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RESEARCH ARTICLE

Synthesis, Characterization and Biological Evaluation of Oxazolone Derivatives

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ABSTRACT

A series of six 4-aryl Benzelidene-2-phenyl-5- oxazolone derivatives were synthesized by condensation of aromatic aldehydes with *N*-benzoyl glycine in the presence of sodium acetate and acetic anhydride at room temperature in ethanol. Six of the compounds are new derivatives. The structures of the compounds were evaluated based on 1H-NMR and FT-IR spectroscopy, and elemental analysis. All the compounds were screened for their antibacterial activity. The antibacterial activity was tested by the agar well diffusion method using Mueller Hinton Agar medium. Compound (O_2) showed excellent activity against *Staphylococcus aureus* exhibiting 15mm (80 %) inhibition and above 10mm (70 %) against *Bacillus subtilis*. Compound (O_3) was the most active compound against *Escherichia coli* having 18mm (80 %) inhibition followed by compound (O_2) having above 14mm (70 %) inhibition.

KEYWORDS

N- Benzoyl Glycine, Aromatic Aldehyde, Oxazolones, Antibacterial Activities

INTRODUCTION

For many decades, increasing resistance against human pathogens that cause serious infections is one of the main topics of interest for medicinal chemists. Many medicines were developed against bacterial infections. Since many decades, active heterocyclic compounds are one of the main topics of interest for the medicinal chemists as it displays a number of pharmacological activities.

Mostly Nitrogen- Sulphur- and Oxygen-containing five- and six-member heterocyclic compounds like oxazolones have enormous significance in the field of medicinal chemistry and these are class of small heterocyclic compounds which have acquired more importance in recent years due to their pharmacological activities.

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Oxazolones are five membered heterocyclic compounds containing nitrogen and oxygen as hetero atoms. The C-2 and C-4 positions of oxazolone are responsible for their various biological activities such as analgesic, anti-inflammatory, antidepressant, anticancer, antimicrobial, antidiabetic and antiobesity[1] Oxazol-5-ones contain correspondence numerous reactive sites allowing for a diverse set of possible modifications. Hence we aimed to design novel derivatives containing a variety of oxazolone derivatives with structural variation at C-2 and C-4 positions were synthesized and evaluated anti-microbial and analgesic activities.

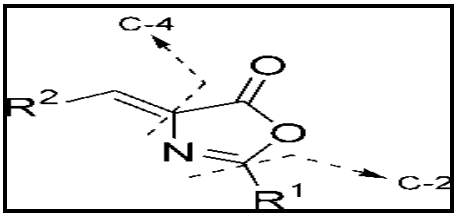


Figure 1: Structure of Oxazalone

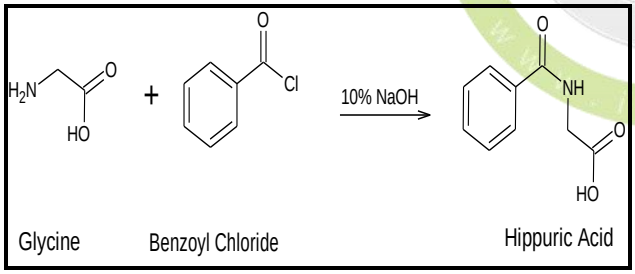
MATERIALS AND METHODS

All the chemicals were of synthetic grade and commercially procured from SD fine Chemicals Ltd. Mumbai, India. Melting points were recorded on a Buchi capillary melting point apparatus and are uncorrected. IR spectra were recorded on FT-IR 8400S, Fourier Transform (SHIMADZU) Infrared spectrophotometer using KBr disc method. The 1H-NMR spectra were recorded in $CDCl_3$ on AVANCE 300MHz NMR Spectrophotometer using TMS as an internal standard. Thin layer chromatography analyses were performed on pre-coated silica gel plates (G 350, Merck).

Procedure

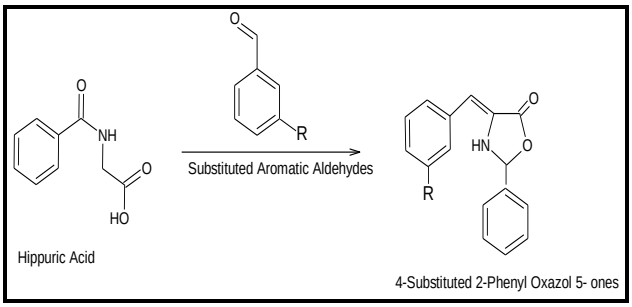
Step 1: General Synthesis of Phenyl Glycine or Hippuric acid from Glycine

Glycine (10gm) is first dissolved in 10% sodium hydroxide solution (100ml) and reaction mixture is kept in ice cold water and benzoyl chloride (21.6ml) is added drop wise with continuous stirring after addition of all benzoyl chloride pH of the reaction mixture is adjusted to 2-3 with concentrated HCl and the precipitate of phenyl glycine obtained.



Step 2: Synthesis of Oxazolone Derivatives from Hippuric acid

Hippuric acid(0.01m), acetic anhydride(0.04m), sodium acetate(0.01m), aromatic aldehyde(0.04m), are taken in a conical flask and the reaction mixture is heated for 15mins on heating mantle then the reaction mixture is cooled for 5mins and 2-3 drops of ethanol is added and the ice cold water is poured into the reaction mixture to get the precipitate of oxazolones.



Antibacterial Assay

Sufficient quantity of MHA (Mueller Hinton Agar) media was prepared and sterilized and left to cool up to 45^0C. The MHA media was then separated into five portion of equal quantity. Each portion was inoculated by pouring 5ml of 24 hour microbial culture into the media. This was then transferred into their respective previously labeled Petri dishes and left for solidification then plates were stored in a refrigerator to ensure that no significant growth or death occurs before the plates are used. Ditch the bores in plate using a sterile metal borer. Add the test solutions in the bores with the control in the centre of the plate. The plates were placed in an incubator at 37^OC for bacteria for a period of 48 hours. The diameter of zone was measured and recorded in zone reader (in mm).

RESULTS AND DISCUSSION

Chemistry

Oxazolone derivatives were synthesized by condensation of substituted aromatic aldehydes with Hippuric acid using sodium acetate as a catalyst in ethanol at room temperature. The synthesized compounds were scaled for yield and purified by recrystallization with suitable solvent system. The purified compounds are identified/characterized by following methods melting point, solubility, thin layer chromatography and results were listed in table 1, the synthesized compounds were characterized using different spectroscopic techniques. The IR spectrum showed characteristic band of carbonyl group at 1772cm^{-1} and C=N at 1352 cm^{-1}. $_1$H-NMR spectrum showed characteristic pattern of peaks. The methyl protons appeared in the region of

3.84 ppm, whereas the aromatic protons appeared at 6.89–8.12 ppm.

Antibacterial Activity

All the compounds O_1 to O_6 were tested for their antibacterial activity against *E. coli, B. subtilis, B. subtilis, S. aureus, P. aeruginosa, and K.pneumoniae*. The results were compared with those of the standard 0.5% Ciprofloxacin. The bacterial zones of inhibition values are summarized in Table. Compounds (O_2) and (O_3) showed excellent activities against *E. coli*, which is very difficult to treat with traditionally used antibiotics. The most active compound against *E. coli* was compound O_3 having 18 mm inhibition zone (80 % inhibition), followed by compound O_2 having above 15 mm inhibition zone (70 %). Thus, compounds O_2 and O_3 would be the better choice for the treatment of infections caused by *E. coli* than the derivatives 1, 4 or 5. All the screened compounds showed low to moderate activities against *P. aeruginosa*, except compound O_3 that showed 50 % inhibition. *S. aureus* is responsible for various throat infections and cholic diseases. Therefore, compound O_2 would be the best choice to treat infections caused by *S. aureus* as it had a 14 mm inhibition zone (60 %). Compound O_3 also showed 60 % inhibition followed by compounds 1,2,4,5 and 6. The results of antibacterial activity are listed in table 2, compound O_2 and O_3 proved they to be very effective antibacterial agents.

Table 1: Physical Constants Data of Synthesized Compounds

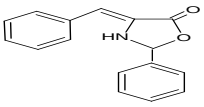
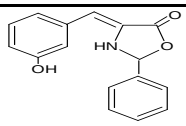
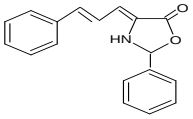
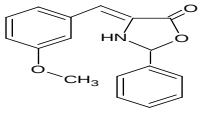
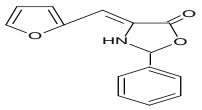
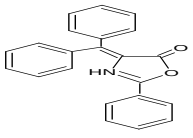
Compound Code		MP(C°)	% Yield	Molecular Formula	Molecular Weight	R_f Value
O1		120	78%	$C_{16}H_{17}NO_2$	255.31	0.87
O2		145	82%	$C_{15}H_{17}NO_3$	259.30	0.76
O3		135	75%	$C_{15}H_{17}NO_2$	243.30	0.82
O4		140	72%	$C_{16}H_{19}NO_3$	273.32	0.74
O5		125	74%	$C_{14}H_{15}NO_3$	245.27	0.88
O6		130	76%	$C_{21}H_{23}NO_2$	321.41	0.62

Table 2: Antibacterial activity

Compound code/ Name of bacteria	Mean zone of inhibition (mm)*						
	O_1	O_2	O_3	O_4	O_5	O_6	STD
E.coli	10	14	18	8	0	10	20
Pseudomonas aeruginosa	2	18	10	0	9	18	25
Staphylococcus aureus	10	15	12	2	6	4	22
Klebsiella pneumoniae	18	9	15	1	10	15	28
Bacillus subtilis	12	10	20	10	8	12	30

STD = Standard drug (0.5% Ciprofloxacin),
O_1-O_6 = Synthesized derivatives (1% concentration of each compound)

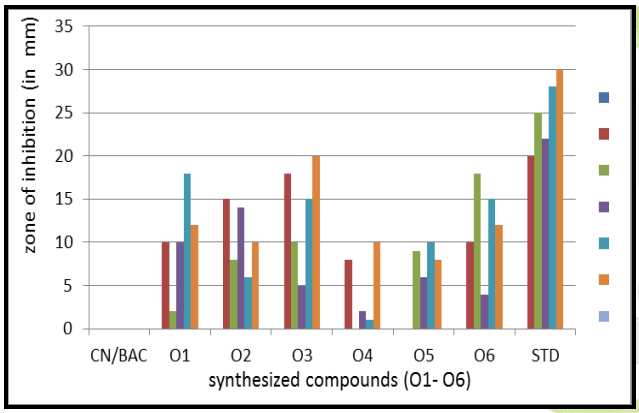


Figure 2: Graphical representation of antibacterial activity

CONCLUSION

It is concluded based on the biological activities of the synthesized oxazolone derivatives, it could be concluded that they are therapeutically active antibacterial agents, among all synthesized compounds the compound O_2 and O_3 showed better antibacterial activity against Escherichia coli bacteria, compared with standard ciprofloxacin.

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