

ANTI-MICROBIAL STUDIES ON NOVEL 1, 3-OXAZOLIDINE ANALOGS

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Summary

In present study several substituted 1, 3-oxazolidines were synthesized by condensation of reduced Schiff base of phenylglycinol with different aldehydes. All the synthesized compounds showed good to moderate antimicrobial activity. The antimicrobial activities were performed by disc diffusion method and minimum inhibitory concentration determination by serial agar dilution method. Thus among the ten compounds, 3-[3-(2-furyl methyl)-4-phenyl-1,3-Oxazolidin-2-yl]-¹H-indole (4a), 2-(2-furyl)-3-(2-furyl methyl)-4-phenyl-1,3-Oxazolidine (4b) and 4-[3-(2-furylmethyl)-4-phenyl-1,3-oxazolidin-2-yl]-2-methoxy phenol (4h) were found to have a moderate to significant antimicrobial activity against all the strains used. Compound 2-(4-chlorophenyl)-3-(2-furylmethyl)-4-phenyl-1, 3-oxazolidine (4j) showed very good antifungal activity than the other compounds tested. Further more, compounds containing -Cl, -OCH₃, -OH groups as substituents were found to be potent antimicrobial agents. Moreover the heteroaromatic substitutions also showed very good antimicrobial activities.

Key words: synthesis, oxazolidines, antibacterial, antifungal, aldehydes

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Introduction

1, 3-oxazolidine derivatives have been found to be associated with several biological activities like antimicrobial (1-4), antiarrhythmic (1), anti-tumor (1), antidiabetic (5), anticonvulsant (6) and antihypertensive activity (7). Linezolid, a 1,3-oxazolidine derivative which has been used clinically since 2000 for treating infections caused by terminal Gram(+) organisms. However, toxicity as well as emergence of resistance in some patients receiving prolonged treatment has been reported. A number of attempts have been made by various research groups to obtain potent and safe analogs without much success. Multi drug resistance among the pathogens represents a serious challenge for health practitioners in treating both nosocomial and community acquired infections (8). The continued rise in microbial resistance has called for antimicrobial agents to be developed that are effective against resistant strains.

This observation prompted us to synthesis some novel 2-substituted-1, 3-oxazolidine derivatives and to evaluate their antimicrobial activities. In this present study, a new series of 2-substituted 1, 3-oxazolidines were synthesized by condensation of different aldehydes with reduced Schiff base of phenylglycinol. All the compounds were characterized by spectral and elemental analysis data. For these compounds, antimicrobial activities and minimum inhibitory concentration were done by disc diffusion and agar streak serial dilution method.

Materials and Methods

Test organism and drugs used

Pure cultures of test organisms *Staphylococcus aureus* (ATCC 9144), *Staphylococcus epidermidis* (ATCC 155), *Micrococcus luteus* (ATCC 8341), *Klebsiella pneumonia* (ATCC 29665), *Escherichia coli* (ATCC 25922), *Candida albicans* (ATCC 2091) and *Aspergillus niger* (ATCC 9029) were procured from the central drugs laboratory (Kolkata, India). All the organisms were maintained on agar slant stocks and were subsequently sub cultured into newly prepared nutrient agar slants. Ciprofloxacin (Dr. Reddy's Lab, Batch no: 1C 666E04, India) was used as a standard in antibacterial studies and ketokonazole was used as a standard in antifungal studies.

Antimicrobial activity

The newly synthesized compounds were screened for their antimicrobial activity by disc diffusion method (9). The sterilized (autoclaved at 120°C for 30 minutes) medium (nutrient agar for antibacterial activity and sabouraud dextrose agar media for antifungal activity) was inoculated with the suspension of microorganism (1ml/100ml of medium) and poured into a Petri dishes to give a depth of 3-4mm. The discs (previously sterilized in UV lamp) impregnated with the test compounds were placed on the solidified medium. The stock solution of test compounds was prepared at 100µg/ml in DMSO. The plates were preincubated for 1h at room temperature. The plates containing bacteria were incubated at 37°C for 24h and those containing fungi were incubated at 37°C for 48h.

Ciprofloxacin and ketokonazole were used as standard drugs for antibacterial and antifungal studies respectively. The zone of inhibition was measured and the values were represented in table-1.

Minimum inhibitory concentration

The minimum inhibitory concentration (MIC) of the synthesized compounds was found by agar streak serial dilution method (10). A stock solution of the synthesized compound in dimethylformamide (10µg/ml) was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (nutrient agar for antibacterial activity and sabouraud dextrose agar media for antifungal activity). Specified quantity of the medium containing the compound was poured into a petri dish to give a depth of 3-4 mm and allowed to solidify. Suspension of the micro organism was prepared to contain approximately 10⁵cfu/ml and applied to plates with serially diluted compounds in dimethylformamide to be tested. The observed MIC values were presented in Table-2.

Results and discussion

The novel 2-substituted-1, 3-oxazolidines were synthesized by the reaction of reduced Schiff base of phenylglycinol under reflux conditions with the appropriate aldehydes in toluene. The structures of the compounds were given in Figure1.

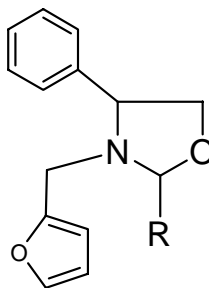


Figure-1

2-substituted-3-(2-furyl methyl)-4-phenyl-1,3-Oxazolidine

COMPOUND	R	COMPOUND	R
4a		4f	
4b		4g	
4c		4h	
4d		4i	
4e		4j	

The compounds were tested in vitro for their antimicrobial activity against seven microorganisms belonging to bacteria and fungi classes. It was observed that all the compounds showed moderate to potent antimicrobial activity. The antimicrobial activity was done at 100µg/ml concentration by disc diffusion method. The data were given in table-1.

Table 1: Antimicrobial activity of the synthesized compounds at 100µg/ml.

cpd	Invitro antibacterial activity-Zone of inhibition (mm)						
	<i>S.aureus</i> ATCC 9144	<i>S.epidermidis</i> ATCC 155	<i>M.luteus</i> ATCC 4678	<i>K.pneumoniae</i> ATCC 29665	<i>E.coli</i> ATCC 2592	<i>C.albicans</i> ATCC 2091	<i>A.niger</i> ATCC 9020
4a	27	28	31	25	28	17	33
4b	28	23	31	23	20	17	28
4c	12	14	16	17	31	15	33
4d	23	25	25	22	21	16	32
4e	26	27	28	22	17	16	30
4f	22	28	25	25	23	16	28
4g	26	25	32	24	19	15	26
4h	28	28	30	25	23	19	32
4i	23	30	22	24	23	15	31
4j	22	32	27	24	19	19	35
CFN	29	33	35	27	31	-	-
KKZ	-	-	-	-	-	22	36
DMF	-	-	-	-	-	-	-

CFN Ciprofloxacin; KKZ Ketokonazole; DMF Dimethylformamide; ATCC American Tube Culture Collection

Minimum inhibitory concentration was performed by agar streak serial dilution method against all organisms used and the data were given in Table-2.

Table 2: Minimum inhibitory concentration of synthesized compounds

cpd	Minimum inhibitory concentration (µg/ml)						
	<i>S.aureus</i> ATCC 9144	<i>S.epidermidis</i> ATCC 155	<i>M.luteus</i> ATCC 4678	<i>K.pneumonia</i> ATCC 29665	<i>E.coli</i> ATCC 2592	<i>C.albicans</i> ATCC 2091	<i>A.niger</i> ATCC 9020
4a	16	24	14	27	08	16	09
4b	12	29	13	25	19	03	23
4c	35	33	34	39	03	25	10
4d	30	26	21	31	17	21	15
4e	19	19	18	30	29	21	19
4f	31	21	20	24	11	18	22
4g	17	25	11	29	19	24	31
4h	10	22	15	25	12	12	14
4i	31	16	25	21	15	30	12
4j	32	14	19	23	20	15	05
CFN	03	02	02	02	03	-	-
KKZ	-	-	-	-	-	01	03
DMF	-	-	-	-	-	-	-

CFN Ciprofloxacin; KKZ Ketokonazole; DMF Dimethylformamide; ATCC American Tube Culture Collection.

From the results, compounds 3-[3-(2-furyl methyl)-4-phenyl-1,3-Oxazolidin-2-yl]-¹H-indole (4a), 2-(2-furyl)-3-(2-furyl methyl)-4-phenyl-1,3-Oxazolidine (4b) and 4-[3-(2-furylmethyl)-4-phenyl-1,3-oxazolidin-2-yl]-2-methoxy phenol (4h) were found to have a moderate to significant antimicrobial activity against all the strains used. Compound 2-(4-chlorophenyl)-3-(2-furylmethyl)-4-phenyl-1,3-oxazolidine (4j) showed very good antifungal activity than the other compounds tested. From the observed MIC values of the compounds, it can be concluded that the hetero aromatic and 4-hydroxy, 3-methoxy or 4-chloro containing phenyl substitutions showed distinct antimicrobial activity that is independent of other substituents.

Therefore the above said compounds can serve as lead molecules for further modification to obtain clinically important or beneficial antimicrobial agents.

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