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Synthesis of 5-(substitutedphenyl)-{3-[4-(2-methyl-4-(4-hydroxy benzylidene)-5-oxo-imidazol-1-yl)]phenyl} -isoxazol and study of the antimicrobial activities

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ABSTRACT

5-(substitutedphenyl)-{3-[4-(2-methyl-4-(4-hydroxy benzylidene)-5-oxo-imidazol-1-yl)]phenyl}-isoxazol have been prepared by the refluxation for ten hours of 4-(4-hydroxybenzylidene)-1-{4-[3-(stituted phenyl)prop-2-enoyl]phenyl}-2-methyl-imidazol-5-one with hydroxylamine hydrochloride and 40% potassium hydroxide in presence of dioxane. The intermidiate 4-(4-hydroxybenzylidene)-1-{4-[3-(stituted phenyl)prop-2-enoyl]phenyl}-2-methyl-imidazol-5-one synthesized by the condensation of 1-(4-acetylphenyl)-4-(4-hydroxybenzylidene)-2-methyl-3,5-dihydro-imidazol-5-one with various aldehydes.

Key word : Synthesis, substitutedChalcones, substituted isoxazolines.

INTRODUCTION

Chalcones and isoxazolines have been reported to possess various biological activities such as antifungal,[1-2]antiviral,[3] anticancer[4] and anti HIV[5] agents.They have also been reported as good chelating agents.[6]

From the literature, we found that several isoxazolines are known to display antimicrobial and therapeutic activies. Literature survey reveals scant mention of the above compounds with antimicrobial properties and hence more and more derivatives are worth tested for the possible medicinal applications. So we have decieded to synthesis 5-(substitutedphenyl)-{3-[4-(2-methyl-4-(4-hydroxy benzylidene)-5-oxo-imidazol-1-yl)]phenyl}-isoxazol

Synthesis of isoxazolines have been reported by the action of hydroxylamine hydrochloride on chalcones. Borkhade et al.[7]

Formation of isoxazolines involves 1,2 addition of NH_2OH to carbonyl group giving an adduct. The adduct then loses water molecules to give monoxime which on cyclization and rearrangement gives isoxazoline. The steps of methanism were suggested by Bernes and Spriggs[8].

EXPERIMENTAL

Melting points were taken in open capillary tube and were uncorrected. IR spectra (KBr) were recorded on I.R. Spectrophotmeter of Buck scientific Model No. 500 and instrument used for NMR Spectroscopy was DUL 13C-1, 300 MHz and tetramethyl silane used as internal standard. Solvent used were $CDCl_3$ and DMSO. Purity of the compounds were checked by tlc on silica- G plates. Anti microbial activities were tested by Cup-Borer method.

Preparation of 4-(4-hydroxybenzylidene)-2-methyl- 1,3-oxazol-5-one.(P-1).

In a 500 ml conical flask equipped with a reflux condenser a mixture of 4-hydroxybenzaldehyde (45.184g, 0.37M), acetyl glycine (29g 0.25 M), acetic anhydride (63.5g, 0.62M) and anhydrous sodium acetate(15g 0.183 M) was placed and heated on an electric hot plate with constant shaking. As soon as the mixture has liquefied completely, transfer the flask to a water bath and heat for 2 hours. Then add 100 ml of ethanol slowly to the contents of the flask, allow the mixture to stand overnight, filter the crystalline product with solution, wash with 25 ml of ice-cold alcohol and then finaly wash with 25 ml of boiling water, dry at 100 °C. The yield of almost pure oxazolone was 70 % , m.p.187^{0}C.

Molecular Formula = $C_{11}H_9NO_3$
Formula Weight = 203.19406
Composition requried = C(65.02%) H(4.46%) N(6.89%)
Composition found = C(65.01%) H(4.43%) N(6.88%)

Preparation of 1-(4-acetylphenyl)-4-(4-hydroxybenzylidene)-2-methyl-imidazol-5-one (P-2).

In a 250 ml conical flask equipped with a reflux condenser a mixture of 4-(4-hydroxybenzylidene)-2-methyl-1,3-oxazol-5-one(20.319g, 0.1M), 1-(4-aminophenyl)ethanone (13.51g, 0.1M), 25 ml pyridine and about one pellet of KOH was placed and was heated on sand bath for 7-8 hours. The mixture was then poured in ice. The precipitates were collected, washed with 10% HCl and re-crystallized from ethanol. The yield of the product was 73 % and the product melts at 124^{0}C.

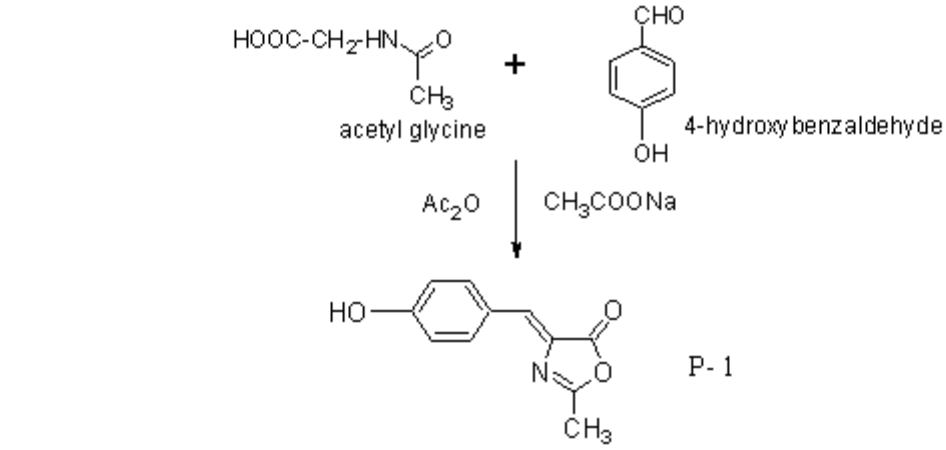
Molecular Formula = $C_{19}H_{16}N_2O_3$
Formula Weight = 320.34194
Composition requried = C(71.24%) H(5.03%) N(8.74%)
Composition found = C(71.22%) H(5.01%) N(8.72%)

Preparation of 4-(4-hydroxybenzylidene)-1-{4-[3-(4-chlorophenyl)prop-2-enoyl]phenyl}-2-methyl-imidazol-5-one (P-3a)

To the solution of 1-(4-acetylphenyl)-4-(4-

Table 1: Physical constant of 5-(substitutedphenyl)-{3-[4-(2-methyl-4-(4-hydroxybenzylidene)-5-oxo-imidazol-1-yl)]phenyl}-isoxazol

No	Sub No	R	Molecular (g/m)	Mol Wt. (%)	Yield (%)	M.P. °C	Carbon (%)		Hydrogen (%)		Nitrogen (%)	
							Found	required	Found	required	Found	required
1	P-4a	-4-Cl	$C_{26}H_{18}ClN_3O_3$	455.8924	60	210	68.48	68.50	3.95	3.98	9.21	9.22
1	P-4b	-2-Cl	$C_{26}H_{18}ClN_3O_3$	455.8924	62	218	68.47	68.50	3.92	3.98	9.20	9.22
3	P-4c	-3-OCH_3-4-OCH_3	$C_{28}H_{23}N_3O_5$	481.49932	63	221	69.81	69.84	4.80	4.81	8.71	8.73
4	P-4d	-H	$C_{26}H_{29}N_3O_3$	421.44736	66	225	74.08	74.10	4.52	4.54	9.94	9.97
5	P-4e	-2-OH	$C_{26}H_{19}N_3O_4$	437.44676	65	292	71.37	71.39	4.37	4.38	9.60	9.61
6	P-4f	-3-OCH_3-4-OH	$C_{27}H_{21}N_3O_5$	467.47274	67	290	69.35	69.37	4.51	4.53	8.97	8.99
7	P-4g	-4-OH	$C_{26}H_{19}N_3O_4$	437.44676	61	>300	71.36	71.39	4.36	4.38	9.59	9.61
8	P-4h	-4-$N(CH_3)$	$C_{28}H_{24}N_4O_3$	464.51516	57	262	72.37	72.70	5.19	5.21	12.03	12.06
9	P-4i	-4-OCH_3	$C_{27}H_{21}N_3O_4$	451.74334	59	206	71.80	71.83	4.67	4.69	9.29	9.31
10.	P-4j	-3-NO_2	$C_{26}H_{18}N_4O_5$	466.44492	58	180	66.91	66.95	3.89	3.89	12.00	12.01



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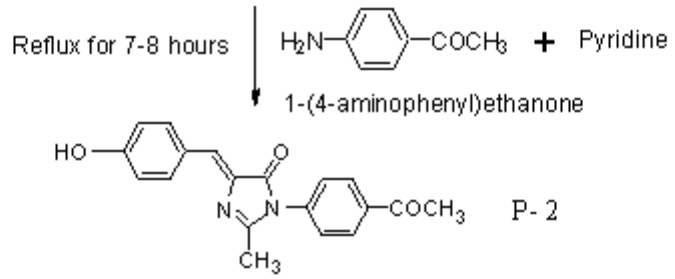

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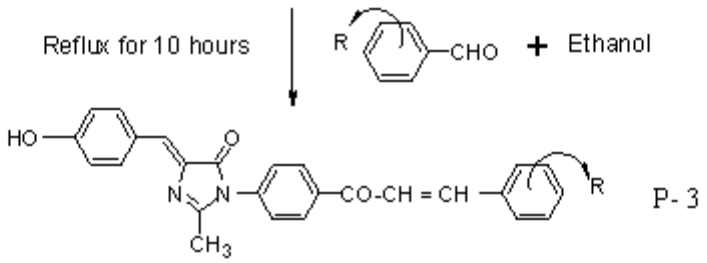

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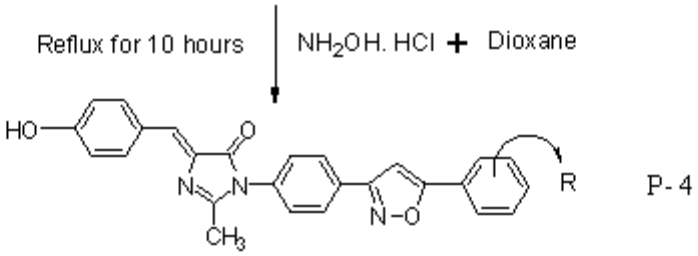
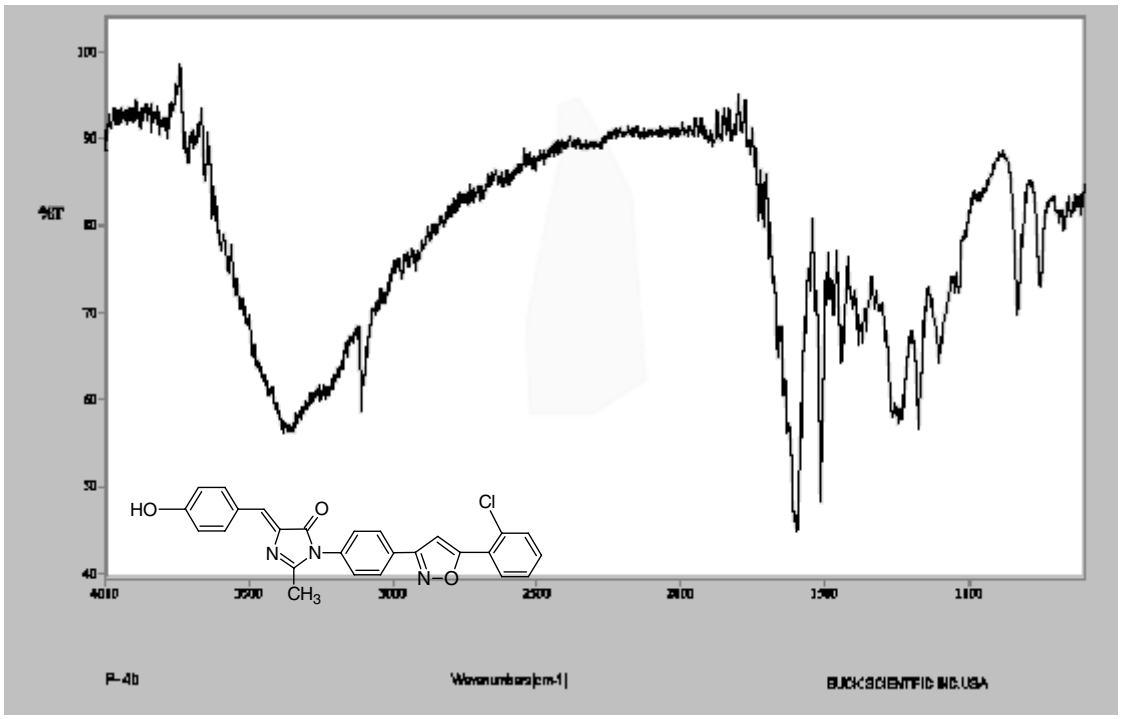


5-(substitutedphenyl)-{3-[4-(2-methyl-4-(4-hydroxybenzylidene)-5-oxo-imidazol-1-yl)]phenyl}-isoxazol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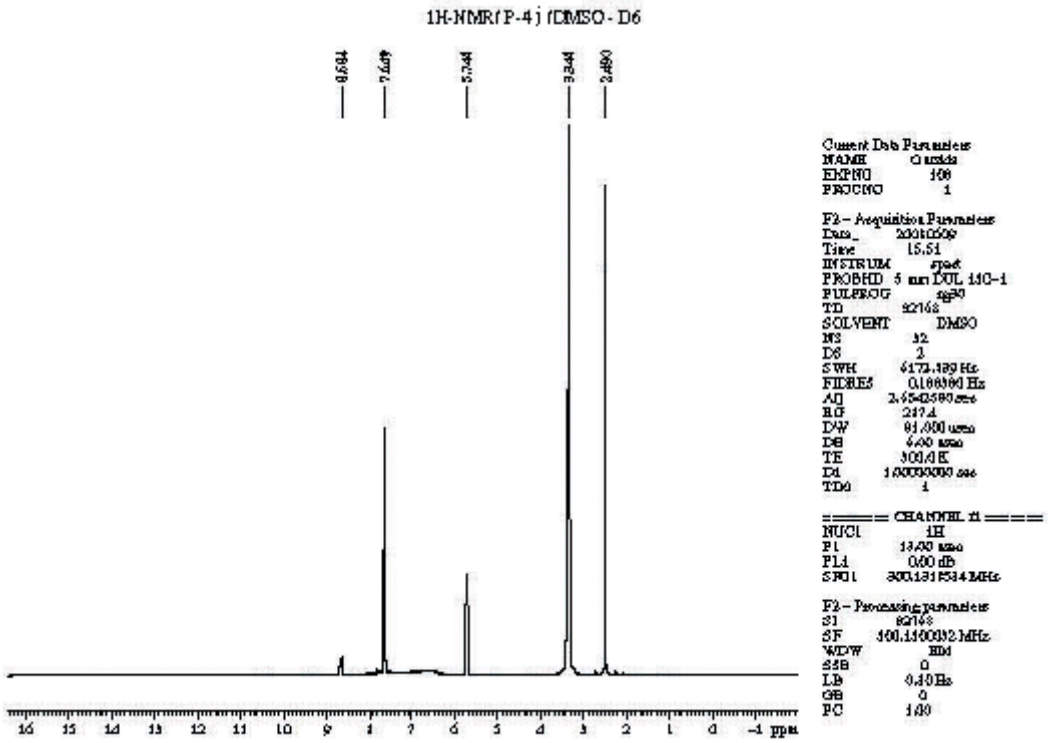
Wavenumbers[cm-1]
BUCK SCIENTIFIC INC. USA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DE 6.00 usec
TE 300.0 K
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P1 13.00 usec
PL1 0.00 dB
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WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm

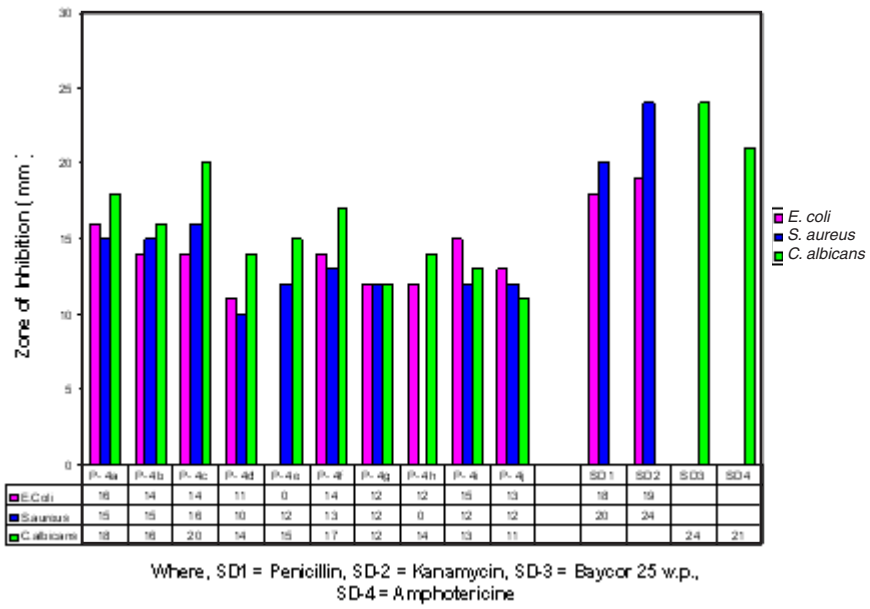
Table 2: Antimicrobial activities of 5-(substitutedphenyl)-{3-[4-(2-methyl-4-(4-hydroxy benzylidene)-5-oxo-imidazol-1-yl)]phenyl}-isoxazol

Sr. No.	Comp. No.	R	Zone of inhibitions in mm		
			E.coli	*S.aureus*	*C.albicans*
1	P-4a	- 4-Cl	16	15	18
2	P-4b	- 2-Cl	14	15	16
3	P-4c	- 3-OCH_3, -4-OCH_3	14	16	20
4	P-4d	- 2-NO_2	11	10	14
5	P-4e	- 2-OH	NA	12	15
6	P-4f	- 3-OCH_3, -4-OH	14	13	17
7	P-4g	- 4-OH	12	12	12
8	P-4h	- 4-$N(CH_3)_2$	12	NA	14
9	P-4i	- 4-OCH_3	15	12	13
10	P-4j	- 3-OCH_3,-4-OCH_3,-5-OCH_3	13	12	11
11	Penicillin	-	18	20	-
12	Kanamycine	-	19	24	-
13	Baycor 25 w.p.	-	-	-	24
14	Amphotericine	-	-	-	21

Graphical representation of antimicrobial activities of 5-(substitutedphenyl)-{3-[4-(2-methyl-4-(4-hydroxybenzylidene)-5-oxo-imidazol-1-yl)]phenyl}-isoxazol

hydroxybenzylidene)-2-methyl-imidazol-5-one (3.203g, 0.01M) in absolute ethanol (50 ml),4-chlorobenzaldehyde (1.40g, 0.01M) and 2 % NaOH (10 ml) were added and reflixed for 10 hours. After refluxing the reaction mixture was concentrated , cooled, filtered and neutralized with dil. HCl. The solid residue thus obtained was recrystallized with suitable solvent.The yield of the product was 62 % and the product melts at 160^{0}C.

Molecular Formula = $C_{26}H_{19}ClN_2O_3$
Formula Weight = 442.89366



Where, SD1 = Penicillin, SD-2 = Kanamycin, SD-3 = Baycor 25 w.p., SD-4 = Amphotericine

Composition requried = C(70.51%) H(4.32%) N(6.33%)
Composition found = C(70.50%) H(4.31%) N(6.31%)

Preparation of 5-(4-chlorophenyl)-{3-[4-(2-methyl-4-(4-hydroxy benzylidene)-5-oxo-imidazol-1-yl)]phenyl}-isoxazol (P-4a)

A mixture of 4-(4-hydroxybenzylidene)-1-{4-[3-(4-chloro phenyl)prop-2-enoyl]phenyl}-2-methyl-imidazol-5-one (4.428g, 0.01M)in 25ml dioxane, hydroxylamine hydrochloride (0.715g, 0.01M) and 40% potassium hydroxide(KOH) was refluxed for 10 hours. Then the reaction mixture was cooled, poured into crushed ice(100g) and neutralized with HCl. The product separated out was filtered, washed with water, dried and recrystallised from alcohol. The yield of the product was 60 % and the product melts at 210^{0}C.

Molecular Formula = $C_{26}H_{18}ClN_3O_3$
Formula Weight = 455.89242
Composition requried = C(68.50%) H(3.98%) N(9.22%)
Composition found = C(68.48%) H(3.95%) N(9.21%) **IR (KBr) :** 3345 cm^{-1}(-OH), 3095cm^{-1}(=CH-), 2920 cm^{-1}(-CH Stretch), P-4b 1720 cm^{-1}(>C=O imidazolone),1605 cm^{-1}(>C=N-), 1505 cm^{-1}(>C = C<), 1370 cm^{-1}(-CH_3bend), 1250 cm^{-1}(C-O),1150 cm^{-1}(C-N), 785 cm^{-1}(C-Cl). **NMR:** δ 2.490 , singlate (3H)(-CH_3)δ 5.746 , singlate (1H) (=CH-vinylic) P-4j δ 7.649 , complex (13H) (Ar-H)δ 8.664 , singlate (1H)(-OH)

The short review of the antibacterial and anti fungal studies being conducted on some comounds of this series is as follows.

Against *Escherichia coli*

The maximum activity was shown by the compounds P-4a, and P-4i, the zone of inhibition are 16mm, and 15mm respectively, and the minimum activity was shown by the compounds P-4d the zone of inhibition is 11mm.

Against *S. aureus*

The maximum activity was shown by the compounds P-4c, P-4a and P-4b, the zone of inhibition are 16mm, 15mm, and 15mm and the minimum activity was shown by the compound P-4d the zone of inhibition is 10mm.

Against *Candida albicans*

The maximum activity was shown by the compounds P-4c and P-4a, the zone of inhibition are 20mm and 18mm and the minimum activity was shown by the compounds P-4j the zone of inhibition is 11mm.

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