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Synthesis, characterization, and evaluation of Antibacterial activities of 2,5-disubstituted 1,3,4-Oxadiazole derivatives

Lincy Joseph
jinisatheesh3108@gmail.com
Pushpagiri College of Pharmacy, Perumthuruthy, Thiruvalla, Kerala

Mathew George
satheeshrari@gmail.com
Pushpagiri College of Pharmacy, Perumthuruthy, Thiruvalla, Kerala

Jinijith S.
lincyjoseph2013@yahoo.com
Pushpagiri College of Pharmacy, Perumthuruthy, Thiruvalla, Kerala

ABSTRACT

Lincy Joseph, et al.: Antibacterial activity of 2,5-disubstituted 1,3,4-Oxadiazole derivatives Synthesized five 2,5-disubstituted 1,3,4-Oxadiazole derivatives. The target compounds J1 – J5 were obtained by treating aromatic acid ester hydrazide derivative and β-Benzoyl propionic acid derivatives using concentrated sulphuric acid as a dehydrating agent. They were purified and characterized by IR, NMR, and Elemental Analysis. The compounds were further subjected to antibacterial study against gram positive and gram negative strains. Compounds J1 & J2 exhibited good antibacterial activity and compounds J3 & J4 were found to have moderate antibacterial activity compared to standard drug ciprofloxacin (30mcg).

Keywords— *Antibacterial, Gram positive, Gram negative, 1,3,4-Oxadiazole*

1. INTRODUCTION

Oxadiazole, a heterocyclic compound contains one oxygen and two nitrogen atoms in a five-membered ring. It exists in different isomeric forms according to the position of heteroatoms in the ring. It is aromatic in nature and its chemical formula is $C_2H_2N_2O$[1]. Oxadiazole possesses four isomers according to the positioning of heteroatoms in the ring. 1,2,3-Oxadiazole (1), 1,2,4-Oxadiazole (2), 1,2,5-Oxadiazole (3) and 1,3,4-Oxadiazole (4). The 1,2,3-isomer is unbalanced and reverts to the diketone tautomer. The isomers are named as Azoxime (1,2,4-Oxadiazole), Furazan (1,2,5-Oxadiazole) and Biazole (1,3,4-Oxadiazole).

Among them, 1,3,4-Oxadiazole forms an important construction motif for the development of new drugs. Compounds possessing 1,3,4-Oxadiazole nucleus shows wide biological activity spectra; including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant and anti-diabetic properties[2]. The ability of 1,3,4-Oxadiazole heterocyclic compounds to perform a variety of chemical reactions made them crucial for molecular planning and that was because of their privileged structure, which has enormous biological potential.

Two drugs which are currently used in clinical medicine, containing the 1,3,4-Oxadiazole nucleus are Raltegravir, an antiviral drug, and Zibotentan[3], an anticancer agent.

Oxadiazole is a weak base. This is due to the inductive effect of the extra heteroatom. Comparing with furan, the aromatic character is reduced in oxadiazole. Because the two –CH= groups in furan is replaced by two pyridine type nitrogen –N= in oxadiazole. The reduction in aromatic character is to such an extent that, the oxadiazole ring exhibits a character of a conjugated diene. Electrophilic substitution at carbon atom is extremely difficult, because of relatively low electron density. The reason is the electron withdrawal effect of pyridine type nitrogen. However, the electrophilic attack will occur at the nitrogen atom, if the oxadiazole ring is substituted with electron- releasing groups. It is generally resistant to nucleophilic attack. Oxadiazoles will undergo electrophilic substitutions, thermal and photochemical reactions.

The 1,3,4-Oxadiazole possess relatively low electron density at carbon atoms (position 2&5) and relatively high electron density at nitrogen atoms (position 3&4). Hence the major reaction it can undergo are a nucleophilic attack at a carbon atom, generally followed by ring cleavage and electrophilic attack at nitrogen.

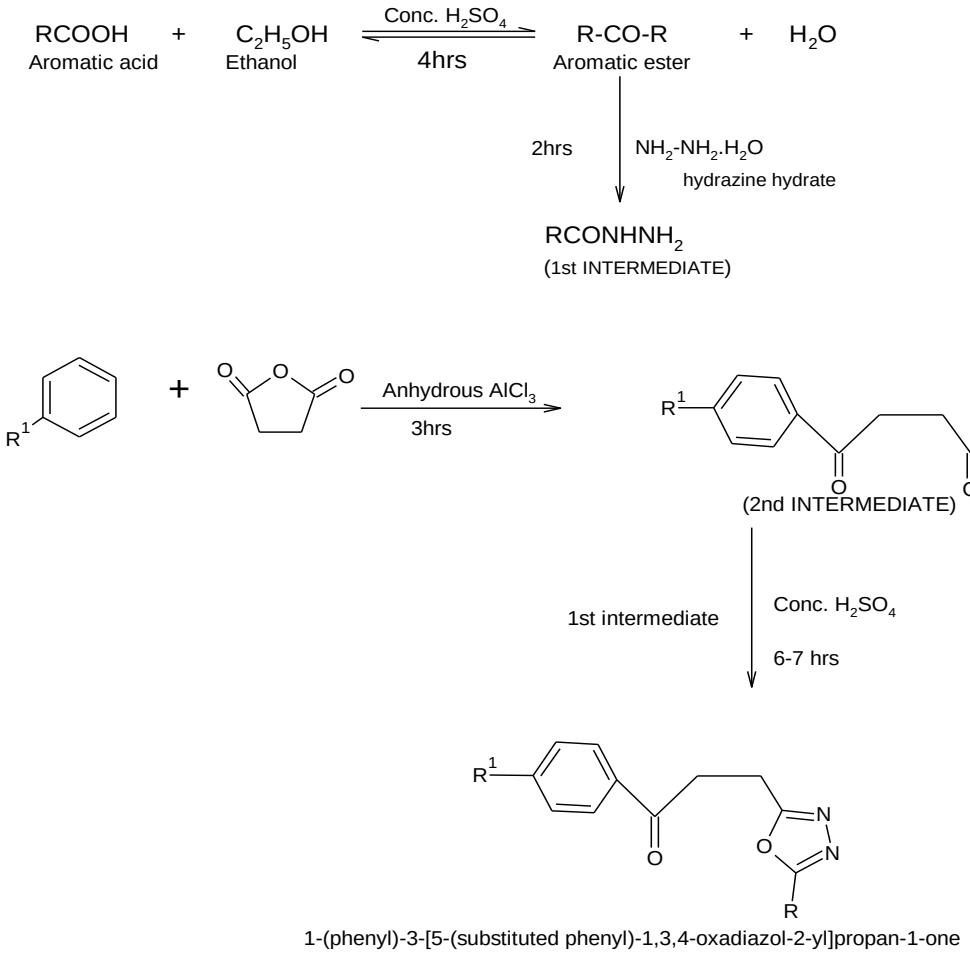
2. MATERIALS AND METHODS

All the chemicals are obtained from commercial suppliers and used without further purification. All the melting points were determined on 'Veego' VMP-D apparatus and are uncorrected. Silica gel G plates of 3×8 cm (Sigma-Aldrich) were used for TLC and spots were located by UV chamber. The IR spectra were recorded in the 4000-400cm^{-1} range using KBr discs on FT-IR 8400

Shimadzu spectrometer. ^1H NMR spectra were recorded on Varian Mercury (300 MHz) spectrometer in $CDCl_3$ with TMS as an internal standard and values are expressed in ppm. Elemental analysis was performed for C, H, N and was found within ±0.4% of theoretical values.

3. SYNTHETIC PROCEDURE

3.1 General Scheme for Synthesis



1-(phenyl)-3-[5-(substituted phenyl)-1,3,4-oxadiazol-2-yl]propan-1-one

Fig. 1: Scheme for Synthesis[18]

3.2 Synthesis of 3-[5-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-methoxyphenyl)propan-1-one (J1)[11-17]

Derivative	R^1	R
J1	O-CH_3	2,4-dinitrophenyl
J2	Br	2,4-dinitrophenyl
J3	O-CH_3	4-chlorophenyl
J4	Br	4-nitrophenyl
J5	Br	4-methoxyphenyl

Dissolved 50g 2,4-dinitrobenzoic acid in 126ml (100g)absolute ethanol. Concentrated H_2SO_4 5.43ml (10g) was added and refluxed for 4 hrs. Half of the alcohol was distilled off and the residue was diluted with distilled water and neutralized using sodium carbonate. The ester separated out (3g) was added in part to 3ml hydrazine hydrate taken in a previously dried RBF. Refluxed for 2hrs and cooled in an ice bath. The crystals of acid hydrazide formed were separated out.

Separately dissolved 10g (0.1mol) succinic anhydride in 50ml anisole. Anhydrous $AlCl_3$ (14.66g =0.11mol) was added in portions with continuous stirring. Refluxed for 2hrs and the mixture was purified by dissolving in NaOH solution. Filtered and added concentrated HCl. The obtained solid β-benzoyl propionic acid derivative was filtered and washed with cold water.

Dissolved 5g acid hydrazide in enough H_2SO_4 and added 5g β-benzoyl propionic acid derivative. The mixture was refluxed for 6hrs, cooled to room temperature and poured into crushed ice. The content was neutralized with 20% $NaHCO_3$ solution. A solid mass of the product was separated out and recrystallized from ethanol.

3.3 Synthesis of 3-[5-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-bromophenyl)propan-1-one (J2)

Dissolved 50g of 2, 4-dinitro benzoic acid in 126ml (100g) absolute alcohol. Concentrated H_2SO_4 5.43ml (10g) was added and refluxed for 4hrs. Half of the alcohol was distilled off and diluted with 300ml distilled water and neutralized using powdered Na_2CO_3. The ester separated out (3g) was added in parts to 3ml hydrazine hydrate taken in a previously dried RBF. Refluxed for 2hrs and cooled in an ice bath. The crystals of acid hydrazide were separated out.

Separately dissolved 10g (0.1mol) succinic anhydride in 50ml bromobenzene. Anhydrous $AlCl_3$ (14.66g = 0.11mol) was added in portions with continuous stirring and refluxed for 2 hrs. The mixture was purified by dissolving in a NaOH solution. Filtered and added concentrated HCl. The obtained solid β-benzoyl propionic acid derivative was filtered and washed with cold water.

Acid hydrazide (5g) was dissolved in enough H_2SO_4 and added 5g β-benzoyl propionic acid derivative. The mixture was refluxed for 6hrs, cooled to room temperature and poured into crushed ice. The content was neutralized with $NaHCO_3$. The solid mass of the product was separated out and was recrystallized from ethanol.

3.4 Synthesis of 3-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-methoxyphenyl)propan-1-one (J3)

Dissolved 50g of 4-chloro benzoic acid in 126ml (100g) absolute ethanol. Concentrated H_2SO_4 5.43ml (10g) was added and refluxed for 4hrs. Half of the alcohol was distilled off and diluted with 300ml distilled water and neutralized using powdered Na_2CO_3. The ester separated out (3g) was added in parts to 3ml hydrazine hydrate taken in a previously dried RBF. Refluxed for 2hrs and cooled in an ice bath. The crystals of acid hydrazide were separated out.

Separately dissolved 10g (0.1mol) succinic anhydride in 50ml anisole. Anhydrous $AlCl_3$ (14.66g=0.11mol) was added in portions with continuous stirring and refluxed for 2hrs. The mixture was purified by dissolving in a NaOH solution. Filtered and added concentrated HCl. The obtained solid β-benzoyl propionic acid derivative was filtered and washed with cold water.

Acid hydrazide (5g) was dissolved in enough H_2SO_4 and added 5g β-benzoyl propionic acid derivative. The mixture was refluxed for 6hrs, cooled to room temperature and poured into crushed ice. The content was neutralized with $NaHCO_3$. The solid mass of the product was separated out and was recrystallized from ethanol.

3.5 Synthesis of 3-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-bromophenyl)propan-1-one (J4)

Dissolved 50g 4-nitro benzoic acid in 126ml (100g) absolute ethanol. Concentrated H_2SO_4 5.43ml (10g) was added and refluxed for 4hrs. Half of the alcohol was distilled off and diluted with 300ml distilled water and neutralized using powdered Na_2CO_3. The ester separated out (3g) was added in parts to 3ml of hydrazine hydrate taken in a previously dried RBF. Refluxed for 2hrs and cooled in an ice bath. The crystals of acid hydrazide were separated out.

Separately dissolved 10g (0.1mol) succinic anhydride in 50ml Bromobenzene. Anhydrous $AlCl_3$ (14.66g=0.11mol) was added in portions with continuous stirring and refluxed for 2hrs. The mixture was purified by dissolving in a NaOH solution. Filtered and added concentrated HCl. The obtained solid β-benzoyl propionic acid derivative was filtered and washed with cold water.

Acid hydrazide(5g) was dissolved in enough H_2SO_4 and added 5g β-benzoyl propionic acid derivative. The mixture was refluxed for 6hrs, cooled to room temperature and poured into crushed ice. The content was neutralized with $NaHCO_3$. The solid mass of the product separated out and was recrystallized from ethanol.

3.6 Synthesis of 3-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-bromophenyl)propan-1-one (J5)

Dissolved 50g 4-methoxy benzoic acid in 126ml (100g) absolute ethanol. Concentrated H2SO4 5.43ml (10g) was added and refluxed for 4hrs. Half of the alcohol was distilled off and diluted with 300ml distilled water and neutralized using powdered Na_2CO_3. The ester separated out (3g) was added in parts to 3ml hydrazine hydrate taken in a previously dried RBF. Refluxed for 2hrs and cooled in an ice bath. The crystals of acid hydrazide were separated out.

Separately dissolved 10g (0.1mol) succinic anhydride in 50ml Bromobenzene. Anhydrous $AlCl_3$ (14.66=0.11mol) was added in portions with continuous stirring and refluxed for 2hrs. The mixture was purified by dissolving in a NaOH solution. Filtered and added concentrated HCl. The obtained solid β-benzoyl propionic acid derivative was filtered and washed with cold water.
Acid hydrazide (5g) was dissolved in enough H_2SO_4 and added 5g β-benzoyl propionic acid derivative. The mixture was refluxed for 6hrs, cooled to room temperature and poured into crushed ice. The content was neutralized with $NaHCO_3$. The solid mass of the product separated out and was recrystallized from ethanol.

4. ANTIBACTERIAL STUDY

The synthesized 1,3,4-oxadiazole derivatives (J1 – J5) were screened for antibacterial activity against different microorganisms by disc diffusion method using Ciprofloxacin as standard. Nutrient agar media was used for the study. All the microorganisms were ob6aned from NCIM, National Collection of Industrial Microorganism, Pune. Gram-positive microorganisms used were *Bacillus subtilis* (NCIM No: 2063) and *Staphylococcus aureus* (NCIM No: 5021). Gram-negative microorganisms used were *Pseudomonas aeruginosa* (NCIM No: 5029) and *Escherichia coli* (NCIM No: 2065).

The antibacterial screening was carried out in a laminar air flow unit and all types of precautions were strictly maintained to avoid any type of contamination during the test. UV light was switched on for half an hour before working in the laminar hood to avoid any accidental contamination. Placed agar plates right side up in the incubator heated to 37ºC for 10min to 20min with the cover adjusted so that the plates are slightly opened. Labeled the covers of each plate with the name of the test organism to be inoculated and with the name of the synthesized derivatives (J1 –J5). Petridishes and other glass wares were sterilized in the autoclave at 121ºC and at a pressure of 151*lbs/sq* inch for 15mins. Micropipette tips, culture media, cork bore, forceps, blank discs and so forth, were also sterilized. In the disc diffusion method, bacterial inoculums were prepared and inoculated into the entire surface of the sold agar plate with a sterile cotton-tipped swab to form an even lawn. The paper disc 6mm n diameter impregnated with diluted test drug solution (200µg/ml in ethanol) was placed on the surface of each of the agar plates using a sterile pair of forceps. The forceps were sterilized using flame. The plates were incubated for 24 hours at 37ºC and observed without opening them and the zone of inhibition was measured[5-10].

5. RESULTS AND DISCUSSION

5.1 Physicochemical properties

Table 1: Physicochemical properties

S. No.	Sample Code	Molecular Formula	Molecular Weight	Physical State	Colour	Melting Point	R_f value
1	J1	$C_{18}H_{14}O_7N_4$	398.3260	Crystalline	Yellow	211	0.82
2	J2	$C_{17}H_{11}O_6N_4Br$	447.1960	Crystalline	Dark yellow	244	0.91
3	J3	$C_{18}H_{15}O_3N_2Cl$	342.7768	Crystalline	White	197	0.54
4	J4	$C_{17}H_{12}O_4N_3Br$	402.1980	Crystalline	Yellow	189	0.49
5	J5	$C_{18}H_{15}O_3N_2Br$	387.2270	Amorphous	Off white	175	0.74

5.2 Solubility Profile

Table 2: Solubility Profile

S. No.	Sample Code	Solvents					
		Ethanol	Acetone	Ethyl acetate	Chloroform	0.1N NaOH	0.1N HCl
1	J1	Soluble	Soluble	Insoluble	Insoluble	Insoluble	Insoluble
2	J2	Soluble	Soluble	Soluble	Insoluble	Soluble	Insoluble
3	J3	Soluble	Soluble	Soluble	Insoluble	Insoluble	Insoluble
4	J4	Soluble	Soluble	Soluble	Insoluble	Insoluble	Soluble
5	J5	Soluble	Soluble	Soluble	Insoluble	Insoluble	Insoluble

5.3 Antibacterial Activity by measuring the radius of the zone of Inhibition

Table 3: Antibacterial Activity by measuring the radius of the zone of Inhibition

Sample code	Radius of the zone of inhibition (mm)			
	Gram positive organism		Gram negative organism	
	Bacillus subtilis	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Escherichia coli*
Ciprofloxacin	18	17	17	16
J1	14	12	13	10
J2	12	11	12	10
J3	8	7	7	6
J4	7	6	5	5
J5	3	3	2	3

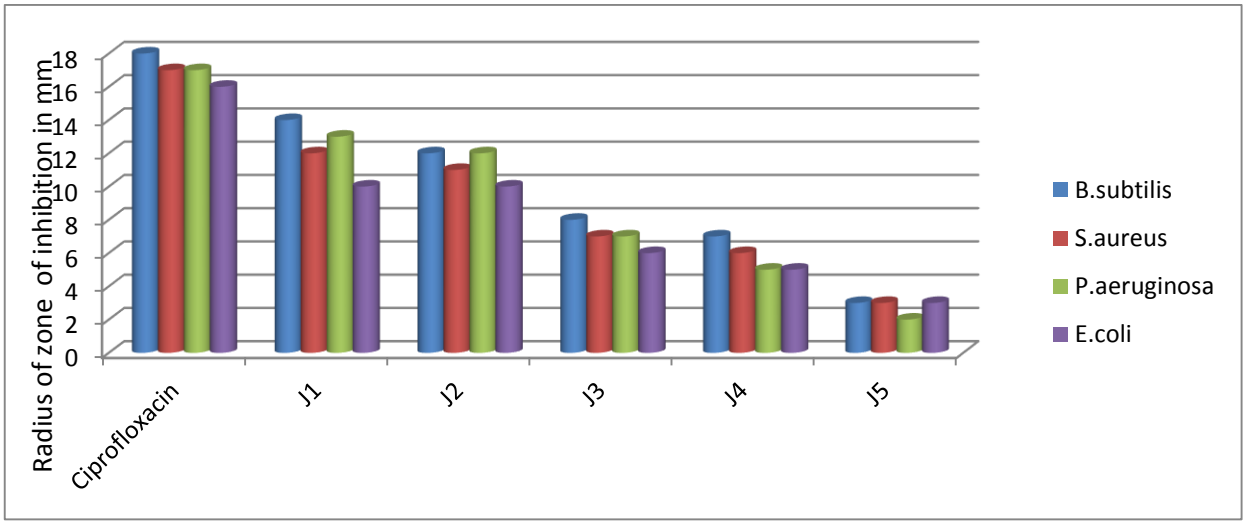


Fig. 2: Graphical Representation of Antibacterial activity

6. SPECTRAL INTERPRETATION

3-[5-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-methoxyphenyl)propan-1-one (J1): Yield 71.3%, yellow crystalline solid, m.p.211ºC, ^{1}H NMR ($CDCl_3$): δ 7.60-7.50 (m, 5H,Ar-H), 7.20-7.10(m,4H, Ar-H), 1.55(s,2H,CH_2)1.26(s,3H, CH_3). IR(KBr, cm^{-1}):3072 (Ar CH), 2910 (aliphatic C-H), 1606(C=N), 1022 (C-O-C). R_f :0.82.

3-[5-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-bromophenyl)propan-1-one (J2) : Yield 69.7%, dark yellow crystalline solid, m.p.244ºC, ^{1}H NMR ($CDCl_3$): δ 7.60-7.50 (m, 4H, Ar-H), 7.40(d, 2H, Ar-H), 1.50(s,2H,CH_2). IR (KBr, cm^{-1}): 2930 (Ar CH), 1615(C=N), 1040 (C-O-C). R_f 0.79.

3-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-methoxyphenyl)propan-1-one (J3): Yield 69.1%, white crystalline solid, m.p. 197ºC, ^{1}H NMR ($CDCl_3$): δ 7.60-7.50 (m, 4H, Ar-H), 7.90-7.80 (m, 3H, Ar-H), 2.95 (s,3H,CH_3). IR (KBr, cm^{-1}): 2921 (Ar-CH), 1608(C=N), 1060 (C-O-C). R_f 0.54

3-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-bromophenyl)propan-1-one (J4) : Yield 72.4%, yellow crystalline solid, m.p.189ºC, ^{1}H NMR ($CDCl_3$): δ 7.60-7.50 (m,4H,Ar-H), 7.90-7.80 (m,3H,Ar-H), 1.53(s,2H,CH_2). IR (KBr, cm^{-1}): 3074(Ar-CH), 2911(Aliphatic CH), 1612 (C=N), 1032 (C-O-C).R_f 0.49

3-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]-1-(4-bromophenyl)propan-1-one (J5) : Yield 58.8%, white amorphous solid, m.p.175ºC, ^{1}H NMR ($CDCl_3$): δ 7.60-7.50 (m, 4H, Ar-H), 7.90-7.80 (m,3H,Ar-H), 1.56(s, 2H, CH_2).IR (KBr, cm^{-1}): 3069 (Ar-CH), 2914(Aliphatic CH), 1616 (C=N),1051 (C-O-C). R_f 0.84.

7. SUMMARY

The titled compounds J1 – J5 were obtained by reacting various derivatives of aromatic acid ester hydrazide and β-benzoyl propionic acid derivatives using concentrated H_2SO_4 as cyclodehydration agent. They were characterized by IR (KBr) as sharp bands were observed around 3056cm^{-1} (Aromatic C-H stretch), 1608cm^{-1} (C=N), 1068 – 1020 cm^{-1} (C-O-C stretching of Oxadiazole ring) and their structures were confirmed by ^{1}H NMR and elemental analysis. Antibacterial screening of all newly synthesized 1-(phenyl)-3-[5-substituted phenyl)-1,3,4-oxadiazol-2-yl]propan-1-one derivatives were carried out on four microorganisms using disc diffusion method by measuring the radius of the zone of inhibition produced by the corresponding derivative on the agar plate. Ciprofloxacin (30mcg) was chosen as the standard drug. Out of the five synthesized derivatives, two of them (J1 & J2) showed good activity.J3 & J4 showed moderate activity.

8. CONCLUSION

The present study was aimed at evaluating the antibacterial potential of the 1,3,4-Oxadiazole nucleus, by providing various substitutions at the 2nd and 5th positions. A series of five compounds were synthesized as outlined in the scheme (figure 1). All the synthesized compounds were then biologically screened for antibacterial activity by disc diffusion method. 3-[5-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-methoxyphenyl)propane-1-one (J1) and 3-[5-(2,4-dinitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-bromophenyl)propane-1-one (J2) showed maximum activity. The most probable reason will be the presence of a benzene ring containing two strong electron withdrawing groups (-NO_2) enhances the antibacterial property of the 1,3,4-oxadiazole nucleus. The moderate action of 3-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-methoxyphenyl)propan-1-one (J3) & 3-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]-1-(4-bromophenyl)propan-1-one (J4) may also be due to the presence of electron withdrawing groups attached to the benzene ring. The increase in extending of activity seemed to be in the order increasing the electron withdrawing effect of the substituent groups.

9. ACKNOWLEDGMENT

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