ORIGINAL RESEARCH PAPER

Chemistry

SYNTHESIS, ANTI-INFLAMATORY AND ANTIBACTERIAL ACTIVITY OF AZLACTONE DERIVATIVES

KEY WORDS: Substituted-1,3-oxazol-4(5*H*)-ylidene; acetyl salicyloyl glycine, anti-inflammatory activity; antibacterial

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ABSTRACT

A novel series of 1-(1-{2-hydroxy-R-substituted-5-[(*E*)-(5-oxo-2- phenyl acetate -1,3-oxazol-4(5H)-ylidene) methyl] phenyl} (phenyl)methyl)-3-[(*E*)-(4-hydroxy-3-methoxyphenyl) methylidene]thiourea (2a–e) were synthesized by the reaction of 1-[(5-formyl-R-substituted phenyl)(phenyl) methyl]-3-[(*E*)-(4-hydroxy-3-methoxyphenyl) methylidene] thiourea/urea with acetyl salicyloyl glycine in presence of fused sodium acetate (1.0 g) and acetic anhydride. The structures of the newly synthesized compounds were established by IR, 1H-NMR, mass spectra and elemental studies. The antibacterial and anti-inflammatory activities of the synthesized compounds were determined. The compounds 3a, 3f, 3h and 3o showed moderate activity.

INTRODUCTION

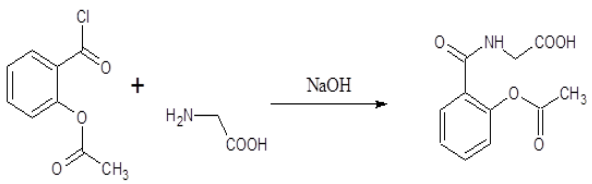
Azalactones have been used in a wide variety of reactions as precursors for biologically active molecules[1]. Synthesis of oxazolone involves the condensation of aromatic aldehydes and hippuric acid with a stoichiometric amount of fused sodium acetate in the presence of acetic anhydrides; as the dehydrating agent, this reaction is known as the Erlenmeyer Plöchl reaction[2]. Azlactones are five membered heterocyclic compounds containing nitrogen and oxygen as hetero atoms. The C-2 and C-4 positions of the oxazolone are crucial for their various biological activities.

In literature, numbers of methods are reported for the synthesis of azalactones by cyclization, condensation of o-hydroxy hippuric acid with various aromatic aldehydes in presence of acetic anhydride and sodium acetate in catalytic amounts[3].Studies have also been focused on the synthesis azlactone derivatives since they possess significant activities as antifungal[4], antibacterial[4], and anticancer activity[5]. In the present investigation, new 1-(1-{2-hydroxy-R-substituted-5-[(*E*)-(5-oxo-2- phenyl acetate -1,3-oxazol-4(5*H*)-ylidene) methyl] phenyl} (phenyl)methyl)-3-[(*E*)-(4-hydroxy-3-methoxyphenyl) methylidene]thiourea were prepared.

Experimental

All melting points were uncorrected. IR spectra were recorded in Shimadzu FTIR 8400 model in the frequency range of 4000-400 cm^{-1} using KBr pellet method. The H1-NMR spectra were determined on were recorded on Bruker Advance III 500 MHz spectrometer by making a solution of samples in CDCl3 solvent using tetramethylsilane (TMS) as the internal standard. EI-MS were measured on Waters QTOF Micro at panjab University. Elemental analysis was carried out at the PerkinElmer 2400 Series II CHNS/O Elemental Analyser (2400 Series II) TLC on silica gel plates (Merk 60,F254) was used to monitor the reaction and for testing the purity of the products. Melting points were recorded on a capillary melting point apparatus and are uncorrected.

Acetyl salicyloyl glycine is prepared by reaction of glycine, aqueous sodium hydroxide and acetyl salicyloyl chloride. It was then reacted with 1-[(R-formyl-R'-substitutedphenyl) (phenyl)methyl]-3-[(*E*)-(4-hydroxy-3-methoxyphenyl)methylidene] thiourea/urea in presence of acetic anhydride and acetic acid to obtain corresponding azlactone derivatives.



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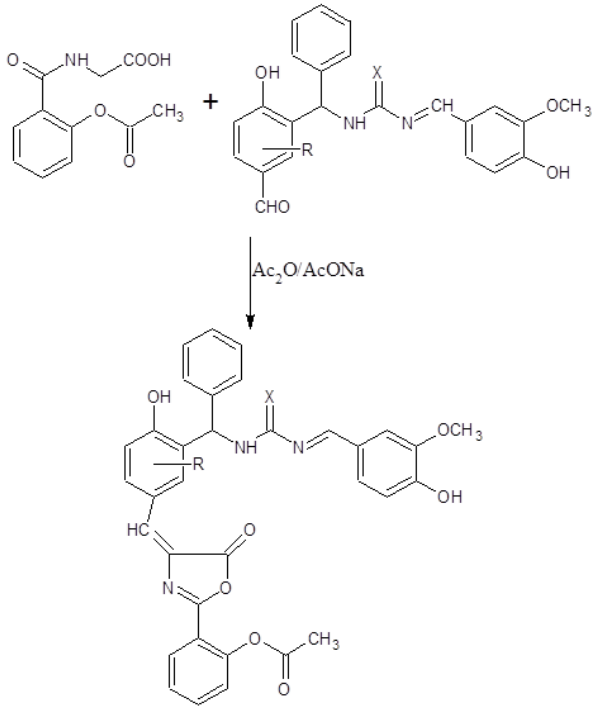

(2)

Compound	R	X	Molecular Formula	M.P. (°C)	Yield (%)
2(a)	H	S	$C_{34}H_{27}N_3O_7S$	130	15.01
2(b)	3-chloro	S	$C_{34}H_{26}ClN_3O_7S$	142	26.61
2(c)	3-methyl	S	$C_{35}H_{29}N_3O_7S$	147	21.5
2(d)	4-methyl	O	$C_{35}H_{29}N_3O_8$	164	21.1
2(e)	4-hydroxy	O	$C_{34}H_{27}N_3O_9$	145	23.6

The IR spectrum of compound 2b showed an absorption band at 1741cm–1 due to the carbonyl group, 1176 cm-1 is due to C-O Lactones. In the 1H-NMR spectrum of compound 3b, the three N-acetyl protons resonated at δ 2.49 ppm as a singlet. The methoxy protons appeared as a singlet at δ 3.66 ppm. The OH and NH protons appeared as a doublet at δ 4.2 and 4.106 ppm in the 1H-NMR spectrum of compound 2b. The mass spectrum of this compound showed the molecular ion peak (M+1) at m/z 656 consistent with its molecular formula $C_{34}H_{26}ClN_3O_7S$.

Anti-inflammatory activity

The anti-inflammatory activity was determined by carrageenan-

induced rat paw oedema method in albino rats (n=6) of either sex (200-340 g). Rats were selected by random sampling technique. Diclofenac (100mg/kg) was administered as a reference drug. The test compounds were administered at dose level of 350 mg/kg orally 30 min. prior to the administration of carrageenan in the right hind paw of the rats. The paw thickness was measured using vernier callipers at 60, 120, 180 and 240 min. after carrageenan administration. The results are presented in Table-2.

TABLE 2: Anti-inflammatory activity (carrageenan induced rat paw oedema method) of compounds.

Compd.	Dose mg/kg	30 min	60 min	120 min	240 min	300 min
Control	-	6.06 ± 0.3	6.06 ± 03	6.05 ±0.1	4.54 ±0.8	3.03 ±0.02
2a	350	7.57±0.2	7.58 ±0.1	6.06 ±0.12	4.54 ±0.6	4.51 ±0.9◦
2b	350	8.33±0.06	6.66 ±0.1	5.0 ±0.05◦	5.01 ±0.01◦	3.33 ±0.05
2e	350	6.66±0.01	6.6 ±0.02	5.03 ±0.01	5.01±0. 12	4.66 ±0.06◦
Diclofenac	100	9.16±0.06	9.66 ±0.05	10.9 ±0.02	10.95 ±0.04	10.99 ±0.2

Results are expressed in mean ± SEM. (n=6) significance levels * P<0.05, ** P < 0.01 and *** P < 0.001 as compared with the respective control.

Antibacterial activity

In vitro antibacterial study was carried by agar diffusion method. All the compounds were screened for antibacterial activity at 100 µg/ml concentration against the following bacterial strains: Staphylococcus aureus, Klebsilla pneumonia. Ciprofloxacin was used as a standards for comparison of antibacterial under the similar conditions. The results are presented in Table-3.

S.No.	Compound Code	Conc. mg/ml		
		100	50	25
1.	2a	+	_	_
2.	2b	_	+	_
3.	2e	+	-	+

+ sign shows growth and – sign shows inhibition.

STATISTICAL ANALYSIS

Data were analysed by one –way ANOVA followed by Dunnett's t-test using computerized Graph Pad Instat version 3.05 (Graph Pad software, U.S.A.).

CONCLUSIONS

A novel series of azlactone derivatives containing a 5-oxo-2-phenyl acetate -1,3-oxazol-4(5H)-ylidene moiety were reported. The results of the antibacterial and anti-inflammatory screening revealed that among all the synthesized compounds, 2a, 2b and 2e showed moderate anti-inflammatory activity.

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