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SYNTHESIS AND ACTIVITY OF A NEW SERIES OF PRENYLOXY CHALCONES AS ANTIBACTERIAL AGENTS

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ABSTRACT

A new series of 4'-prenyloxy 2'-hydroxychalcons has been synthesized. They have been characterized by physical and spectral data (IR, 1H, NMR, and MS). All these chalcones have been tested for antibacterial activity. Their ability to inhibit different pathogens is assessed. Except few, all the chalcones displayed antibacterial activity to a remarkable extent.

Key Words: 4'-prenyloxy 2'-hydroxy acetophenone, 4'-prenyloxy 2'-hydroxychalcons, anti bacterial activity, percentage of inhibition.

INTRODUTION

There is growing interest in the pharmacological potential of natural products is chalcones constitute an important group of natural products. In recent years a variety of chalcones have been reviewed by *Dimmock et al*., for their cytotoxic, anticancer chemoprevenive and mutagenic as well as antiviral, insecticidal and enzyme inhibitory properties[1]. A number of chalcones having hydroxy, methoxy groups in different position have been reported to possess anti-bacterial[2], antiulcer[3] antifungal[4], anticoagulating[5], vasodilatory[6], antipepticulcer[7], antimitotic[8], anticonvulsant, narcosis potentiation[9] and antileshmanial [10] activites.The interests in 2-hydroxy chalcones as antibiotics [11] has stimulated effects to synthesis and isolated chalcones starting from 2'-hydroxy arylketones. Several workers[12, 13]. Alkyl group present in 2'-hydroxy acetophenone enhances its activities due to its electron releasing nature and facilitates the formation of chalcones [14].

EXPERIMENTAL

Melting points were determined in open capillary tubs and were not corrected. IR spectra (KBr, λ max in cm^{-1}) were recorded on a Bruker IFS 66V spectrometer, ^1H NMR spectra in $CDCl_3$ (chemical shifts in δ, Ppm) on a Gemini-400 MH_z spectrometer using TMS as an internal standard; and mass spectra on a VG 7070H mass spectrometer. The purity of the compounds was verified by TLC (benzene/ethyl acetate, 9:1), using silica gel plates.

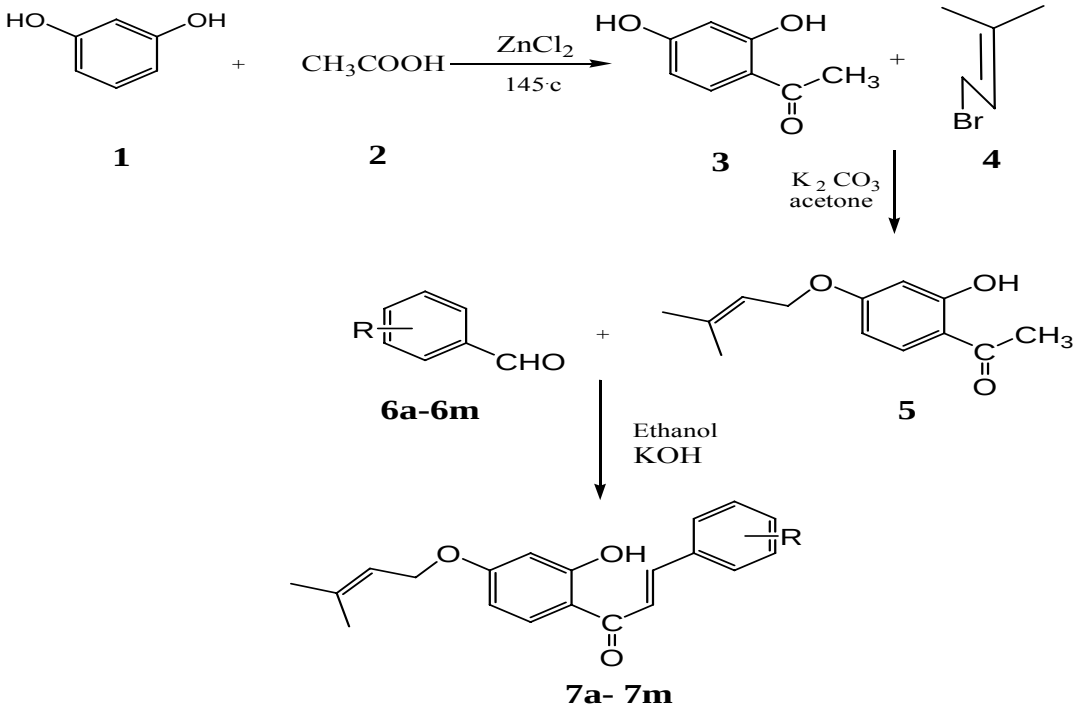
4'-prenyloxy, 2'-hydroxyacetophenone (5); A solution of β-resacetophenone (0.5g) in acetone (10ml) was refluxed with prenyl bromide (0.4ml) and anhydrous potassium carbonate (2gms) for 3hrs. The product crystallized from light petroleum ether at low temperature as colourless thick needles (0.5gms), m.p. 45 -47°c, red ferric reaction; R_f 0.30 (solvent benzene – light petroleum 1:1); V_{max} 1640cm^{-1}.

4'-prenyloxy, 2'-hydroxychalcones (7a-7m); 4'-prenyloxy, 2'-hydroxyacetophenone **(5)** (0.02mole) and aromatic or hetero aldehyde **(6a-6m)** (0.02 mole) were dissolved in EtOH (15mL), under stirring, and aqueous KOH (50%, 12mL) was added drop wise. The reaction mixture was stirred at room temperature and kept over night. After 24hr, the reaction mixture was diluted with H_2O and acidified with HCl (10%).

The separated solid was filtered and recrystallised from glacial AcOH. The physical and chemical data of **(7a-7m)** are given in **(Table-1).**

Antibacterial activity

All the prenyloxy chalcones were screened for their antibacterial activity against *Escherichia coli* and *staphylococcus aureus* using *streptomycin* as standard drug. Nutrient Agar was used as culture medium. Test solution and standard drug having 400and 600 µg / ml concentration were prepared in acetone and used for testing growth inhibition by filter paper disc technique of Vincent and Vincent.



Scheme-1

Where-

Compd	R	Compd	R
7a	p-OCH_3	7h	O-Cl
7b	P-CH_3	7i	m-NO_2
7c	P-Cl	7j	Furan
7d	P-$N(CH_3)_2$	7k	Thiophene
7e	p-OH	7l	Pyridine
7f	P-NO_2	7m	3,4-di methoxy
7g	P-H		

RESULTS AND DISSCUSION

The biological and pharmacological activities of chalcones have been found to increase with number of hydroxyl or methoxy substitution in both the rings A and B[15].Synthesized chalcones and related compounds using nuclear prenylation with prenyl bromide substituted 2', 4'-dihydroxy acetophenone (β-resacetophenone)

A new series of 2'- hydroxyl chalcone derivatives has been synthesized and reported as aldose reductase inhibitors [(16)]. i.e. as antidiabetic agents. Different 2'-hydroxy chalcones have been synthesized and evaluated pharmacologically as inhibitors of inflammatory mediator's generation.

Such wide utility of hydroxyl chalcones has prompted us to undertake the present investigation in this study. We have tried to assess the effect of substituent prenyl bromide in the aromatic ring (2, 4 - di hydroxy acetophenonering) of chalcones on the bactericidal activities.

4'-prenyloxy-2'-hydroxy chalcones (**7a-7m**) were prepared from the corresponding 4'-prenyloxy-2'-hydroxy acetophenone (**5**) and different aromatic or hetero aldehydes (**6a-6m**) in alkaline medium. (**Scheme-1**) the chalcones were crystallized as dark brown. Yellowish to orange crystals. They developed characteristic colors on TLC plates.

Further the structures of chalcones prepared were confirmed by spectral by studies (IR, MS and NMR); The chalcones carbonyl absorbed around 1640cm^{-1} in their IR spectra. Their ^{1}H NMR Spectra exhibited singlets due to gemdimethyl of prenyl group (1.75) and aromatic *P*-methoxy protons (3.95) and doublets around (7.4 and 8.0) due to olefinic α, β-proton respectively. However, these doublets are coalesced with aromatic protons. Phenolic proton (2'-OH) appeared as a singlet at δ 13.79 and aromatic protons around 7.0 δ **(Table-3)**. The mass spectra for the chalcones exhibited intense molecular ion peaks followed by cleavage on either side of the carbonyl group. It is found to be in agreement with the literature.

The results of the compounds of preliminary antibacterial testing are shown in **Table 2.** The results revealed that majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the inhibitory activity against the Gram-negative bacteria was higher than that of the Gram-positive bacteria. The 7j showed excellent activity against Gram-negative bacteria, *E. coli* (percentage of inhibition 65.2) and 7m showing good activity against Gram-positive bacteria *S. aureus* (percentage of inhibition 58.6). On the other hand, compounds 7e (percentage of inhibition 44.0) and 7b (percentage of inhibition 43.8) showed weak activities against *E. coli* and *S. aureus* respectively.

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Table-1: physical and chemical data of chalcones

Compd	M.p°C	Yield (%)	Mol.formula	%Found (Caled)			IR cm^{-1}			
				C	H	O	**(OH)**	**(C=O)**	**(C=C)**	**MS.m/z**
7a	87	73	$C_{21}H_{22}O_4$	74.54 (74.63)	6.55 (6.16)	18.91 (18.78)	3500	1650	1350	322
7b	91	74	$C_{21}H_{22}O_3$	78.23 (77.86)	6.88 (6.33)	14.89 (14.12)	3530	1650,	1350	338
7c	185	60	$C_{20}H_{19}ClO_3$	70.07 (69.37)	5.59 (5.24)	14.00 (14.00)	----	----	----	--
7d	95	52	$C_{22}H_{25}O_5N$	75.19 (75.00)	7.17 (7.03)	13.66 (13.54)	----	----	----	--
7e	80	58	$C_{20}H_{20}O_4$	74.06 (73.67)	6.21 (6.01)	19.73 (19.27)	---	----	----	--
7f	161	62	$C_{20}H_{19}NO_5$	67.98 (67.24)	5.42 (5.13)	22.64 (22.04)				
7g	67	56	$C_{20}H_{20}O_3$	77.90 (77.45)	6.54 (6.50)	15.57 (14.87)	----	----	----	--
7h	89	72	$C_{20}H_{19}ClO_3$	70.07 (68.54)	5.59 (5.51)	14.00 (13.87)	----	----	---	--

7i	103	66	$C_{20}H_{19}O_5N$	67.98 (67,87)	5.42 (5.12)	22.64 (22.64)	3540	1650	- 1350	314
7j	78	71	$C_{18}H_{18}O_4$	72.47 (72.24)	6.08 (5.98)	21.45 (21.29)	----	----	----	--
7k	92	70	$C_{18}H_{18}SO_3$	68.76 (68.07)	5.77 (5.67)	15.27 (15.01)	3560	1650,	1360	298
7l	75	67	$C_{19}H_{19}NO_3$	73.77 (73.45)	6.19 (6.05)	15.52 (15.32)	---	---	---	---
7m	97	64	$C_{22}H_{24}O_5$	74.83 (73.86)	5.68 (5.06)	18.46 (17.64)	---	---	---	---
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Table-2: antibacterial activity of the synthesized chalcones (**7a-7m)**

Compd	Antibacterial activity (%Inhibition)		Compd	Antibacterial activity (%Inhibition)	
	E.coli(-)	*S.aureus*(+)		*E.coli*(-)	*S.aureus*(+)
7a	64.7	54.5	7h	47.0	55.6
7b	55.5	43.8	7i	63.9	50.7
7c	53.8	46.5	7j	65.2	49.8
7d	48.5	54.3	7k	60.2	52.4
7e	44.0	55.0	7l	51.9	49.6
7f	54.5	54.0	7m	61.9	58.6
7g	62.5	54.6	*streptomycin*	100.0	100.0

Table-3:1H NMR Spectra of selected chalcones in (δ.ppm)

7a **1.72**(S, 6H) 4.51(d, 2H) 5.46(t, 1H) 3.90(S, 3H, OCH3) 6, 26(S, 1H Ar H-3) 6.35(d,1H ArH-5) 7.01(d, Ar1H, H-6), 8.12(d, 1Hβ), 7.92(d, 1Hδ), 7.00(d, HX2Ar') 7.2(d, 1HAr'), 13.6(s, 1H -OH)

7b 1.72(S,6H) 4.62(d,2H) 5.25(t,1H), 2.21(S,3H,CH3) 6,50(S,1H Ar H-3) 6.61(d,1H ArH-5) 8.00(d, Ar1H, H-6) 8.25(d, 1HB), 7.90(d, 1H), 7.80(d, HX2Ar'), 7.25(d, 1HAr'), 13.49(s, 1H -OH)

7j 1.72(S, 6H) 4.51(d, 2H) 5.46(t, 1H), 6.38(S, 1H Ar H-3) 6.48(d, 1H ArH-5) 7.01(d, Ar1H, H-6), 7.60(d, 1Hα), 7.78(d, 1Hβ), 6.7(d, 1H, furan), 6.50(t, 1H, furan) 7.40(d, 1H, furan), 13.4(s, 1H -OH)

7h 1.72(s, 6H, =C $(CH_3)_2$) 4.52(d, 2H, -CH_2-CH=) 5.45(t, 1H) 6.2(S, 1H, ArH-3), 6.35(d, 1H, ArH-5) 6.71(d,1HArH-6),6.50(t,1H,thiophene),6.52(d,1H,thio),6.58(d,1H,thio), 7.90(d, 1Hά), 7.60(d, 1Hβ), 13.4(S, 1H, Chelated-OH).

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