

SYNTHESIS AND BIOLOGICAL EVALUATION OF 1,3,4-OXADIAZOLE DERIVATIVES AS POTENTIAL ANTIBACTERIAL AND ANTIFUNGAL AGENTS

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Abstract

1,3,4 oxadiazole derivatives are the heterocyclic compounds with very important biological activities such as anti-inflammatory, antimicrobial, antifungal, antiviral, analgesic, antimycobacterial, antidepressant and antiamebic. 1, 3, 4 oxadiazole was synthesized by condensation reaction between 2-hydroxybenzohydrazine and carbon disulfide. This derivative on treatment with different aromatic halides produced the desired final products.

The in-vitro antibacterial activity of synthesized compound was tested against Gram-positive and Gram-negative microorganisms (*Staphylococcus aureus* ATCC 9144, *Bacillus subtilis* ATCC 6633, *Pseudomonas aeruginosa* MTCC No. 1688, Gram negative: *Escherichia coli* ATCC 25922) by filter paper disc method. The in-vitro antifungal activity was tested against *Candida albicans* by filter paper disc method. All the compounds showed good activity against all cultures.

Key words:

Oxadiazole, microorganisms

How to Cite this Paper:

Palak K. Parikh*, Hiren M. Marvaniya and Prof. Dr. Dhrubo Jyoti Sen "Synthesis and Biological evaluation of 1,3,4-Oxadiazole derivatives as potential Antibacterial and Antifungal agents", Int J. Drug Dev. & Res., April-June 2011, 3(2): 248-255

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Article History:-----

Date of Submission: 01-03-2011

Date of Acceptance: 31-03-2011

Conflict of Interest: NIL

Source of Support: NONE

Introduction:-

The major drawback of current treatment of infectious diseases are challenging due to resistance to antimicrobial agents and their side effects. In order to overcome this situation, it is necessary to continue the search for new antibacterial agents. In recent scenario heterocycles plays a major role in

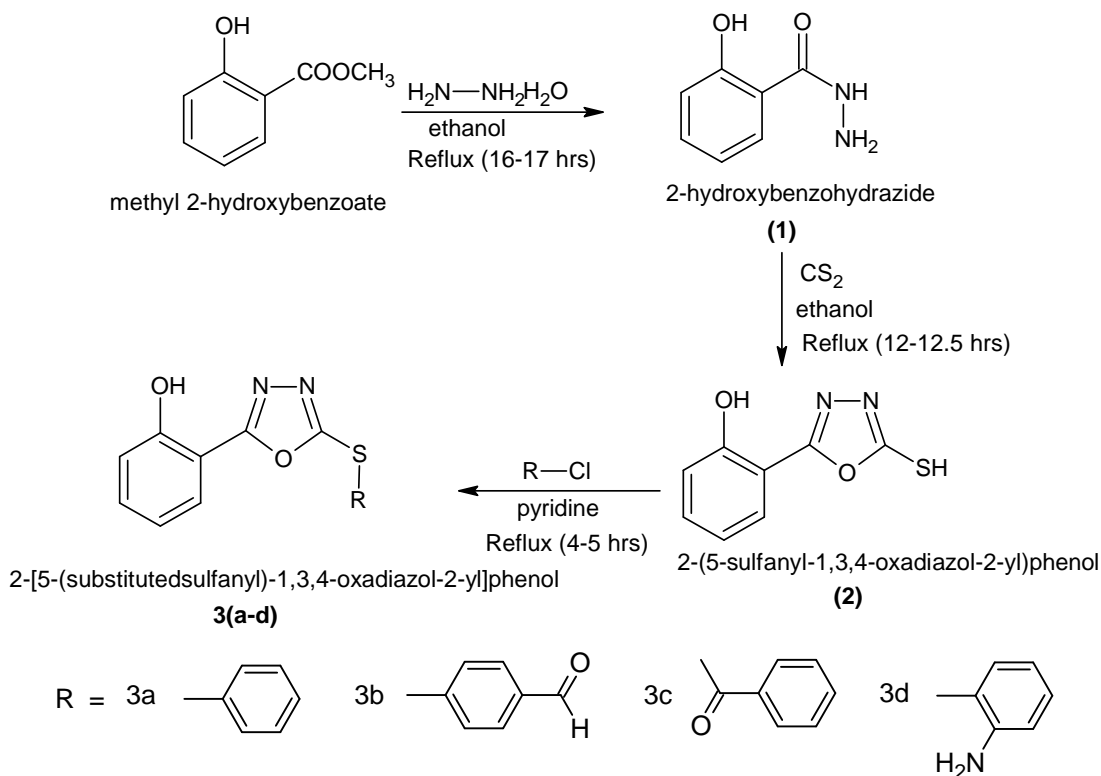
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drug synthesis. In that respect oxadiazole plays a significant role among other heterocycles. From the literature survey oxadiazole was found to be having diverse activity like anti-inflammatory, antimicrobial, antifungal, antiviral, analgesic, anti-mycobacterial, antidepressant and anticancer etc. So it was planned to synthesize a novel series of 1,3,4 oxadiazole derivatives and to check their activity as antimicrobial and antifungal agent.¹⁻⁷

Experimental:-

The entire chemicals were supplied by S. D. Fine Chem. (Mumbai), Finar Chem. Ltd (Ahmedabad) and Loba Chemie. Pvt. Ltd. (Mumbai). Melting points were determined by open tube capillary method and were uncorrected. Purity of compounds were checked by thin layer chromatography (TLC) on silicagel-G in solvent system hexane-ethyl acetate (1:1) and the spots were located under iodine vapours and UV light. IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr. Mass spectra were obtained using 2010EV LCMS Shimadzu instrument.

Scheme of Synthesis:



Synthetic procedure of 2-hydroxybenzohydrazine:-

A mixture of (12.94ml, 0.1mole) methyl salicylate and (10ml, 0.2mole) hydrazine hydrate were refluxed in 50ml ethanol for 17hours. The resultant mixture was concentrated, cooled and poured into crushed ice. The solid mass thus separated out was dried and recrystallized from ethanol.⁷

Synthetic procedure of 2-(5-sulfanyl-1,3,4-oxadiazol-2-yl)phenol:-

A mixture of (1.52g, 0.01mole) of 2-hydroxybenzohydrazine, (0.56g, 0.01mole) of KOH and 10ml of CS₂ were refluxed in 50ml of 95% ethanol for 12-12.5hours. The resultant mixture was concentrated and cooled to room temperature, acidified with dil.HCl. and the crude product was filtered and recrystallized from ethanol.⁷

General procedure of 2-(5-substituted sulfanyl-1,3,4-oxadiazol-2-yl)phenol derivatives:-

A mixture of (0.97g, 0.005mol) of 2-(5-sulfanyl-1,3,4-oxadiazol-2-yl)-phenol and (0.005mol) of different aryl halides were refluxed in 25ml of

pyridine solution for 3.5hours. The resultant mixture was cooled and poured into crushed ice. The solid mass is thus separated out was dried and recrystallized from ethanol.

Table-1: Physicochemical Parameters

Compound Code	Molecular Formula	Molecular Weight (g/mol)	Melting Point (°C)	%Yield
1	C ₇ H ₈ N ₂ O ₂	152.15	140-142°C	75.65
2	C ₈ H ₆ N ₂ O ₂ S	194.21	186-188°C	66.67
3a	C ₁₄ H ₁₀ N ₂ O ₂ S	270.3	172-174°C	62.96
3b	C ₁₅ H ₁₀ N ₂ O ₃ S	298.3	210-214°C	67.12
3c	C ₁₄ H ₁₁ N ₃ O ₂ S	285.3	156-158°C	52.45
3d	C ₁₅ H ₁₀ N ₂ O ₃ S	298.3	110-112°C	52.45

Spectral characterization data:-

- IR(KBr) [cm⁻¹]:- **-OH** (3321), **-NH₂** (3257.55, 3245), **>C=O** (1710)
- IR(KBr) [cm⁻¹]:- **-OH** (3321), **-C-S-H** (2600), **>C=N** (1650), 2910 (**Ar**, C-H stretching)
- 3a.** IR (KBr) [cm⁻¹]:- **-OH** (3328), **-C-O-C-** (1265), MS [m/z]=270 [M⁺]
- 3b.** IR (KBr) [cm⁻¹]:- **-OH** (3305), **-CHO** (1700, 2854), **-C-O-C** (1230), MS [m/z]=297 [M⁻¹]
- 3c.** IR (KBr) [cm⁻¹]:- **-OH** (3285), **>C=O** (1681), **C-O-C** (1292), MS [m/z]=298 [M⁺], ¹H NMR (DMSO-d₆): δ: 6.9-8.2 (m, 9H, ArH), 10.6 (s, 1H, OH).
- 3d.** IR (KBr) [cm⁻¹]:- **-OH** (3217), **-NH₂** (3182, 3139), **C-O-C** (1260), MS [m/z]=285 [M⁺]

Antibacterial Activity

The microbiological assay was based upon a comparison of inhibition of growth of microorganisms by measured concentrations of test compounds with that produced by known concentration of a standard antibiotic. Two methods generally employed were turbidometric (tube-dilution) method and filter paper disc method. In the turbidometric method inhibition of growth of

microbial culture in a uniform dilution of antibiotic in a fluid medium is measured. It was compared with the synthesized compounds. Here the presence or absence of growth was measured. The cylinder plate method depends upon diffusion of antibiotic from a vertical cylinder through a solidified agar layer in a petridish or plate to an extent such that growth of added micro-organisms is prevented entirely in a zone around the cylinder containing solution of the antibiotics. The cup-plate method is simple and measurement of inhibition of microorganisms was also easy. Here we have used this method for antibacterial screening of the test compounds.⁸⁻¹²

Name of Microorganism

- Gram +ve microorganisms
Staphylococcus aureus (MTCC No. 96)
Pseudomonas aeruginosa (MTCC No. 1688)
Bacillus subtilis (MTCC No. 121)
 Gram -ve microorganisms
Escherichia coli (MTCC No. 521).

Preparation of medium:-

- Nutrient agar 2%
 Peptone 1%
 Beef extract 1%

Sodium chloride 0.5%

Distilled water up to 100ml

All the ingredients were weighed and added to water. This solution was heated on water bath for about one and half-hour till it became clear. This nutrient media was sterilized by autoclave at 121°C at 15psi.

Apparatus:-

All the apparatus like petridishes, pipettes, glass rods, test-tubes etc. were properly wrapped with papers and sterilized in hot air oven.

Antimicrobial screening method

- All the Petri dishes were sterilized in oven at 160°C for 1 hour.

- Agar media, borer and test solutions were sterilized in autoclave at 121°C at 15psi.
- Molten sterile agar was poured in sterile petri dishes aseptically.
- The agar was allowed to cool and the bacterial suspension was poured into the petridishes aseptically.
- Placing the sterile filter paper discs in the agar plate and solution of the compounds was added by using pipette (0.1ml) in appropriate four quadrants of petridishes aseptically.

Petridishes were incubated at 37°C for antimicrobial and 24°C for antifungal for 24 hrs and observed the zone of inhibition.¹³⁻¹⁷

Table 2: ANTIMICROBIAL SCREENING BY ZONE OF INHIBITION IN MILIMETER (FILTER PAPER DISC METHOD)

Compound Code	Concentration (µg/ml)	Zone of inhibition (mm)			
		Gram +ve			Gram -ve
		<i>S.aureus</i>	<i>B.subtilis</i>	<i>P.aeruginosa</i>	<i>E.coli</i>
3a	250	07	-	06	00
	500	08	07	09	08
	750	12	07	14	10
	1000	14	10	19	11
3b	250	07	08	12	08
	500	09	09	15	10
	750	11	11	18	12
	1000	13	15	22	16
3c	250	08	06	14	09
	500	12	08	17	12
	750	18	12	22	14
	1000	22	15	28	18
3d	250	09	00	14	08
	500	11	08	14	11
	750	12	09	16	12
	1000	15	12	20	15
Ciprofloxacin	100	26	27	25	27
	250	29	30	28	28
	500	34	32	30	31
Ampicillin	100	21	23	20	22
	250	23	25	21	25
	500	26	28	23	27

HISTOGRAM: ANTIMICROBIAL SCREENING BY ZONE OF INHIBITION IN MILIMETER (FILTER PAPER DISC METHOD)

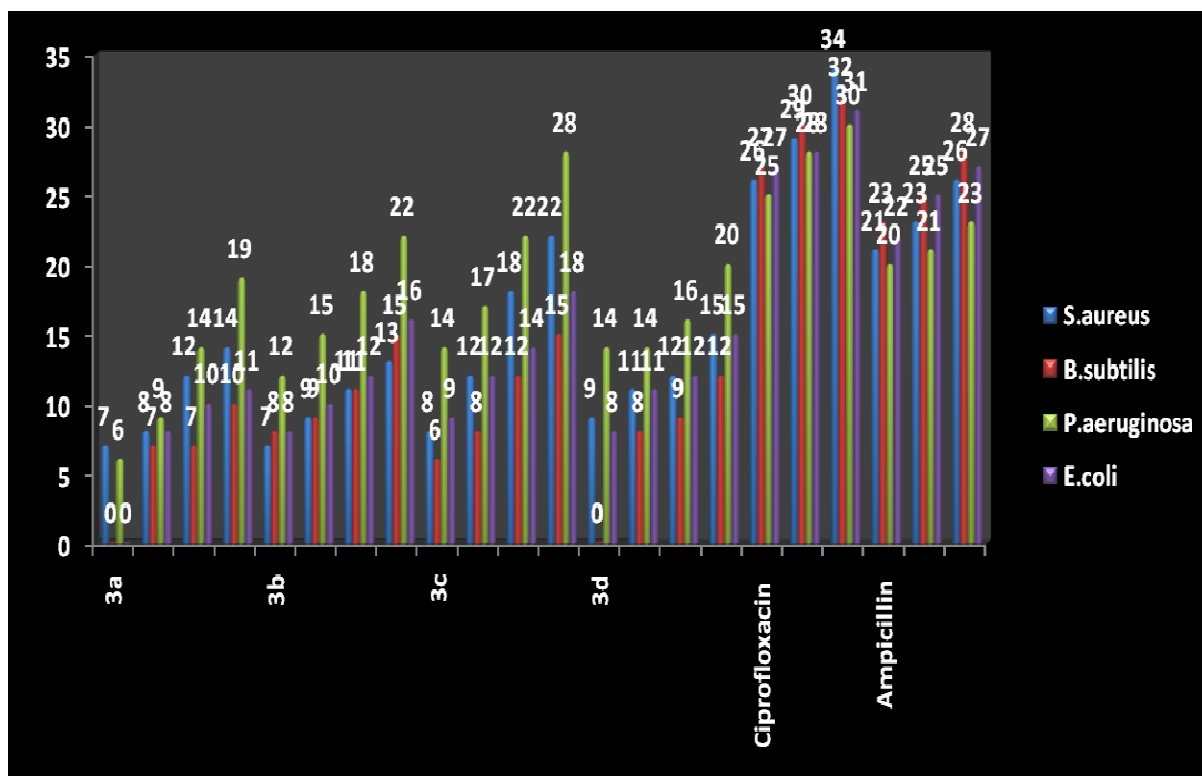


Table 3: MIC VALUES OF THE COMPOUNDS WITH GRAM POSITIVE AND GRAM NEGATIVE MICROORGANISMS

Compound code	MIC ($\mu\text{g/ml}$)			
	<i>S.aureus</i>	<i>B.subtilis</i>	<i>P.aeruginosa</i>	<i>E.coli</i>
3a	250	500	200	500
3b	250	250	150	250
3c	200	250	100	200
3d	250	500	200	250
Ciprofloxacin	6.25	6.25	6.25	6.25
Ampicillin	25	25	25	25

Antifungal activity:-¹³⁻¹⁷

Preparation of standard solution

The standard drug fluconazole and ketoconazole were dissolved in appropriate quantity of DMF to obtain the concentration range of 100, 250 and 500 $\mu\text{g/ml}$ and the zone of inhibition was checked.

Preparation of test solution

Specified quantity (100mg) of the compound was accurately weighed and dissolved in 100ml of DMF to get the 1000 $\mu\text{g/ml}$ stock solution. Further dilution was made to obtain the concentration in the range 750 $\mu\text{g/ml}$, 500 $\mu\text{g/ml}$ and 250 $\mu\text{g/ml}$.

Fungi used

The synthesized compounds were screened for their antifungal activity against fungi *Candida albicans* (MTCC No. 22).

Preparation of Sabouraud Dextrose Broth

Formula/Liter

Enzymatic digest of Casein	5g
Enzymatic digest of Animal Tissue	5g
Dextrose	20g
Final pH	5.6 \pm 0.2 at 25 $^{\circ}\text{C}$
Purified water	1000ml

Procedure

30g of the medium was suspended in 1000ml of purified water. The mixture was allowed to boil till it

forms a homogeneous solution. The medium was autoclaved at 121°C for 15 minutes at 15psi.

Table 4: ANTIFUNGAL SCREENING BY ZONE OF INHIBITION IN MILIMETER (FILTER PAPER DISC METHOD)

Compound Code	Concentration (µg/ml)	Zone of inhibition (mm)
		<i>C.albicans</i>
3a	250	08
	500	12
	750	20
	1000	21
3b	250	11
	500	14
	750	20
	1000	23
3c	250	09
	500	12
	750	14
	1000	15
3d	250	12
	500	15
	750	18
	1000	22
Ketoconazole	100	26
	250	29
	500	34
Fluconazole	100	20
	250	22
	500	27

HISTOGRAM: ANTIFUNGAL SCREENING BY ZONE OF INHIBITION IN MILIMETER (FILTER PAPER DISC METHOD)

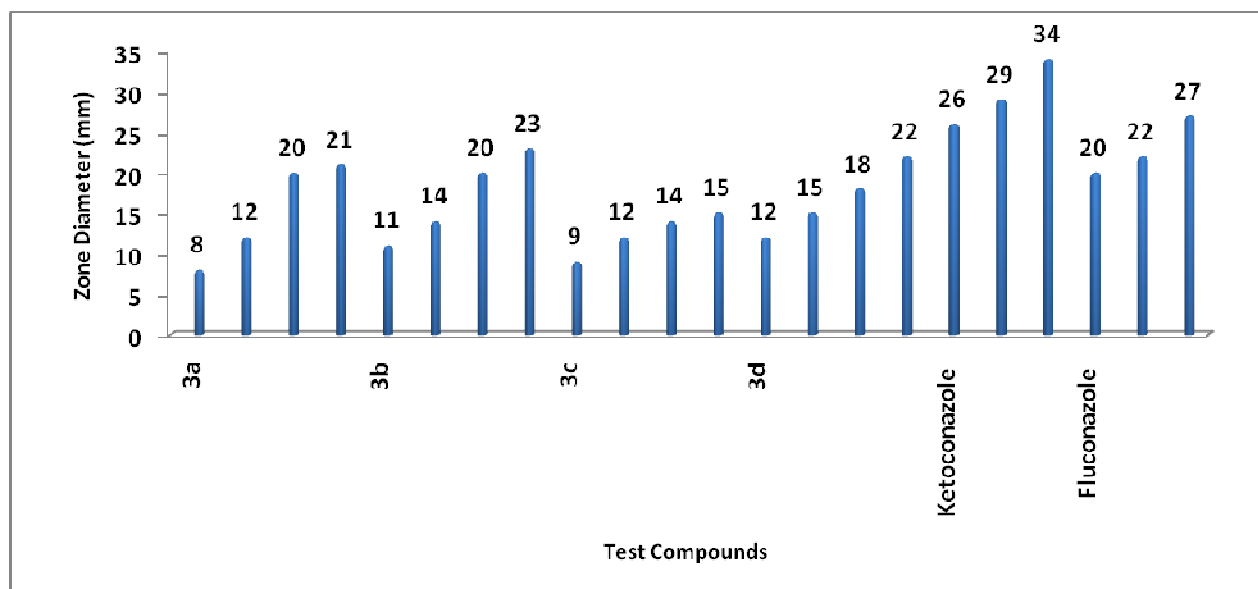
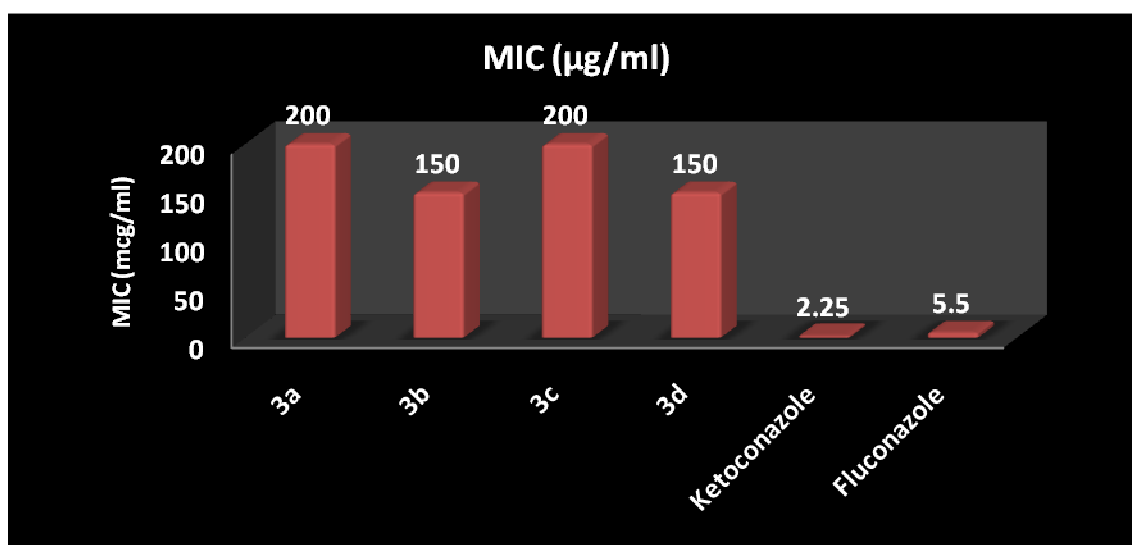


Table 5: MIC VALUES OF COMPOUNDS WITH ANTIFUNGAL AGENTS

Compound code	MIC ($\mu\text{g/ml}$)
3a	200
3b	150
3c	200
3d	150
Ketoconazole	2.25
Fluconazole	5.5

HISTOGRAM: MIC of test compounds



CONCLUSION:

Antibacterial activity:

From the result it was found that 3c compound has maximum antibacterial activity against *P. aeruginosa*. Compounds 3b and 3c have found maximum activity against *B. subtilis*. Compound 3c has maximum activity against *S. aureus*.

Antifungal activity:

Maximum antifungal activity against *C. albicans* was found in compound 3b.

All compounds were less potent than standard drugs ampicillin, ciprofloxacin, fluconazole and ketoconazole.

ACKNOWLEDGEMENT: The author Palak K. Parikh is thankful to the project guide Prof. Dr. Dhruvo Jyoti Sen and the staff members of Shri Sarvajanic Pharmacy College, Mehsana, Gujarat to fulfil the project successfully. All the authors are

thankful to the Quality Assurance Department of Shri Sarvajanic Pharmacy College, Mehsana for UV and IR spectral data, Oxygen Healthcare, Ahmedabad for Mass spectral data and Punjab University for NMR spectral datas.

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