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Synthesis and Antibacterial Evaluation of Pyrazole Integrated Oxadiazole Derivatives

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ABSTRACT

Pyrazole, Pyridine, and oxadiazole are important scaffolds because of having medicinal applications like anticonvulsant, hypoglycemia, molluscicidal, stimulant, and anticancer, etc. At present, to achieve a highly potent molecule we have synthesized a novel series of pyrazole bearing 1,3,4-oxadiazole heterocycles 4a–o (1-(3,5-substituted-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one) were and characterized by mass spectroscopy, 1H and 13C NMR spectroscopy, and Infrared spectroscopy. All synthesized compounds were evaluated against gram-positive and gram-negative bacterial strains.

Keyword: Pyrazole, Oxadiazole, pyridine, Antibacterial.

I. INTRODUCTION

At present, the dramatic rise in antimicrobial resistance (AMR) among important human bacterial pathogens is reaching a state of global crisis threatening a return to the pre-antibiotic era. AMR, already a significant burden on public health and economies, is anticipated to grow even more severe in the coming decades[1]. There are few known mechanisms of bacterial drug resistance particularly, in some cases, deactivation of the antibiotics through enzymatic degradation or modification of the antibiotic molecule rendering it inactive.Some bacteria employ protection, alteration or overexpression of the antibiotic target[2].therefore, investment in development of new synthetic small molecules and their innovative chemistry and modes of action to overcome public health menace posed by antimicrobial resistance[3].

Heterocyclic compounds are very useful for our health maintaining because of they are rich source of activemolecules with versitile biological functionsranging from oxygen carriers (haemoglobin), the storehouseof energy (ATP), genetic materials(DNA), active components of protein synthesis machinery(RNA) neurotransmitters and natural antimicrobial agents(diketopiperazines)[4].

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Owing to the various biologicalactivities, heterocyclic compounds with varying functionalmoieties have been studied for their antibacterial properties.

Pyrazole and Oxadiazole are five membered heterocycles compounds. Pyrazole contains two nitrogen atoms and oxadiazole containone oxygenand two nitrogen atoms. In literature, considerable evidences have accumulated to demonstrate the efficacy of 1,3,4-oxadiazole including anticancer[5–7], antitubercular[8–10], antiviral[11,12], anti-HIV[13], analgesic[14,15], anti-inflammatory[16,17] and antimicrobial[18–21]. Pyrazole and its derivatives have attracted considerable attention from both synthetic and medicinal chemists perspective due to wide range of biological activities such as antimicrobial[22–25], antiviral[26], anticancer[27], anti-inflammatory[28]and antioxidant[29].

Many natural products having nitrogen containing pyridine ring like vitamins such as vitamin B6 and niacin's, alkaloids as trigonelline, coenzymes like nicotinamide adenine dinucleotide (NAD)[30]. Pyridine is used in medicinal chemistry for improve water solubility and pH, because of its weak basicity. Additionally, some reported biological activity of pyridine like antitubercular[31], anticancer[32], antiviral[33], and antimicrobial[34].

In the present study, we work on designing hybrid heterocycles by conjugating 1,3,4-oxadiazoles with different pyrazole nuclei to form novel heterocyclic compounds exhibiting better potency toward established microbes. The synthesized compounds are equally promising for medicinal chemists when compared with commercially available drugs containing pyrazole and 1,3,4-oxadiazole scaffolds. The structural similarities of these compounds are shown in Figure 1.

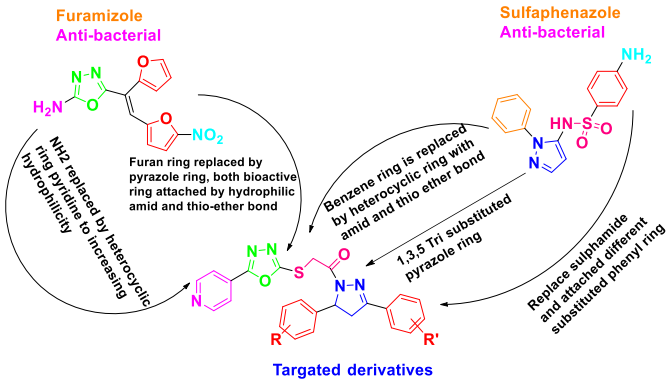


Figure: 1 Concept of design based on clinical drugs containing the pyrazole and 1,3,4-oxadiazole moieties.

II. MATERIALS AND METHODS

All starting material purchased from sigma Aldrich Infrared spectra were recorded through Perkin– Elmer RX1 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were measured in DMSO-d_6 or $CDCl_3$ solutions on a Brucker 500 MHz spectrometer. All the novel molecules were analyzed for C, H and N by ElementarVario EL III elemental analyzer.

III. RESULT AND DISCUSSION

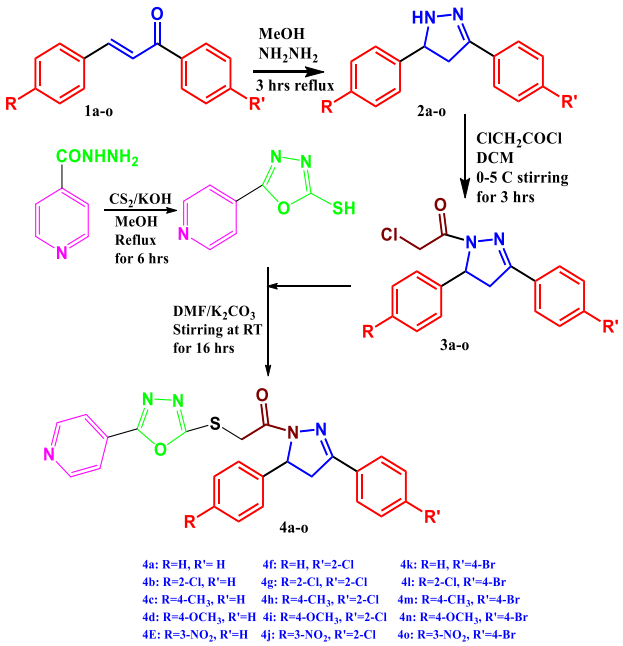
Chemistry

Synthetic pathway of the Compounds 1-(3,5-disubstitutedphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridine -4-yl)-1,3,4-oxa diazol-2-yl)thio)ethan-1-one **(4a-o)** are illustrated in **scheme 1.** Compounds **1a-o**were synthesized by using different aldehyde and different acetophenone in presence of catalytic amount of NaOH. Compounds 1a-o reaction with hydrazine hydrate obtained compounds 2a-o, further reaction with chloroacetylachloride to obtained compounds 3a-o. Final desired compounds were synthesized by nucleophilic substitution of compounds 3a-o on 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol.

All obtained compounds **4a-o** were characterized using elemental analysis, Mass, FT-IR, and NMR spectroscopic techniques. Both ^{1}H- and ^{13}C-NMR data were consistent with the presence of pyrazole and oxadiazole moieties. The ^{1}H-NMR data of all

derivatives revealed the absence of -SH proton of 5-mercaptooxadiazole ring and absence of chloride ion band in IR spectrum which was assigned to be the formation of **4a-o**. Mass spectrum of compound **3a** revealed the molecular ion peak M^+ at m/z= 298, corresponding to molecular mass of this compound.

Aromatic C-H, aliphatic C-H, C=O, C=N, C=C like common functional groups that are presented in all synthesized compounds 4a–o had shown their IR signals at 3034, 2922, 1689, 1507, 1437 cm^{-1} respectively, which indicated the formation of the desired product. Furthermore, in IR spectrum strong pick observed of C-S-C at 1202 cm^- due to C-S stretching. ^{1}H-NMR spectrum recorded a double dublate peak at δ = 3.21, 3.90 ppm attributable to the pyrazole ring protons. Signal at 1689 cm^{-1} in IR spectra reviled that =N-CO- amid bond present in targeted compounds. It was a confirmed that different compound 3a-o are attached with oxadiazole ring by amid formation and it is also confirmed by the ^{1}H NMR spectrum give a double doublet peak at δ = 4.68 to 4.85 ppm of methylene group -S-CH2-CO- protons, and also obtained peak at 8.87ppm in aromatic region due to pyridine ring . Mass spectra of compounds 4a revealed themolecular ion peak M^+ at m/z = 441, it is corresponding to the molecular mass of this compound. In the ^{13}C NMR spectrum, synthetic product 4a revealed a signal at δ=165.31 ppm arising from the C=O group, and the signal obtained in the region of δ = 36.06 ppm confirmed the presence of carbon of methylene group.



Scheme 1: Synthetic pathway of targeted compounds 4a-o.

Biological Studies

All novel synthesized derivatives **4a-o** were evaluated for their *in-vitro* antibacterial activity against *Staphylococcus aureus* (ATCC-25923) and *Bacillus subtilis*(ATCC 6633) of two Gram-positive bacterial strains and *Escherichia coli* (ATCC-25922) and *Enterobacter aerogenes* (ATCC-27853) of two Gram-negative bacterial strains using the well diffusion method[35]. Amoxicillin and ciprofloxacin were used as the reference standard. The results show that (Table 1) all synthesized compounds were more potent against gram-negative bacteria strain compared to gram-positive bacterial strains. Among the series, compound **4o** was most potent against both bacterial strains with MIZ value of *Staphylococusaureus*(MIZ = 38mm), *Basillussubtilis*(MIZ = 24mm), *Escherichia coli(MIZ = 20mm)* and *Enterobacter aerogenes(MIZ = 25mm)*.As well as compounds **4e**was alsoexhibited excellent antibacterial activity against Gram-negative *Escherichia coli* and *Enterobacter aerogenes* bacterial strains with a MIZ value 20 and 23mmrespectively. Compound **4e** and **4o** both are possess higher activity against gram negative bacterial strains compare to amoxicillin (MIZ = 16mm).

Therefore, the biological results obtained for the new pyrazole clubbed oxadiazole analogues **4o** showed promising antibacterial activity against Gram-positive and Gram-negative bacteria (Table 1). A brief investigation of the structure-activity relationship (SAR) revealed that 3rd position of benzene ring was substituted with electron withdrawing group like 3-NO_2 and 4th position of second benzene ring was substituted with electron donating group like –OCH_3 and -Br substitution at the benzene ring contributed to better antibacterial activity(Compounds **4e** and **4o**). And also 2-Cl substituted benzene ring give promising activity(Compounds **4b, 4g** and **4l**). In addition, the linkage of pyrazole to oxadiazole with tertiary amide and thio-ether linkage was found to enhance the antibacterial activities of the final products.

IV. EXPERIMENTAL PROCEDURE

Chalcon derivatives (1a-o)

Different chalcone derivatives were synthesized by reported method[36].

Synthesi of 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol(2).

5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol were synthesized by reported method[37].

Synthesis of3,5-diphenyl-4,5-dihydro-1H-pyrazole (2a-o)

A mixture of different chalcone (0.01mole) and hydrazine hydrate (0.014mole) was reflux in 25ml methanol for 3 hours. After completion of reaction excess methanol remove by distillation and reaction mass was poured into cold water white solid obtained filtered and wash with water. Yield: 76%, M.P.: 78ºC of 2a.

Synthesis of 2-chloro-1-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one (3a-o)

A solution of compound (2) 0.01 mole in dichloromethane 30ml stirred for 10 minutes at 0-5ºC then drop wise adding chloroacetylchloride 0.012 mole and stirring for 3 hours at room temperature. After completion of reaction excess DCM was distilled out and then concentrated mass was poured into water light yellow solid observed, filter and wash with water. Yield: 80%, M.P. : 124ºC of 3a.

Synthesis of 1-(3,5-substituted-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxa diazol-2-yl)thio)ethan-1-one.

Stirring the solution of 5-(pyridin-4-yl)-1,3,4-oxadiazole-2-thiol (0.01mole) and 2-chloro-1-(3,5-substituted-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one(0.01mole) in DMF 10ml presence of K_2CO_3 (0.02mole) at room temperature. After the reaction was completed (monitored by TLC, n-Hexane/ethyl acetate, 1/1, V/V) the reaction mass was poured into ice cold water, precipitated was generated filter it and wash with Methanol. Further purify by column chromatography.

4a) 1-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 158-160ºC;^{1}H-NMR *δ*: 7.23-8.78 (m, 14H, Ar-H), 5.60 (T, 1H, Pyrazole –CH-), 4.71-4.89(dd, 2H, -S-CH_2-CO-),3.21-4.00(dd, 2H, Pyrazole-CH_2-);^{13}C-NMR *δ*: 165.27,164.05,155.42,151.37, 139.00, 137.07,132.29,130.43,130.35,129.63,129.29,125.98,124 .62,120.40,60.55,42.56,36.10; IR (cm^{-1}): 3055(Ar-CH str), 2970(CH2 str), 1674 (C=O), 1427 (C=N), 1211 (ether, C– O–C)247, 694 (C-S), m/z: 441.13; Anal. Calcd. For $C_{24}H_{19}N_5O_2S$;C, 65.29; H, 4.34; N, 15.86; Found: C, 65.14; H, 4.40; N, 15.97.

4b)1-(5-(2-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 166-168ºC;^{1}H-NMR *δ*: 7.20-8.89 (m, 13H, Ar-H), 5.58 (T, 1H, Pyrazole –CH-), 4.70-4.82(dd, 2H, -S-CH_2-CO-), 3.22-3.97(dd, 2H, Pyrazole-CH_2-); ^{13}C-NMR *δ*:164.87,164.12,155.42,151.32, 138.91, 137.12,132.31,130.37,130.42,129.55,129.11,126.08,125 .04,120.56,60.42, 42.45,36.12; IR (cm^{-1}): 3067(Ar-CH str), 2935(CH2 str), 1674 (C=O), 1427 (C=N), 1225

(ether, C– O–C) 248 , 688 (C-S); m/z: 475.06; Anal. Calcd. For $C_{24}H_{18}ClN_5O_2S$; C, 60.57; H, 3.81; N, 14.71. Found: C, 60.62; H, 3.57; N, 14.60.

4c) 1-(3-phenyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 170-172ºC;^{1}H-NMR *δ*: 7.22-8.81 (m, 13H, Ar-H), 5.62 (T, 1H, Pyrazole –CH-), 4.68-4.87(dd, 2H, -S-CH_2-CO-), 3.22-4.03(dd, 2H, Pyrazole-CH_2-), 2.22(s, 3H, Ar-CH_3); ^{13}C-NMR *δ*: 165.44,164.57, 151.49, 139.37, 137.18,132.44,130.48,130.57,129.68,129.31,125.90,124.60,120.44,60.61, 42.42,36.08,21.22; IR (cm^{-1}): 3056(Ar-CH str), 2956(CH2 str), 1672 (C=O), 1427 (C=N), 1211 (ether, C– O–C) 248 , 696 (C-S); m/z: 455.00; Anal. Calcd. For $C_{25}H_{21}N_5O_2S$; C, 65.92; H, 4.65; N, 15.37; Found: C, 65.97; H, 4.55; N, 15.49.

4d) 1-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyri dine-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one White solid; M.P.; 178-180ºC;^{1}H-NMR *δ*: 7.17-8.79 (m, 13H, Ar-H), 5.57 (T, 1H, Pyrazole –CH-), 4.7-4.89(dd, 2H, -S-CH_2-CO-), 3.16-4.01(dd, 2H, Pyrazole-CH_2-); 3.8(s, 3H, Ar-OCH_3); ^{13}C-NMR *δ*: 165.40,164.08,155.46,151.19, 138.79, 137.12,132.30,130.51,130.41,129.63,129.30,125.97,124.52,120.18,60.56, 42.58,36.08; IR (cm^{-1}): 3041(Ar-CH str), 2935(CH2 str), 1674 (C=O), 1460 (C=N), 1209 (ether, C– O–C), 694 (C-S); m/z: 471.15; Anal. Calcd. For $C_{25}H_{21}N_5O_3S$; C, 63.68; H, 4.49; N, 14.85; Found: C, 63.75; H, 4.43; N, 14.92.

4e). 1-(5-(3-nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one; Yellow solid; M.P.; 134-136ºC;^{1}H-NMR *δ*: 7.20-8.69 (m, 13H, Ar-H), 5.66 (T, 1H, Pyrazole –CH-), 4.68-4.85(dd, 2H, -S-CH_2-CO-), 3.15-3.94(dd, 2H, Pyrazole-CH_2-); ^{13}C-NMR *δ*: 166.32,165.12,155.98,151.36, 139.14, 136.84,132.44,130.17,129.86,129.60,129.25,125.56,124.68,120.42,60.71, 42.53,36.11;IR (cm^{-1}): 3055(Ar-CH str), 2940(CH2 str), 1673 (C=O), 1428 (C=N), 1210 (ether, C– O–C), 695 (C-S); m/z: 486.11; Anal. Calcd. For $C_{24}H_{18}N_6O_4S$; C, 59.25; H, 3.73; N, 17.27; Found: C, 59.21; H, 3.70; N, 17.42.

4f) 1-(3-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one;White solid; M.P.; 166-168ºC;^{1}H-NMR *δ*: 7.20-8.88 (m, 13H, Ar-H), 5.55 (T, 1H, Pyrazole –CH-), 4.71-4.92(dd, 2H, -S-CH_2-CO-), 3.20-4.00(dd, 2H, Pyrazole-CH_2-); 3.76(s, 3H, Ar-OCH_3); ^{13}C-NMR *δ*: 165.20,164.07,155.40,151.42, 139.11,
137.18,132.32,130.34,130.06,129.79,129.36,126.12,124.65,120.45,60.36, 42.45,36.12,26.88; IR (cm^{-1}): 3046(Ar-CH str), 2956(CH2 str), 1670 (C=O), 1432 (C=N), 1211 (ether, C– O–C), 695 (C-S); m/z: 471.14; Anal. Calcd. For $C_{25}H_{21}N_5O_3S$; C, 65.29; H, 4.34; N, 15.86; O; Found: C, 65.14; H, 4.40; N, 15.97.

4g) 1-(5-(2-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 178-180ºC;^{1}H-NMR *δ*: 7.23-8.78 (m, 12H, Ar-H), 5.54 (T, 1H, Pyrazole –CH-), 4.65-4.86(dd, 2H, -S-CH_2-CO-), 3.18-3.99(dd, 2H, Pyrazole-CH_2-); 3.65(S, 3H, Ar-CH_3);^{13}C-NMR *δ*: 165.42,164.05, 156.30,151.42, 138.88,136.92,132.44,130.22,130.18,129.58,129.44,125.90,124.63,120.42,60.56, 42.72,36.11,26.71,21.08; IR (cm^{-1}): 3032(Ar-CH str), 2942(-CH str), 1672 (C=O), 1472 (C=N), 1205 (ether, C– O–C), 700 (C-S); m/z: 506.00; Anal. Calcd. For $C_{25}H_{20}ClN_5O_3S$; C, 59.35; H, 3.98; N, 13.84; Found: C, 59.54; H, 4.12; N, 13.90.

4h)1-(3-(4-methoxyphenyl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(py ridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 174-176ºC;^{1}H-NMR *δ*: 7.08-8.76 (m, 12H, Ar-H), 5.66 (T, 1H, Pyrazole –CH-), 4.72-4.90(dd, 2H, -S-CH_2-CO-),3.17-3.99(dd, 2H, Pyrazole-CH_2-); 3.66(S, 3H, Ar-OCH_3), 2.2(S, 3H, Ar-CH_3);^{13}C-NMR *δ*: 165.20,164.17,155.18, 151.21, 139.02, 136.97,132.31,130.54,130.44,129.54,129.2,125.96,124.

58,120.30,60.51, 42.32,36.07,26.26,21.23; IR (cm^{-1}): 3054(Ar-CH str), 2936(CH2 str), 1674 (C=O), 1433 (C=N), 1211 (ether, C– O–C), 688 (C-S); m/z: 485.56; Anal. Calcd. For $C_{26}H_{23}N_5O_3S$; C, 64.31; H, 4.77; N, 14.42; Found: C, 64.56; H, 4.52; N, 14.22.

4i)1-(3,5-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 188-190ºC;^{1}H-NMR *δ*: 7.12-8.80 (m, 12H, Ar-H), 5.61 (T, 1H, Pyrazole –CH-), 4.68-4.85(dd, 2H, -S-CH_2-CO-), 3.20-3.99(dd, 2H, Pyrazole-CH_2-); 3.7(S, 6H, Ar-OCH_3);^{13}C-NMR *δ*: 166.02,165.12,155.86,151.45, 139.18, 137.24,132.32,130.54,130.53,129.60,129.17,125.62,124 .7,120.57,60.72, 42.44,36.18;IR (cm^{-1}): 3050(Ar-CH str), 2945(-CH str), 1670 (C=O), 1430 (C=N), 1214 (ether, C– O–C), 702 (C-S); m/z: 501.56; Anal. Calcd. For $C_{26}H_{23}N_5O_4S$; C, 62.26; H, 4.62; N, 13.96; Found: C, 62.18; H, 4.69; N, 14.08.

4j) 1-(3-(4-methoxyphenyl)-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 180-182ºC;^{1}H-NMR *δ*: 7.05-8.86 (m, 12H, Ar-H), 5.54 (T, 1H, Pyrazole –CH-), 4.66-4.88(dd, 2H, -S-CH_2-CO-), 3.21-4.00(dd, 2H, Pyrazole-CH_2-); 3.65(S, 3H, Ar-OCH_3)^{13}C-NMR *δ*: 165.32,164.32,155.06,151.42,139.08, 136.56,132.50,130.56,130.27,129.56,129.33,126.12,124 .68,120.47,60.54, 42.26,36.11,26.78,21.15; IR (cm^{-1}): 3052(Ar-CH str), 2962(CH_2str), 1675 (C=O), 1427 (C=N), 1201 (ether, C– O–C), 695 (C-S); m/z: 516.53; Anal. Calcd. For $C_{25}H_{20}N_6O_5S$; C, 58.13; H, 3.90; N, 16.27: Found: C, 58.31; H, 3.78; N, 16.35.

4k) 1-(3-(4-bromophenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one; White solid; M.P.; 182-184ºC;^{1}H-NMR *δ*: 7.18-8.75 (m, 13H, Ar-H), 5.64 (T, 1H, Pyrazole –CH-), 4.70-4.88(dd, 2H, -S-CH_2-CO-), 3.14-3.78(dd, 2H, Pyrazole-CH_2-); ^{13}C-NMR *δ*: 165.27,154.05,155.42,151.37, 139.00, 137.07,132.29,130.43,130.35,129.63,129.29,125.98,124 .62,120.40,60.55, 42.56,36.10,26.80,21.06; IR (cm^{-1}): 3056(Ar-CH str), 2932(CH2 str), 1678 (C=O), 1436 (C=N), 1211 (ether, C– O–C) 249 , 702 (C-S); m/z: 520.41; Anal. Calcd. For $C_{24}H_{18}BrN_5O_2S$; C, 55.39; H, 3.49; N, 13.46: Found: C, 55.53; H, 3.39; N, 13.32.

4l) 1-(3-(4-bromophenyl)-5-(2-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one; White solid; M.P.; 154-156ºC;^{1}H-NMR *δ*: 7.21-8.82 (m, 12H, Ar-H), 5.62 (T, 1H, Pyrazole –CH-), 4.72-4.88(dd, 2H, -S-CH_2-CO-), 3.20-3.98(dd, 2H, Pyrazole-CH_2-); ^{13}C-NMR *δ*: 165.33,155.28,151.42, 139.17, 137.12,132.31,130.49,130.24,129.64,129.31,125.97,124 .64,120.44,60.54, 42.57,36.10; IR (cm^{-1}): 3031(Ar-CH str), 2923(-CH str), 1670 (C=O), 1429 (C=N), 1216 (ether, C– O–C), 672 (C-S); m/z: 553.45; Anal. Calcd. For $C_{24}H_{17}BrClN_5O_2S$; C, 51.95; H, 3.09; N, 12.62; Found: C, 52.22; H, 3.01; N, 12.67.

4m) 1-(3-(4-bromophenyl)-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 168-170ºC;^{1}H-NMR *δ*: 7.07-8.78 (m, 12H, Ar-H), 5.58 (T, 1H, Pyrazole –CH-), 4.69-4.85(dd, 2H, -S-CH_2-CO-), 3.16-3.93(dd, 2H, Pyrazole-CH_2-); 2.22(S, 3H, Ar-CH_3); ^{13}C-NMR *δ*: 165.27,164.06,155.42,151.37, 139.00, 137.07,132.29,130.43,130.35,129.63,129.29,125.98,124 .62,120.40,60.55, 42.56,36.10,26.80,21.06; IR (cm^{-1}): 3032(Ar-CH str), 2931(CH2 str), 1674 (C=O), 1427 (C=N), 1211 (ether, C– O–C) 249 , 702 (C-S); m/z: 533.05; Anal. Calcd. For $C_{25}H_{20}BrN_5O_2S$; C, 56.19; H, 3.77; N, 13.10; Found: C, 56.22; H, 3.54; N, 13.18.

4n) 1-(3-(4-bromophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 190-192ºC;^{1}H-NMR *δ*: 7.04-8.78 (m, 12H, Ar-H), 5.55 (T, 1H, Pyrazole –CH-), 4.66-4.84(dd, 2H, -S-CH_2-CO-), 3.21-4.00(dd, 2H, Pyrazole-CH_2-); 3.72(S, 3H,

Ar-OCH_3); ^{13}C-NMR δ: 165.32,155.28,151.40,139.07,137.12,132.23,130.39,130.27,129.60,129.22,125.97,124.56,120.41,60.56, 42.60,36.08,32.64,26.81; IR (cm^{-1}): 3067(Ar-CH str), 2974(CH2 str), 1670 (C=O), 1478(C=N), 1210 (ether, C– O–C)250, 674 (C-S); m/z: 549.05; Anal. Calcd. For $C_{25}H_{20}BrN_5O_3S$; C, 54.61; H, 3.78; N, 12.50; Found: C, 54.55; H, 3.66; N, 12.72.

4o) 1-(3-(4-bromophenyl)-5-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one. White solid; M.P.; 134-136ºC;^{1}H-NMR δ: 7.03-8.78 (m, 12H, Ar-H), 5.53 (T, 1H, Pyrazole –CH-), 4.64-4.82(dd, 2H, -S-CH_2-CO-), 3.14-3.91(dd, 2H, Pyrazole-CH_2-); ^{13}C-NMR δ: 166.54,156.07,151.57, 139.14, 137.12,132.27,130.41,130.42,129.71,129.33,126.03,124.56,120.42,60.56, 42.56,36.11; IR (cm^{-1}): 3045(Ar-CH str), 2924(CH2 str), 1678 (C=O), 1428 (C=N), 1344 (-NO_2), 1208 (ether, C– O–C), 685 (C-S); m/z: 564.02; Anal. Calcd. For $C_{24}H_{17}BrN_6O_4S$; C, 50.98; H, 3.03; N, 14.86: Found: C, 51.23; H, 3.12; N, 14.94.

Compound Code	Zone of Inhibition (mm)			
	Gram Positive		Gram negative	
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Enterobacter aerogenes*
4a	16	14	15	12
4b	25	19	18	16
4c	16	13	16	14
4d	15	14	18	19
4e	27	19	20	23
4f	15	20	14	14
4g	32	21	17	21
4h	25	22	15	19
4i	24	20	16	17
4j	30	22	17	17
4k	16	13	11	14
4l	28	20	17	22
4m	20	21	16	15
4n	19	16	17	17
4o	38	24	20	25
Amoxicilin	40	26	16	18
ciprofloxacin	40	36	25	34

V. CONCLUSION

In this monitoring and management for green environment.

Some new derivatives of pyrazole bearing 1,3,4-oxadiazole heterocycles 4a–o (1-(3,5-substituted-diphenyl-4,5-dihydro-1H-pyrazol-1-yl)-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)ethan-1-one) were synthesized and characterized by mass spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and infrared spectroscopy. All synthesized compounds were evaluated for their Anti-bacterial activity of

different gram positive and gram negative bacterial strains. 3-nitro substituted benzene ring derivatives 4e (E. coli, MIZ= 21mm and E. aerogenes, MIZ = 24mm) and 4o (E. coli, MIZ= 21mm and E. aerogenes, MIZ = 24mm) showed higher activity against gram negative bacterial strain in vitro) with comparison of amoxycilin (E. coli, MIZ= 16mm and E. aerogenes, MIZ = 18mm). While Compound 4j (S. aureus, MIZ = 30mm ;) and 4o (S. aureus MIZ = 38mm) were most active against Gram-positive bacteria of the series.

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