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SYNTHESIS AND BIOLOGICAL EVALUATION OF SUBSTITUTED 4-BENZYLIDENE-2-PHENYL OXAZOLE-5-(-4*H*)-ONES

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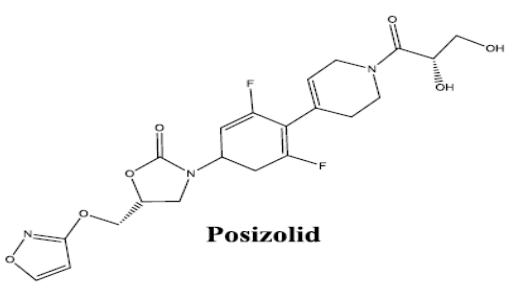
Abstract:

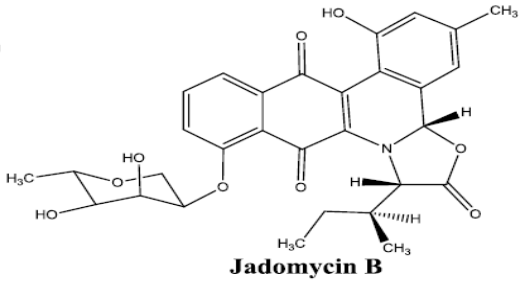
Oxazolone is a 5 membered ring system. It has oxygen and nitrogen in 1st & 3rd position and also having ketone group at 5th position. Oxazolone ring was performed by the condensation of benzoylglycine with appropriate substituted aldehyde in presence of acetic anhydride and anhydrous sodium acetate by applying heating method. All the synthesized compounds have been characterized by TLC, M.P and spectral data. The antibacterial activity was checked against gram positive & gram negative organisms for all the compounds and antifungal activity was also screened.

KEYWORDS: Oxazolones, antibacterial activity & antifungal activity

INTRODUCTION:

Heterocyclic chemistry has been known for many years but in recent years heterocyclic's received great attention. Oxazolone is one of the most important moieties. It is important synthons for the synthesis of various biologically active compounds and is an important pharmcophore of synthesized drugs. Oxazolone is being synthesized in many ways since 1883. It shows marked pharmacological activities such as: antimicrobial, antifungal, anti-diabetic, anti-cancer and anti-inflammatory. Oxazolone is crucial for the manufacturing of various biologically active drugs. 6-β-Naltrexol is the major active metabolite of naltrexone, a potent μ-opioid receptor antagonist used in the treatment of alcohol dependence and opioid abuse. Posizolid is an oxazolidinone antibiotic effective against phase 2 tuberculosis is under investigation. Deflazacort contains oxazolone scaffold derived from prednisone, has anti-inflammatory and immunosuppressive effects. Jadomycin B, an antifungal antibiotic, produced by the bacterium *Streptomyces venezuelae.* it also having oxazolone in their structure.





METHODOLOGY:

Preparation of (4*Z*)-4-(4-chlorobenzylidiene)-2-phenyloxazol-5(4*H*)-one:

A mixture of benzoylglycine (1 gm, 5.5 mmol), p-chloro benzaldehyde (5.5 mmol), anhydrous sodium acetate (0.45 gm, 5.5 mmol) and acetic anhydride (2.5 ml, 27.5 mmol) were heated at 150^{0}C for 2 h. The reaction mixture was then cooled in refrigerator for overnight. The hard solid mass was cursed with ice-cold water and filtered under suction. The residue was thoroughly washed with each 10 ml of warm water and ether. The crude product obtained was dried in vacuum desiccators. Purified by ethanol, characterized by M.P and TLC (1:1 n-hexane & ethyl acetate).

Preparation of (4*Z*)-4-(3, 5-dimethoxybenzylidiene)-2-phenyloxazol-5(4*H*)-one:

A mixture of benzoylglycine (1 gm, 5.5 mmol), 3, 5-dimethoxybenzaldehyde (5.5 mmol), anhydrous sodium acetate (0.45 gm, 5.5mmol) and acetic anhydride (2.5 ml, 27.5 mmol) were heated at 150^{0}C for 2 h. The reaction mixture was then cooled in refrigerator for overnight. The hard solid mass was cursed with ice-cold water and filtered under suction. The residue was thoroughly washed with each 10 ml of warm water and ether. The crude product obtained was dried in vacuum desiccators and purified by ethanol, characterized by M.P and TLC (1:1 n-hexane & ethyl acetate).

Preparation of (4*Z*)-4-(4-hydroxybenzylidene)-2-phenyloxazol-5(4*H*)-one:

A mixture of benzoylglycine (1 gm, 5.5 mmol), p-hydroxy benzaldehyde (5.5 mmol), anhydrous sodium acetate (0.45 gm, 5.5 mmol) and acetic anhydride (2.5 ml, 27.5 mmol) were heated at 150^{0}C for 2 h. The reaction mixture was then cooled in refrigerator for overnight. The hard solid mass was cursed with ice-cold water and filtered under suction. The residue was thoroughly washed with each 10 ml of warm water and ether. The crude product obtained was dried in acuum desiccators and purified by ethanol, characterized by M.P and TLC (1:1 n-hexane & ethyl acetate).

Preparation of (4*Z*)-4-(4-(dimethylamino) benzylidene)-2-phenyloxazol-5(4*H*)-one:

A mixture of benzoylglycine (1 gm, 5.5 mmol), p-dimethyl amino benzaldehyde (5.5 mmol), anhydrous sodium acetate (0.45 gm, 5.5 mmol) and acetic anhydride (2.5 ml, 27.5 mmol) were heated at 150^{0}c for 2 h. The reaction mixture was then cooled in refrigerator for overnight. The hard solid mass was cursed with ice-cold water and filtered under suction. The residue was thoroughly with each 10 ml of warm water and ether. The crude product obtained was dried in vacuum desiccators and purified by ethanol, characterized by M.P and TLC (1:1 n-hexane & ethyl acetate).

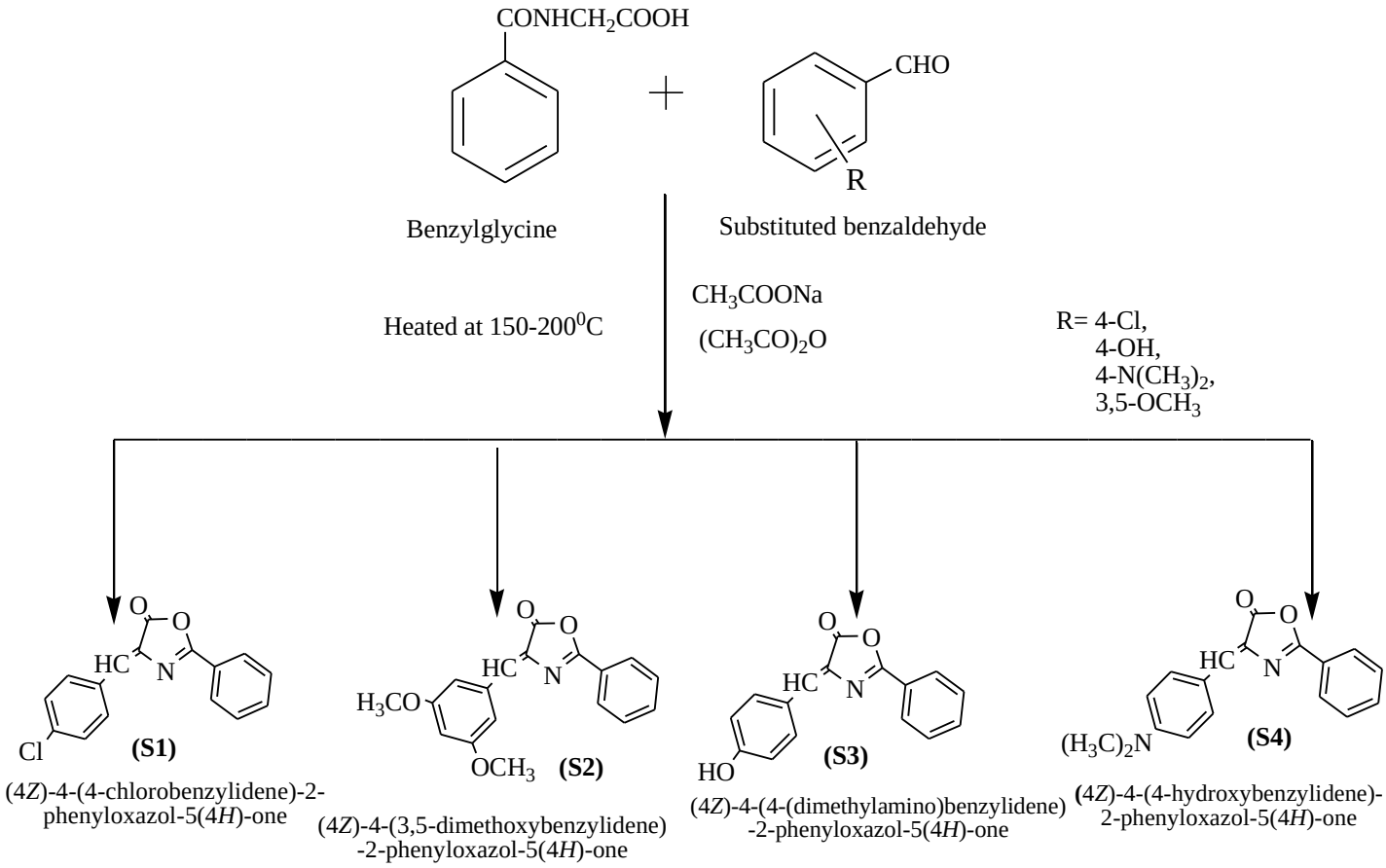
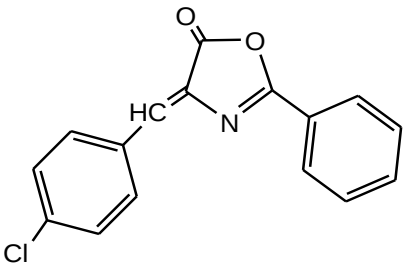


Fig 1: Scheme of the work

SPECTRAL DATA:
COMPOUND S_1

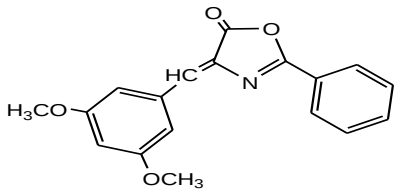


(4*Z*)-4-(4-chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one

^{1}H NMR (400 MHz, $CDCl_3$): 7.50-7.57 (m, 5H, ArH) 7.6 (s, 1H, =CHAr), 7.54-7.56 (d, 2H, ArH), 7.92-7.94 (d, 2H, ArH).

IR (KBr) (cm^{-1}): 688cm^{-1} (C-Cl str), 3067cm^{-1} (C-H str in Ar), 1600cm^{-1} (C=C Str), 1550cm^{-1} (C=N Str in Oxazolone), & 1739cm^{-1} (C=O Str in Oxazolone)

COMPOUND S_2

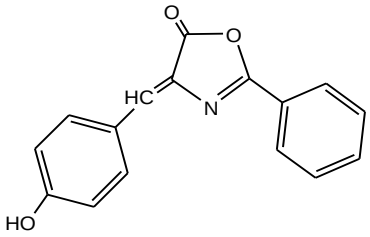


(4*Z*)-4-(3,5-dimethoxybenzylidene)-2-phenyloxazol-5(4*H*)-one

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 6H, 3, 4- diOCH_3), 6.93-6.95 (d, 2H, ArH), 7.6 (s, 1H, =CHAr), 7.3-7.6. (m, 5H, ArH).

IR (KBr) (cm^{-1}): 3030 cm^{-1} (C-H Str in Ar), 1600 cm^{-1} (C=H str in Ar), 1550 cm^{-1} (C=N Str in Oxazolone), 1739 cm^{-1} (C=O Str in Oxazolone), 1135cm^{-1} (C-O Str in OCH_3),

COMPOUND S_3

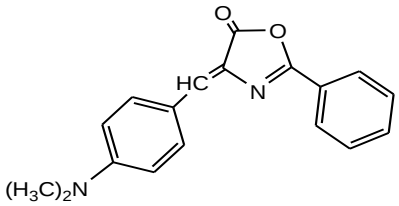


(4*Z*)-4-(4-hydroxybenzylidene)-2-phenyloxazol-5(4*H*)-one

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.0 (s, 1H, 3, OH), 6.63-7.35 (d, 2H, ArH), 7.6 (s, 1H, =CHAr), 7.3-7.6. (m, 5H, ArH).

IR (KBr) (cm^{-1}): 3336 cm^{-1} (O-H Str), 3030 cm^{-1} (C-H Str in Ar), 1600 cm^{-1} (C=H Str in Ar), 1550 cm^{-1} (C=N Str in Oxazolone), 1739 cm^{-1} (C=O Str in Oxazolone),

COMPOUND S_4



(4*Z*)-4-(4-(dimethylamino)benzylidene) -2-phenyloxazol-5(4*H*)-one

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86 (s, 3H, N $(CH_3)_2$), 6.74-7.54 (d, 2H, ArH), 7.3-7.6 (m, 5H, ArH), 7.21 (s, 1H, =CHAr).

IR (KBr) (cm^{-1}): 3030 cm^{-1} (C-H Str in Ar), 1600 cm^{-1} (C=H Str in Ar), 1550 cm^{-1} (C=N Str in Oxazolone), 1739 cm^{-1} (C=O Str in Oxazolone), 1417cm^{-1} (C-N Str).

BIOLOGICAL EVALUATION:

Anti Microbial Activity:

Experimental Work: The bacteria are grown in the sterile nutrient broth under submerged conditions a few hours prior to the experiment. About 0.1 ml of this culture medium is inoculated on the nutrient agar plate uniformly. Once set, wells are bored using a sterile cork borer. Solution containing 100 µg/ml both standard and test compounds were added to the wells using a micropipette. The plates are incubated at 25 degree Celsius for 15-16 hours. The zone of inhibition around the wells is checked and measured. The method of testing for fungicidal activity is the same as that of antibacterial testing and dextrose agar medium is used as fungal medium. The data was given in Table-2**.**

RESULTS AND DISCUSSION:

In the present work, substituted oxazolone derivatives were synthesized. Oxazolones are prepared by condensation of benzoylglycine with substituted benzaldehydes. All the synthesized compounds (S1-S4) were characterized by TLC, Melting point, and spectral analysis (IR & ^{1}HNMR). The Synthesized compounds were evaluated to their antibacterial activity and antifungal activity at 100 µg/ml concentrations by cup-plate method using ciprofloxacin & clotrimazole as standard drugs respectively. In the study of antibacterial activity S1 (p-Cl) & S3 (p-OH) showed maximum activity against *Escherichia coli* & *Bacillus cereus***.** S4 (p-Di methyl amino) also showed moderate activity against E.coli, P.aeruginosa, & bacillus cereus. But the S2 (3, 4 di OCH3) compound produce negative result. None of the compounds showed any anti fungal action towards the growth of the fungus *Aspergillus niger* whose growth covered the entire plate over a period of 5 days. To study the effect of the compounds the experiment was repeated but without any inhibitory action from the compounds. The results are summarized in Table No-2.

CONCLUSION:

From the results one can establish that the synthesized substituted Oxazolones compound can rich source of exploitation. Therefore, the synthesized compounds were shows antibacterial activity except OCH_3 derivative (S2). Finally the anti bacterial activity revealed that, the compounds bearing Electronic

nature of the substituent's of electron withdrawing groups (NO_2, Cl) and electron donating groups (OH, NH_2). None of the compounds showed any inhibitory action towards the growth of the fungus.

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REFERENCES:

1. Suman Bala, Minaxi Saini and Sunil Kamboj, Methods for synthesis of Oxazolones: A Review, Int. J. Chem.Tech. Res., 2011; 3(3): 1102-1118.
2. Janmajoy Banerjee, Niraj Sharma, Nomi Shrestha and Deepak Chaudhury, review on oxazolones its method of synthesis and biological activity, EJBPS, 2015; 2(3): 964-987.
3. Theivendren Panneer Selvam, Parthasarathi Ramu, & Arumugam Siva Kumar, Synthesis, Characterization and anthelmintic activity of novel 3-benzyl-2-(4'-substituted phenyl)-4(5*h*)-(4''-nitrophenyl amino)-1, 3-oxazolidines derivatives. JPRHC, 2011; 3(1): 9-14.
4. Vachala Dinakaran, Jessy E. Mathew1, Panneerselvam P, Sivagurunathan, Anti-microbial studies on novel 1,3-oxazolidine analogues**.** Pharmacologyonline, 2008; 2, 192-197.
5. V. Shankarananth, D. Ranganayakulu, C. Sridhar, K. K. Rajasekhar the synthesis and anti inflammatory activity of some oxazolidinedione derivatives, J. of Pharm. Res., 2012; 5(3): 1633-1635.
6. Vivek Gupta, A. Pandurangan Synthesis, characterization and antimicrobial activity of 4-oxo-oxazolidine derivatives, WJPPS, 2014; 3(11): 541-549.
7. Alessia Catalano, Alessia Carocci, Giovanni Lentini, Antonia Di Mola, Claudio Bruno, and Carlo Franchinifacile preparation of 3, 4-disubstituted 1, 3-oxazolidines and 1, 2, 5-trisubstituted imidazolidin-4-ones, J. Heterocyclic Chem.,2011; 48, 261-266.
8. Asif Husain Anthelmintic activity, Evaluation of 2-arylidene-4-(biphenyl-4-yl) but-3-en-4-olides, J. Biol. Engg. Res. & Rev., 2015; 2(2): 07-09.
9. Neha Pandit, Rajeev K. Singla, and Birendra Shrivastava1 synthesis and evaluation of oxazolidinones having benzothiazine moieties as antimicrobial and anti inflammatory agents, Int. J. of Med. Chem.,2011; (2012): 1-24.
10. Mohammad Al-Masum, Baillie W. Lott, Nazanin Ghazialsharif, an efficient reaction process for the synthesis of oxazinanes, and oxazolidines in the presence of air. IJOC, 2012; 2, 362-365.
11. Parastoo Karimi Alavijeh, Parisa Karimi Alavijeh and Devindra Sharma a Study of antimicrobial activity of few medicinal herbs, Asian J. Plant Sci. Res.,2012; 2(4): 496-502.
12. Tandel R.C. Synthesis and Study of Oxazolone Derivatives Showing Biological Activity, Res. J. Pharmaceutical Sci., 2012; 1(3): 1-5.
13. Laboratory methodologies for bacterial antimicrobial testing, OIE terrestrial manual-2012.

14. Table 1: Physical Characterization data of synthesized compound (S_1-S_4)

S. No	Compound code	R	Molecular formula	Mol. wt (g)	Melting point (^{0}C)	% Yield	Rf Value
1	S1	4-Cl	$C_{16}H_{16}O_2NCl$	289.5	164	62.20	0.19
2	S2	3,5-di OCH_3	$C_{18}H_{22}O_4N$	316	168	55.50	0.57
3	S3	4-OH	$C_{15}H_{17}O_3N$	259	169	66.80	0.55
4	S4	4-$N(CH_3)_2$	$C_{18}H_{22}O_2N_2$	298	166	40.08	0.87

Table 2: Anti microbial activity of Synthesized Compounds (S1-S4)

Sample Code	Zone of Inhibition in mm			
	E. coli	P. aeruginosa	B. ceures	A. niger
	100µg/ml	100 µg/ml	100µg/ml	100µg/ml
S1	**18**	11	**20**	-
S2	-	-	-	-
S3	**17**	10	**20**	-
S4	12	15	15	-
Ciprofloxacin	**20**	**19**	**20**	**-**
Clotrimazole				**20**
DMSO	**-**	**-**	**-**	**-**

Note. "-"Indicates Negative Results, 4-10 mm poor activity, 11-15 mm moderate activity, 16mm and above 16mm good activity.