390/molecules16097736

Skocibusic M, Odzak R, Ramic A, et al. (2018) Novel Imidazole Aldoximes with Broad-Spectrum Antimicrobial Potency against Multidrug Resistant Gram-Negative Bacteria. Molecules, 23(5): 1212. https://doi.org/10.3390/molecules23051212

Srinivas K, Kumar KP (2010) Synthesis, Antimicrobial and Anthelmintic Activity of 1-[(5-Sustituted-1,3,4-oxadiazol-2-yl) methyl]-4- propylpiperazines. International Journal of Biopharmaceutics, 1(1): 14-9.

Tabassum K, Ekta P, Kavitkumar P (2018) Imidazole and Pyrazole: Privileged Scaffolds for Anti-Infective Activity. Mini-Reviews in Organic Chemistry, 15(6). https://doi.org/10.2174/1570193X15666171211170100

Tahlan S, Kumar S, Narasimhan B (2019) Antimicrobial potential of 1H-benzo[d]imidazole scaffold: a review. BMC Chemistry, 13: 18. https://doi.org/10.1186/s13065-019-0521-y

Veeraragavan V, Narayanaswamy R, Chidanbaram R (2017) Predicting the biodegradability nature of imidazole and its derivatives by modulating two histidine degradation enzymes (urocanase and formiminoglutamase) activities. Asian J pharm Clin Res, 10(11): 383-6. https://doi.org/10.22159/ajpcr.2017.v10i11.20999

Verma BK, Kapoor S, Kumar U, et al. (2017) Synthesis and biological evaluation of novel imidazole based compounds. Universal Journal of pharmaceutical Research, 2(1). https://doi.org/10.22270/ujpr.v2i1.R5

Zavada OO, Tkachenko OV, Kazmirchuk VV (2018) Synthesis and biological activity evaluation of 3-[2-(1H-Imidazol-2-YL)Alkyl]-2-Thioxo-2,3-Dihydroquinazolin-4 (1H) –One derivatives. International Journal of Green pharmacy, 12(4): 5847. https://doi.org/10.22377/ijgp.v12i04.2265