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NEWER SYNTHETIC APPROACHES AND BIOLOGICAL EVALUATION OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES

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ABSTRACT

A Series of new 2,5-disubstituted-1,3,4-oxadiazole derivatives are synthesized from hydrazone derivatives along with various aldehydes and ketones derivatives in presence of bromine water, sodium acetate and glacial acetic acid. All the newly synthesized aldehyde and ketone derived 1,3,4-oxadiazoles are characterized using elemental analysis. IR, ^{1}H NMR, ^{13}CNMR spectral characterization was carried out. All the synthesized compounds of 1,3,4-oxadiazole derivatives are evaluated for their anti-microbial activity against several gram-positive bacterial strains (*Bacillus subtilis, Bacillus cereus, S.pyrogenous, S.aureus)* and gram-negative bacterial strains (*E. coli, P. aeruginosa*) using broth dilution technique with the discdiffusion method. From the tested compounds OD-2, OD-7, OD-9 showed better activity compared to others. All the derivatives are synthesized by green synthesis techniques.

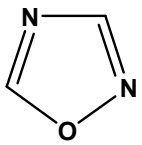
Keywords: 1,3,4-oxadiazole, Broth dilution technique, Disc Diffusion method, Anti-microbial, Green Synthesis

INTRODUCTION:

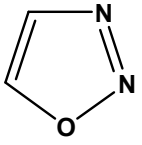
Oxadiazoles, heteroaromatic rings, which is five membered containing one oxygen atomand two nitrogen atoms and two carbon atoms with the molecular formula

$C_2N_2H_2O$.These oxadiazoles exist in different regioselective isomeric forms. Out of these different forms of oxadiazoles, 1,3,4-Oxadiazoles plan an important role in various chemical and biological activities due to their acceptable profile in the aqueous solubility, more potent like anti-microbial **[1-3]**, anti-cancer **[4-6]**, anti-inflammatory **[7-10]**, anti-diabetic **[11-14]**, anti-malarial **[15-17]**, anti-tubercular **[10-20]**, anti-oxidant **[21-23]**, anti-convulsant **[24-25]**, anti-psychotic **[26]**, anti-depressant **[27-29]**, hemolytic **[30]**. Apart from these, they have industrial applications in field of dyes, photosensitive, liquid and crystals. Likewise various substituted 1,3,4-oxadiazoles play an important role in treating various disease conditions.

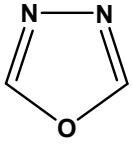
The various isomeric forms are 1,2,4-oxadiazoles, 1,2,3-oxadiazoles, 1,3,4-oxadiazoles and 1,2,5-oxadiazoles.



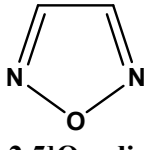
[1,2,4]Oxadiazole



[1,2,3]Oxadiazole



[1,3,4]Oxadiazole



[1,2,5]Oxadiazole

This requirement in the present scenario triggers us to develop various types of anti-microbial derivatives with high efficiency, minimal side effects and also with decrease in chemical usage used in the development of those drug molecules. Conventional synthesis of drug products involving certain random synthesizers, distillation apparatus etc., which requires a large usage of chemicals, and also requires high temperature and are synthesized for several hours or days to get final drug product which results in emission of certain gases damaging the environment. Though conventional synthesis is natural type of method, it has its disadvantages. Statistical analysis shows that 80% of industrial waste is solvent related, hence to reduce those effects we opt for green synthesis which addresses the usage of solvent, its reuse and recovery. Green synthesis involves the usage of parallel synthesizer, microwave assisted synthesis, ultra sonication method of synthesis. Green synthesis technique, an environmentally sustainable process in synthesis of various pharmaceutical ingredients and products, has its own kind of advantages like reducing the solvent usage chemical usage, reduces emission of certain gases, completes the reaction time less than conventional type and thus yields high amount of product. Hence, different types of 2,5-disubstituted 1,3,4-oxadiaxoles are here synthesized by using one of the green synthesis techniques involving parallel synthesizer.

MATERIALS AND METHODS:

All the chemicals procured are of

laboratory grade and are obtained from NSP, Guntur. Melting points are determined using open capillary tubes and are uncorrected. Formation of compounds were checked by TLC on silica gel-G plates of 0.5mm thickness and spotswere located by iodine and UV light. All the compounds were purified by recrystallisationwith suitable organic solvents like alcohol, dimethyl ether. IR spectra were recorded on Brooker-ALPHAFT-IR instrument using KBr pellet method. 1^{H} NMR and 13^{C} NMR was determined in $CDC1_3$ solution on a Brooker Ac 100 MHz spectrometer. The results are in agreements with structures assigned. All the chemicals are of reagent grade and used without further purification.

EXPERIMENTALPROCEDURE:

Procedure for the preparation of hydrazides:

To the solution of methyl salicylate (0.1M) and hydrazine hydrate (0.1M) in methanol (20ml) were mixed at room temperature. Reaction mixture was kept under reflux at 60°C for 6 hoursand simultaneously reaction was carried out in parallel synthesizer at 60°C for 1 hour. The resulting solid was separated and washed with cold water and vacuum dried.

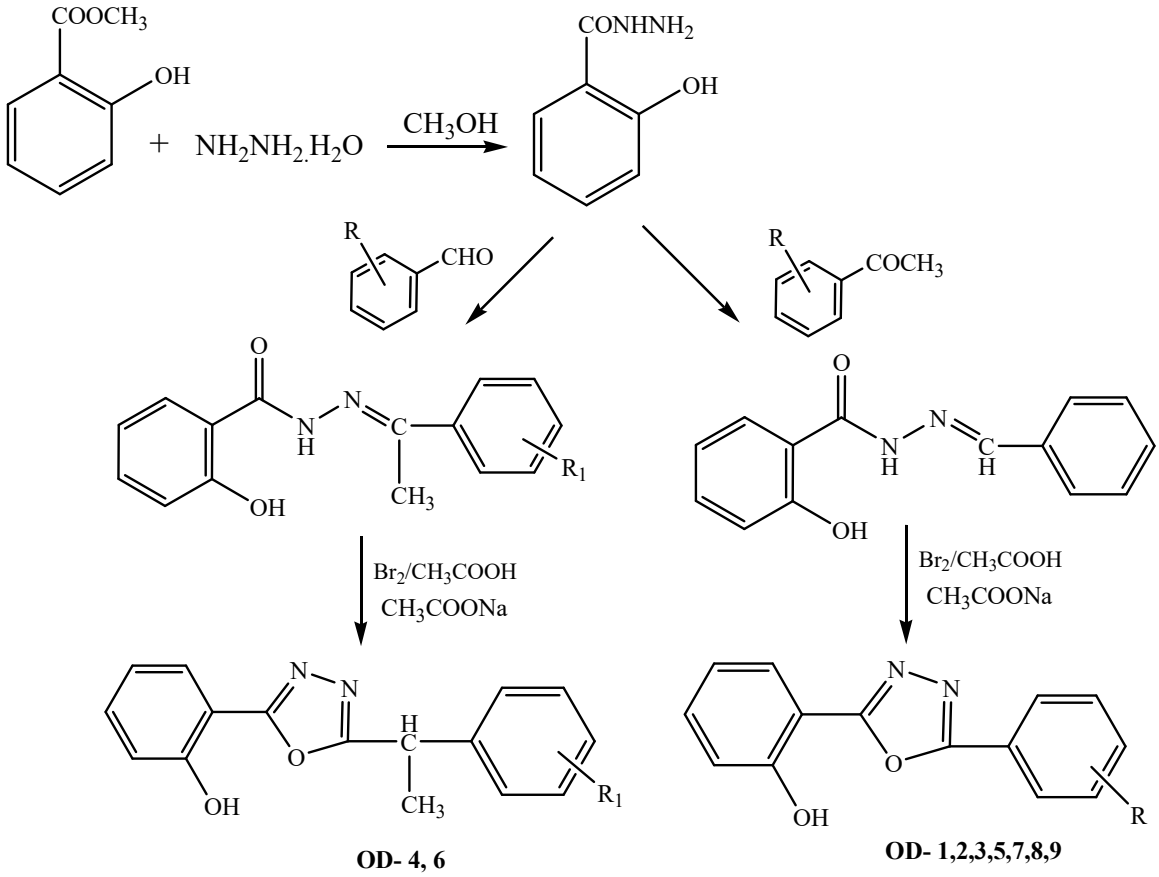
Procedure for the preparation of hydrazone derivatives:

To the above formed hydrazides (0.03M) chloroform (20ml) was added and they are allowed to solubilize in presence of methanol (10ml) allowed to react with various benzaldehyde and acetophenone derivatives. The reaction mixture was kept under reflux at 60°C for 6 hours and simultaneously reaction was carried out in parallel synthesizer at 60°C for 1 hour. The resulting solid was separated and washed with cold water and vacuum dried.

Procedure for the preparation of 2,5-disubstituted 1,3,4 oxadiazole derivatives:

To the mixture of hydrazone derived aldehydes and ketone derivatives (0.01M) anhydrous sodium acetate (0.01M) and glacial acetic acid (20ml) was placed in beaker. Bromine water (0.8ml in 5 ml of glacial acetic acid) was slowly added to the above mixture while stirring magnetically. After 2 hours of continuous stirring the mixture was poured on to crushed ice. The resulting solution was filtered off and the product was separated, washed with cold water and vacuum dried. The product was recrystallized using methanol to obtain pure compound.

Scheme: Synthesis of 2,5-disubstituted 1,3,4 oxadiazole derivatives (OD-1 to OD-9)



OD- 4, 6 **OD- 1,2,3,5,7,8,9**

RESULTS AND DISCUSSION:

All the synthesized oxadiazole derivatives physical data was given in **Table 1**. All the results from anti-microbial evaluation given in **Table 2**. It reveals that all the tested compounds showed moderate to significant anti-bacterial activity. All the derivatives were found to be active against all gram-positive and gram-negative strains. The zone of inhibition values for all the synthesized derivatives were recorded and given in the following tables.

(OD-1):2-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol:

White Amorphous Powder, MP: 282-284°C, Yield 79.86%, IR(KBr, cm^{-1})3857.63 (OH), 1694.49 (C=N), 1603.30 (C=N), 1232.12 (C-O),746.94(C-Cl). ElementalAnalysis:C,61.66;H,3.33;Cl,13.00;N,10.27;O,11.73.

(OD-2):2-(5-p-nitro- [1,3,4] oxadiazol-2-yl)-phenol: Paleyellowcrystals,MP:258-260°C,Yield:76.43%, IR(KBr, cm^{-1})3858.09 (OH), 1628.96 (C=N), 1600.76 (C=N), 1522.29 (N=O),1247.19(C-O). Elemental Analysis: C, 59.37; H,3.20; N,14.84; O, 22.59.

(OD-3):2-[5-(2-Nitro-phenyl)- [1,3,4] oxadiazol-2-yl]-phenol: Pale yellow crystals, MP: 236-238°C, YIELD: 82.34%, IR (KBr,cm^{-1})3890.58(OH), 1628.85 (C=N),

1600.59(C=N),1521.63(N=O).Elemental Analysis: C, 59.37; H, 3.20; N, 14.84; O, 22.59.

(OD-4): 2-[5-(1-Phenyl-ethyl)- [1,3,4] oxadiazol-2-yl] phenol: Yellow crystals,MP:278-280℃**,** Yield-81.09%, IR (KBr,cm^{-1}) 3837.68 (OH), 3552.23 (N-H), 1629.86 (C=N), 1602.71 (C=N),1280.79(C-0). ElementalAnalysis: C,72.16; H, 5.30; N,10.52; O, 12.02.

(OD-5):2-[5-(4-Amino-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol*:* LightYellowcrystals,MP:242-244℃,Yield:86.73%,IR(KBr,cm^{-1})3857.07(OH),1700.53 (C=N),1601.54 (C=N),1447.87(C-C),1233.05(C-O). Elemental Analysis: C, 66.40;H, 4.38;N,16.59; O,12.63.

(OD-6):2-{5-[1-(4-Chloro-phenyl)-ethyl-[1,3,4]oxadiazol-2-yl}-phenol: Yellow crystals, MP:278-280℃, Yield: 81.09%, IR(KBr,cm^{-1})3856.50(OH), 1669.78 (C=N), 1638.70(C=N), 1474.97(C-C), 1297.09(C-O), 750.25(C-Cl). Elemental Analysis: C, 63.90; H, 4.36; Cl, 11.79; N, 9.31; O, 10.64.

(OD-7):4-[5-(2-Hydroxy-phenyl)-[1,3,4]oxadiazol-2-yl]-2-methoxy-phenol: Buffcolouredpowder,MP:266-268℃,Yield:80.47%, IR(KBr,cm^{-1}) 3857.97(OH), 3737.13(OH), 2117.86(O-CH), 1603.22(C=N). Elemental Analysis: C, 63.38; H,4.25; N, 9.85; O, 22.51.

(OD-8):2-[5-(4-Dimethylamino-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol: Pale yellow coloured Solid, MP: 258-260℃, Yield: 86.85%, IR (KBr,cm^{-1}) 3738.15(OH), 1245.21(C-O),1669.84(C=N),3378.21(C-N-C). Elemental Analysis: C, 68.31; H,5.37; N, 14.94; O, 11.37.

(OD-9):4-[5-(2-Hydroxy-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol: Yellow powder, Yield 89.80%, MP: 232-234℃, IR(KBr,cm^{-1})3736.99(OH),3674.66(OH),1669.99(C=N), 1646.65(C=N),1278.38(C-O),1208.92(C-O). Elemental Analysis: C, 66.14; H, 3.96; N, 11.02; O, 18.88.

Table 1: Physical data of 2,5-disubstituted 1,3,4-oxadiazole derivatives:

Compd	M.F	M.W	M.P (℃)	R_f
OD-1	$C_{14}H_9ClN_2O$	272	282-284	0.78
OD-2	$C_{14}H_9N_3O_4$	283	258-260	0.83
OD-3	$C_{14}H_9N_3O_4$	283	236-238	0.87
OD-4	$C_{16}H_{14}N_2O_2$	266	278-280	0.69
OD-5	$C_{14}H_{11}N_3O_2$	253	242-244	0.81
OD-6	$C_{16}H_{13}ClN_2O_2$	300	278-280	0.78
OD-7	$C17H_{16}N_2O$	328	266-268	0.82
OD-8	$C_{16}H_{15}N_3O_2$	281	240-242	0.76
OD-9	$C_{14}H_{10}N_2O_3$	254	232-234	0.67

Table 2: Anti-microbial evaluationof synthesized 2,5-disubstitued-1,3,4-oxadiazole derivatives.

Compd	Conc. (µg/ml)	Zone of inhibition (mm)					
		B. subtilis	*B. cereus*	*S. aureus*	*S. pyrogenous*	*E.coli*	*P. aeruginosa*
OD-1	100	12.8	13.2	14.0	17.5	12.8	13.2
	200	14.3	13.9	12.8	16.8	14.3	13.9
	400	14.8	14.3	15.1	16.4	14.8	14.3
OD-2	100	15.6	14.5	13.7	15.3	15.6	14.5
	200	16.8	13.6	13.5	15.9	16.8	13.6
	400	18.2	14.7	15.8	14.5	18.2	14.7
OD-3	100	13.4	15.8	14.8	15.8	13.4	15.8
	200	14.0	15.7	14.3	15.7	14.0	15.7
	400	17.9	17.8	15.6	17.8	17.9	17.8
OD-4	100	13.6	16.3	15.3	14.5	13.6	16.3
	200	13.8	16.5	15.9	13.6	13.8	16.5
	400	14.7	15.9	14.5	14.7	14.7	15.9
OD-5	100	14.2	13.8	15.8	14.5	14.2	13.8
	200	16.8	14.9	15.7	13.6	16.8	14.9
	400	15.6	14.3	17.8	14.7	15.6	14.3
OD-6	100	17.9	23.2	15.3	15.9	17.9	23.2
	200	17.3	19.3	15.9	16.7	17.3	19.3
	400	16.8	19.6	14.5	18.2	16.8	19.6
OD-7	100	16.4	15.9	16.8	14.9	16.4	15.9
	200	17.0	15.3	16.4	12.0	17.0	15.3
	400	17.3	16.7	15.9	18.2	17.3	16.7
OD-8	100	13.7	13.9	16.2	13.7	13.7	13.9
	200	14.7	13.2	15.9	13.5	14.7	13.2
	400	17.8	12.9	15.3	15.8	17.8	12.9
OD-9	100	18.6	14.9	15.7	17.8	18.6	14.9
	200	18.6	15.4	16.8	16.4	18.6	15.4
	400	17.3	15.8	18.2	18.7	17.3	15.8

CONCLUSION:

Oxadiazoles are the essential pharmacophores with a wide range of applications andtheir derivatives have special significance among wide range of bioactive compounds. Requirement in the present scenario triggered us to develop anti-microbial oxadiazole derivatives with high efficiency and also with decrease in chemical usage, reactiontime, increasing the yield and purity of the compounds. All the derived oxadiazole derivatives (OD-1to OD-9) are screened for their anti-microbial activity and measured their zone ofinhibition values. Among all the compounds of oxadiazole derivatives, OD-2,3,4,7, 8exhibited good zone of inhibition.

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