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Synthesis Characterization and Antimicrobial Activity of Some Novel Oxadiazole Derivatives

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***Abstract*: In the present study 1,3,4-Oxadiazole derivatives were synthesized and antimicrobial activities of different derivatives were checked with various microbial stains. Various intermediates were synthesized and characterized in between time-to-time by chromatographic and spectral methods. Substituted benzaldehyde and o-phenylenediamine were the starting material and finally formed of 1,3,4-oxadiazol-2-ylmethyl)-2-phenyl-1H-benzimidazole derivatives steps 1, dry acetone and ethyl chloro acetate react at room temperature and to of ethyl2phenyl1benzimidazole1yl) acetate 1,3,4-oxadiazole derivative have been synthesize from Schiff base of the corresponding hydrazine by using ethanol with reflex. finally treated with phosphorus chloride oxide to get the title compound. The structures of all the synthesized compound were established on the basic of elemental, chromatographic and spectral analysis. The synthesized compound was evaluated for their antimicrobial activity. The compound most active be against Escherichia coli and staphylococcus aureus.**

***Keywords*: Antimicrobial activity, Oxadiazole, Hydrazine hydrate, O-Phenylenediamine.**

1. Introduction

Oxadiazoles are cyclic compounds that containing one oxygen and two nitrogen atoms in a five membered ring structure. [1] Literature survey reveals that 1, 3, 4-oxadiazoles have attracted an interest in medicinal chemistry as ester and amide bioisosteres for a number of biological targets. As a consequence of these characteristics the 1,3,4-oxadiazole derivatives have been found malarial, hypoglycemic and other biological to biological activities such as antimicrobial [2], [3] anti-AIDS [4], ant tubercular [5]-[7], analgesic [8], anti-inflammatory [9], anticonvulsant [10], [11], anti-properties such as genotoxic studies and lipid per oxidation inhibition. The sequence of these atoms may be different as following. Researchers have already reported that gram positive bacteria are much more susceptible to antimicrobial agents as compared to gram negative bacteria.[12] The most numerous and important heterocyclic systems are those having five and six member rings having hetero atoms such as N, O, S, P, Si and B etc. Many hetero cyclic compounds are employed in the treatment of infectious diseases due to their specific antimicrobial activity. Heterocyclic compounds have attracted attention of medicinal chemists because of having broad spectrum of pharmacological activities and hence it continues to yield new medicinal agents. One such heterocyclic nucleus of medicinal importance is oxadiazole nucleus, they are named as 1,2,3-oxadiazole, 1,2,4- oxadiazo1,2,5-oxadiazole and 1,3,4-oxadiazole.

2. Chemistry of Oxadiazole

Due to the presence of a heteroatom in the ring, oxadiazole shows inductive effect and thus it is considered to be a weak base. It consists of 2 pyridine like nitrogen, due to which it exhibits conjugate diene type character. Electrophillic substitution at carbon is very difficult in this case due to less electron density which is mainly due to the presence of pyridine like nitrogen in the ring that shows electron withdrawal effect. Due to the presence of two pyridine type nitrogen, the aromaticity will be removed. Many studies on comparison between 1,2,4-and 1,3,4- oxadiazole pairs shows that, in all cases, 1,3,4-oxadiazole isomer shows lower magnitude lipophilicity (log D) as compared to its isomeric partner. Other differences involve metabolic stability, hERG inhibition, and aqueous solubility. All these studies favored the 1, 3, 4-oxadiazole isomers. The difference in profile between the 1, 2, 4 and 1, 3, 4 Regio isomers can be rationalized by their intrinsically different charge distributions.

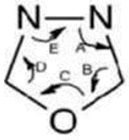

Table 1
Angles and bond length of oxadiazole

Angles	Bond Angle (°)
A	105.6
B	113.4
C	102.0
D	113.4
E	105.6

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3. Experimental Method

Step-I: Procedure for the synthesis of 2-PHENYL -1-benzimidazole (Compound-A)

Take in 500ml round bottom flask place of o-phenylenediamine 1 (0.05 mol; 5.40 g) and benzaldehyde 2 (0.05 mol) was re-fluxed in 4N HCl for 4 h on a heating mantle. After completion of reaction, the solution was poured onto crushed ice, ammo-nia solution was added drop wise to neutralize and the result-ing solid was filtered, washed with cold water, dried and recrystallized with ethanol. which in white or pale yellow in color Yield 84%, m.p.155-160, IR (KBr)CM-1:1240(C-O),1542(C=N),3444(N-H).

Step II: Synthesis of ethyl2phenyl1benzimidazole1yl) acetate)

To a suspension of 2-(phenyl)-1H-benzimidazole 3(0.01 mol), anhydrous potassium carbonate (2 g) in dry ace-tone, ethyl chloro acetate (0.01 mol; 1.2 ml) was added drop wise at room temperature for a period of 20–30 min. The reaction mixture was stirred at room temperature for10–12 h. The inorganic solid was filtered off and the filtrate was concentrated under reduced pressure. Yield 75%, mp 92-950C. IR(KBr)cm-1:1240(C-O),1550(C=N),1645((C=O).

Step III: Synthesis of ethyl2-[2-(phenyl)-1binzimidazole-1-yl] acetohydrazide

Take in 500ml round bottom flask place an ethanolic solution of ethyl [2-(phenyl]-1H-benzimidazole-1-]acetate(0.01 mol), hydrazine hydrate (98%), (0.01 mol;0.49 ml) was add and the mixture was refluxed for 3 h. After completion of the reaction, the mixture was cooled and the solid was obtained and filtered, washed with cold water and recrystallized from methanol. Yield 85%, mp-175-180^{0}C., IR(KBr)cm-1:1030(N-N),1240(C-O), 1610(C=N),1645(C=O),3250(N-H).

Step IV: Synthesis of 1,3,4-oxadiazol-2-ylmethyl)-2-phenyl-1H- benzimidazole derivatives

Take in 500ml round bottom flask place a mixture of 2-{2-(phenyl)-1H-ben-zimidazol-1-yl}acetohydrazide(0.0025 mol) and suitable aromatic acid (0.0025 mol) was refluxed in the presence of Synthesis, characterization and ant microbial evaluation POCl3(5 ml) for 5 h at a temperature of 110–120°C. After completion of reaction, the mixture was cooled at room temperature and poured onto crushed ice. On basification with sodium bicarbonate (5%), a solid mass separated out was filtered to get crude product. Finally, the product was heated with charcoal in hydrated ethanol and then re-crystallized from ethanol to obtain 1R. Yield 70%, mp-150-152, IR(KBr)cm-1:1030(N-N),1240(C-O),16OO(C=N),

Step IV-R_1: 2-(Phenyl)-1-{2-phenyl-1,3,4-oxadiazol-2-yl} methyl Benzimidazole

Step IV-R_2: 2-(Phenyl)-1-{2-Methyl phenyl-1,3,4-oxadiazol-2-yl}methyl Benzimidazole

Step IV-R_3: 2-(Phenyl)-1-{3-Methyl phenyl-1,3,4-oxadiazol-2-yl}methyl Benzimidazole

Step IV-R_4: 2-(Phenyl)-1-{2-Chloro phenyl-1,3,4-oxadiazol-2-yl}methyl Benzimidazole

Step IV-R_5:-2-(Phenyl)-1-{2-Chloro phenyl-1,3,4-oxadiazol-2-yl}methyl Benzimidazole

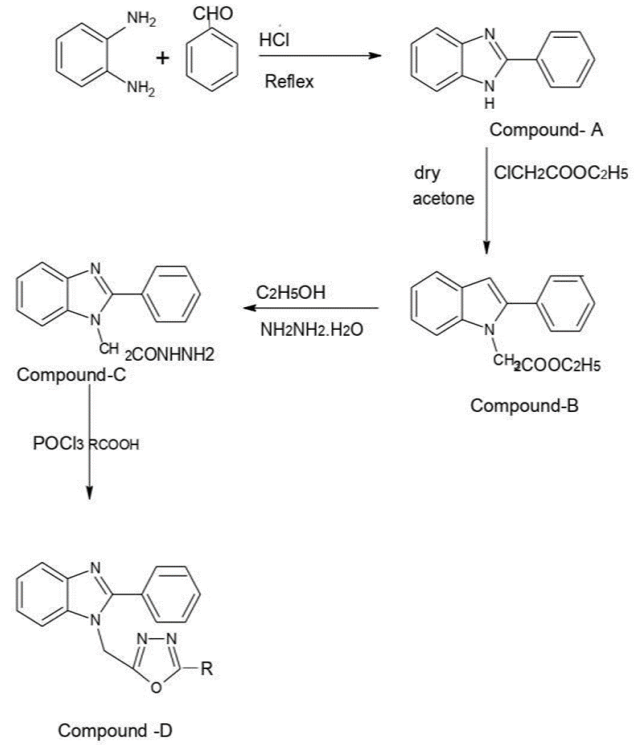
Step IVR_6: 2-(Phenyl)-1-{2-Bromo phenyl-1,3,4-oxadiazol-2-yl}methyl Benzimidazole

Step IV-R_7: 2-(Phenyl)-1-{4-Bromo phenyl-1,3,4-oxadiazol-2-yl}methyl Benzimidazole

Step IV-R_8: 2-(Phenyl)-1-{2-Nitro phenyl-1,3,4-oxadiazol-2-yl}methyl Benzimidazole

Step IV-R_9: 2-(Phenyl)-1-{4-Nitro phenyl-1,3,4-oxadiazol-2-yl}methyl Benzimidazole

Scheme:



Spectral Data:

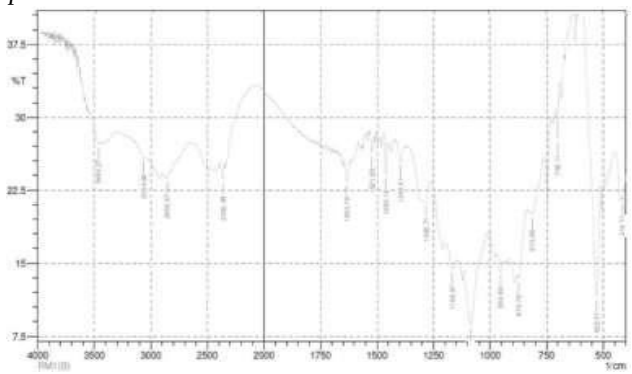


Fig. 1. IR-Spectra of compound 5R

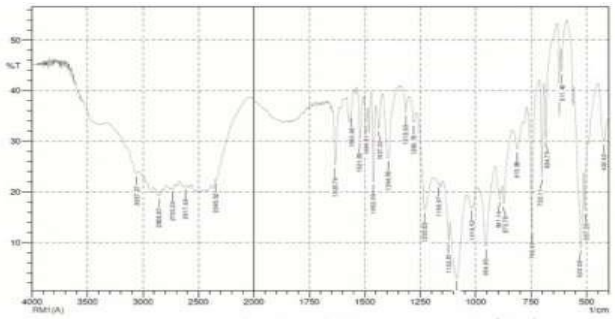


Fig. 2. IR-Spectra of compound B

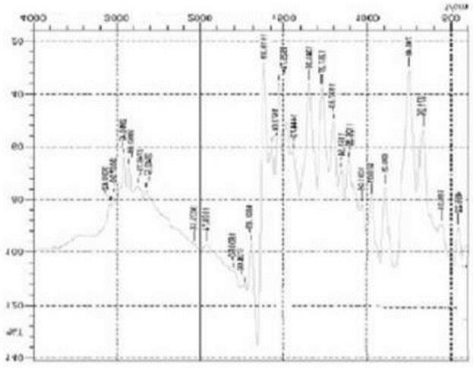


Fig. 3. IR-Spectra of compound D

4. Antimicrobial Studies

In our current study, the antimicrobial activity was carried out by the Filter Disk method. Here responses of microorganisms to the synthesized compounds were measured and compared with the response of the standard reference drug. The standard reference drugs used in the present work was linezolide.

Microorganisms used: Two microorganisms Escherichia coli (Gram–ve) and Staphylococcus aureus (Gram +ve) were selected for the antimicrobial potency test. The bacterial stock cultures were obtained from microbiology department Choithram Hospital Indore.

Nutrient Agar Media:

Nutrient agar media is used for making plate, slant and stab for surface surface activity of microorganism.

Table 2

S. No.	Ingredients	Qty.
1	Beef extract	10.0 g
2	Peptone	10.0 g
3	NaCl	5.0 g
4	Agar	20.0 g
5	Distilled water	Up to1000 ml

Preparation of Agar media:

Procedure:

1. Weight all additives separately by physical balance.
2. Add all weighed additive in suitable containers.
3. Dissolve with the aid of heat with stirring.
4. Adjust to pH8.0-8.4 with 5M sodium hydroxide.
5. Boil in ten minutes
6. If necessary, filter it and adjust to paha7.2-7.4.
7. Sterilize by autoclave, using 15 Ib pressure at 1150C for thirty minutes.
8. Add 1-2% agar powder in nutrient both before sterilization.

Preparation of incubation:

- Prepare microbial inoculums with the required quantity or suspension of test organism.
- Add prepare microbial suspension in the media and mix it and transfer into Petri-dish.
- Prepare solution of known concentration of the standard preparation with respect to the assumed concentration of the antibiotic to be examined.
- Apply the solution to the surface of the solid media in sterile cylinder or in cavities prepare in agar plate.
- Leave the dishes or plates for one to four hour at room temperature.
- Incubate the plate or dishes at 20-30^0 C for 18 hours.

Sample solution:

Sample of test compounds and controlled antibiotic were prepared in same solvent and diluted till the level of standard preparation.

Preparation of standard curve:

- Take 12 Petri dishes or plate having six holes. Thus, total number of holes in twelve petridishes will be 12x6 equal to 72. A set of three plates is used for each dilutions.
- On each of these sets fill alternate cavities or cylinder with solution s3 and each of the remaining nine cavities with one of the (s1, s2, s4, s5) dilution of standard solution.
- For each unknown sample, prepare a set of three plate (18 cylinder or cavities) and till alternately with the sample solution and each of the remaining nine cavities are filled with solution s3.
- Incubate the plate for about 18-48 hour at the specified temperature and measure the diameter of the zone of inhibition.

5. Results and Discussion

Starting with the 2-phenyl-1-benzimidazole total 11 compounds were prepared and characterized physiochemically as well as biologically. Based on the results the compound 4R that is *2-(phenyl)-1-{2-Chlorophenyl- [1,3,4]oxadiazole -2-ylmethyl)-1H benzimidazole* showed the best results among all the 11 derivatives synthesized and evaluated**.**

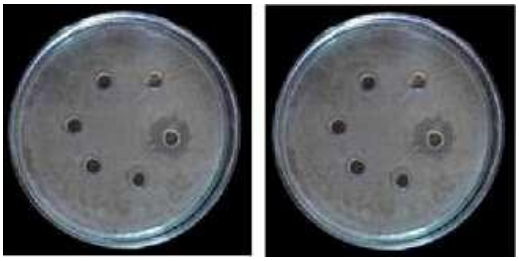


Fig. 4. Antimicrobial activities by zone of inhibition method

Table 3

Comparative results of antimicrobial activities by zone of inhibition method

S.No.	Compound Code	Zone of Inhibitoin	
		1*	2*
1.	Compound 1R	+	++
2.	Compound 2R	+	+
3.	Compound 3R	-	+
4.	Compound 4R	+	+
5.	Compound 5R	+++	++
6.	Compound 6R	+	-
7.	Compound 7R	+	+
8.	Compound 8R	+	+
9.	Compound 9R	++	+
Std.	Linezolid	+++	+++

1* S. aureus, 2* E.coli,

(+) less active, (++) mild active, (+++) more active

6. Summary and Conclusion

- The main focus of this research work was to synthesize, characterize and evaluate antibacterial activities of the some novel oxadiazole derivatives.
- A series of titled compounds i.e. [1R-11R] have been synthesized using appropriate synthetic procedures, as per the scheme given in the methodology and the biological evaluations of the synthesized compounds were performed.
- The practical yield of the synthesized compounds was found to be in the range of 50% - 85%.
- Structures of the synthesized compounds were characterized and confirmed with the help of analytical studies such as chromatographic and IR data.
- The antimicrobial activity was carried out by zone of inhibition method (Filter disc method).
- Among the 11 synthesized compounds *2-(2-phenyl)1-{(5-methylphenyl)-1,3,4-oxadiazole2-yl)}1-methyl-1H-benzimidazole derivatives* was found most significant active biologically.

The development of oxadiazole bearing benzimidazole system has new potentially active antibacterial series of compounds. The result of *in vitro* antimicrobial activity showed that the compound having electron withdrawing group (like NO2, Br and Cl) were the most active against *E. coli* and *S. aurous.*

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