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Synthesis and Biological Evaluation of Chalcones as Potential Anti Fungal Agents

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Abstract:*Aseriesofchalconesweresynthesizedandelucidatedstructurallybyand*^{1}*HNMRspectroscopies.The syntheticcompounds were then screened for antifungal activity using cup plate method against three fungal strains Aspergillus niger, Candida albicans, and Micro sporumgypseum. Among them M. gypseumwas found to be more sensitive to the two chalcones 2'- Hydroxy-4-chlorochalcone and 2'-Hydroxy-4-nitrochalcone were more effective than the clinical candidate ketoconazol fromamongthesevencompoundsscreenedandthusmaybeapotentialcandidatetotreatdermatomycoses.*

Keywords: *chalcone; Claisen-Schmidt condensation reaction, antifungal, dermatomycoses,*

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I. Introduction

Chalconesordiaryl-2-propen1ones,aresecondarymetabolitecompoundswhichareconsideredastheprecursors of various flavonoids and is flavonoids as well as many biologically important heterocycles such as diketones and pyrazolines.Theyarearomaticcompoundswithanunsaturatedsidechainandaresaidtobeoftencytotoxicinvitro [1]. They also possess many biological properties, [2] including anti-inflammatory [3, 4], antimicrobial [3, 4],antifungal [3,4] l,antioxidant [3,4],andantitumoractivities [3,4].Theantimicrobialpropertyofchalconesisdueto thepresenceofareactiveunsaturatedketogroupinthemolecule [5]whileantifungalpropertiesarepresentinsome phenolicsyntheticchalcones [6,7].Theirinterestingpharmacologicalactivitiespromptedustodesignanovelseries of chalcones and attempts were made to get chalcones with remarkable antifungal activity. In the present work chalcones were synthesized byClaisen Schmidt condensation reaction of acetophenone and benzaldehyde derivatives [8] and then were evaluated for their antifungal activity against three fungal species: Aspergillus niger, Candida albicans, andMicrosporumgypseum.

II. Experimental

Measurement-

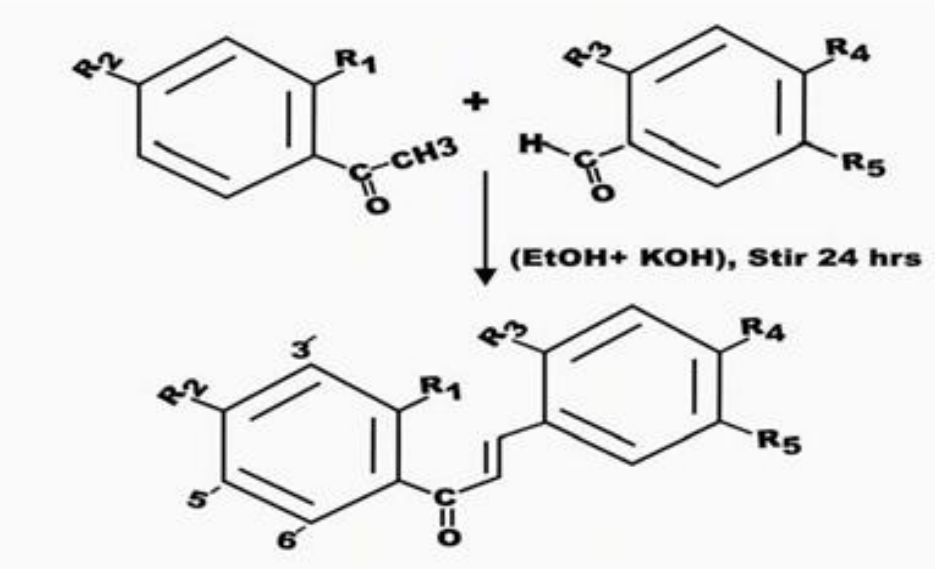
All the chemicals used for the synthesis of the compounds were of analytical grade and were purchased from reliable firms and institutes (Merck, SD Fine chemicals, Sigma etc.). Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on1650 FT-IR spectrometer (Perkin Elmer) using KBr discmethod.The1H(400MHz)NMRexperimentswererecordedonaBrukerAdvancespectrometerwithCDCl3a s the solvent. The compounds were analyzed for elemental analysis. Physical data of the synthesized chalcones are recordedinTable-1,reactionpathwayinscheme1andantifungalactivitiesintable2andfigure

2.2 Synthesis

2.2.1 General Procedure for the Preparation of Chalcones:

Equimolar quantities (0.01mol) of acetophenone and respective aldehydes were mixed and dissolved in minimum amount (3 ml) of alcohol. To this, aqueous potassium hydroxide solution (0.03 mol) was added slowly and mixed occasionally for 24 h, at room temperature. After that the reaction mixture was poured into crushed ice and neutralized with dilHCl (10%). The precipitate was washed with EtOH and purified by recrystallization and chromatographic technique [8]. Reaction pathway is represented in scheme-1

Scheme-1



Chalcone 1 R_1 □*OH,* R_2 □R_4 □*H,* R_3 □R_5 □*Cl*

,, 2 R_1 □R_4 □*H,* R_2 □*OH* R_3 □R_5 □*Cl*

,, 3 $R_1=R_3=R_5=H,$ $R_2=OH$ $R_4=Cl$

,, 4 $R_1=R_3=R_5=H,$ $R_2=OH$ $R_4=NO_2$

,, 5 $R_1=R_3=R_5=H,$ $R_2=OH$ $R_4=N(CH_3)_2$

,, ,, 6 7 $R_1=R_3=R_5=H,$ $R_2=OH$ $R_4=OCH_3$

R_4 □*H,*
R_1 *Oprenyl*□R_2
□*OH,*R_3 □R_5□*Cl*

2.3 Characterization of the SynthesizedCompounds

2.3.1 4′-Hydroxy-2, 6-dichlorochalcone (1)[10]

IR (v cm-1): 3345 (–OH), 1660 (C=O), 1615 (C=C alkene), 1597 and 1568 (C=C aromatic), 1230 (C-O) and 775 (C–Cl);
1H NMR (400 MHz, CDCl3): δ 6.98 (2H, d, J=8.2 Hz, H–3′ and H–5′), 7.25 (1H, t, J=8.0 Hz, H–4), 7.44 (2H,d,
J=8.0Hz,H–3andH–5),7.68(1H,d,J=16.0Hz,H–α),7.86(1H,d,J=16.0Hz,H–β),8.04(2H,d,J=8.4Hz,H–2′ and H–6′).

2.3.2 2′-Hydroxy-2,6-dichlorochalcone (2)[11]

IR (v cm-1): 3440 (–OH), 1690 (C=O), 1660 (C=C alkene), 1590 and 1440 (C=C aromatic), 1310 (C–O) and 772 (C–Cl);
1HNMR(400MHz,CDCl3):δ6.98(1H,ddd,J=2.0,8.0and8.0Hz,H–5′),7.06(1H,dd,J=2.0and8.0Hz,H–3′), 7.28(1H,dd,J=8.0and8.0Hz,H–4),7.45(2H,d,J=8.0Hz,H–3andH–5),7.56(1H,ddd,J=2.0,8.0and8.0Hz, H–4′),7.91(1H,dd,J=2.0and8.0Hz,H–6′),7.90(1H,d,J=16.0Hz,H–α),8.04(1H,d,J=16.0Hz,H–β),and 12.68 (1H, s, –OH).

2.3.3 **2′-Hydroxy-4-chlorochalcone(3)**

IR (v cm-1): 3448 (–OH), 1640 (C=O), 1580 (C=C alkene), 1566 and 1490 (C=C aromatic), 1210 (C–O alcohol)
and 768 (C–Cl);
1HNMR(400MHz,CDCl3):δ6.95(1H,ddd,J=1.6,8and8Hz,H–5′),7.08(1H,dd,J=1.6and8Hz,H–3′),7.48 (2H,d,J=8Hz,H–3andH–5),7.60(1H,ddd,J=1.6,8and8Hz,H–4′),7.65(2H,d,J=8Hz,H–2andH–6),7.64 (1H, d, J=15.6 Hz, H–α), 8.02 (1H, d, J=15.6 Hz, H–β), 7.96 (1H, dd, J=1.6 and 8 Hz, H–6′) and 12.80 (1H, s, – OH).

2.3.4 2′-Hydroxy-4-nitrochalcone(4)

IR(vcm-1):3450(–OH),1702(C=O),1648(C=Calkene),1610and1448(C=Caromatic),1545and1348(N=O), 1197 (C–N) and 1106 (C–O);
1HNMR(400MHz,CDCl3):δ7.03(1H,ddd,J=1.6,8.0and8.0Hz,H–5′),7.08(1H,dd,J=1.6and8.0Hz,H–3′),7.56(1H,ddd,J=1.6,8.0and8.0Hz,H–4′),7.77(1H,d,J=15.6Hz,H–α),7.83(2H,d,J=8.0Hz,H–2andH–6),7.96(1H,d,J=15.6Hz,H–β),7.99(1H,dd,J=1.6and8.0Hz,H–6′),8.34(2H,d,J=8.0Hz,H–3andH–5),and 12.64 (1H, s, –OH).

2.3.5 2′-Hydroxy-4-(dimethyl) aminochalcone(5)

IR(vcm-1):3442(–OH),2920(C-Hsp3),1626(C=O),1598(C=Calkene),1524and1488(C=Caromatic),1179 (C–O) and 1036 (C–N);
1HNMR(400MHz,CDCl3):δ3.08(6H,s,2xCH3),6.76(2H,d,J=8.8Hz,H–3andH–5),6.97(1H,ddd,J=1.6, 8.0 and 8.0 Hz, H–5’), 7.05 (1H, dd, J=1.6 and 8.0 Hz, H–3’), 7.48 (1H, ddd, J=1.6, 8.0 and 8.0 Hz, H–4’),7.54
(1H,d,J=16.0,H–α),7.64(2H,d,J=8.8Hz,H–2andH–6),7.95(1H,d,J=16.0Hz,H–β),7.96(1H,dd,J=1.6and 8.0 Hz, H–6’), and 13.25 (1H, s,–OH).

2.3.6 2′-Hydroxy-4-methoxychalcone(6)

IR (v cm-1): 3432 (–OH), 1692 (C=O), 1626 (C=C alkene), 1626 and 1464 (C=C aromatic) and 1136 (C–O);
1HNMR(400MHz,CDCl3):δ3.88(3H,s,OCH3),6.96(1H,ddd,J=1.6,8.0and8.0Hz,H–4′),6.98(2H,d,J=8.8 Hz,H–3andH–5),7.05(1H,dd,J=2.0and8.0Hz,H–3′),7.48(1H,ddd,J=1.6,8.0and8.0Hz,H–5′),7.58(1H, d,J=15.2,H–α),7.66(2H,d,J=8.8Hz,H–2andH–6),7.93(1H,d,J=15.2Hz,H–β),7.96(1H,dd,J=2.0and8.0 Hz, H–6′) and 12.98 (1H, s,-OH).

2.3.7 2′-Hydroxy-4′-O-prenyl-2,6-dichlorochalcone(7)

IR (v cm-1): 3446 (–OH), 3099 (C–H sp2), 2954 (C–H sp3), 1656 (C=O), 1599 (C=C alkene), 1508 and 1468
(C=C aromatic), 1234 (C–O) and 775 (C–Cl);
1HNMR(400MHz,CDCl3):δ1.77(3H,s,H–4□),1.84(3H,s,H-5□),4.59(2H,d,J=6.8Hz,H-1□),5.49(1H,t, J=6.8Hz,H–2′′),6.52(1H,d,J=2.4and8.8Hz,H–5’),6.56(1H,d,J=2.4Hz,H-3′),7.24(1H,dd,J=8.0and8.0

Hz,H–4),7.43(2H,d,J=8.0Hz,H-3andH–5),7.78(1H,d,J=8.8Hz,H–6′),7.80(1H,d,J=15.6,H–α),7.96(1H, d, J=15.6 Hz, H–β) and 13.29 (1H, *s,–OH).*

2.4Biological activity-The antifungal activity of synthesized chalcones was evaluated by the cup-plate method [9] againstthree fungal species: C. albicansATCC 10231, A nigerATCC 1015, and M. gypseumC 115 2000, dermatophyte fungal species. Stock solutions of synthesized compounds were prepared in DMSO. Aliquots of the stock solution wereusedtoprepareseriesofsubsequentconcentration.Thelowestconcentrationthatproducesnovisiblefungal growth after the incubation time is termed as minimum inhibitory concentration (MIC) [9]. Control experiments wereperformedundersimilarconditionswithoutthesynthesizedcompounds.Standardusedforantifungalactivit y wasKetoconazole.

III. RESULTS ANDDISCUSSION

3.0 Chemistry

The synthetic approach of the target compounds is illustrated in Scheme 1

A high concentration of KOH was used for the Claisen Schmidt condensation reaction of acetophenone and benzaldehyde derivatives [8]. Chalcones were obtained by neutralization of the reaction mixture followed by washing with ethanol and chromatographic purification. The structures of compounds (1-7) were ascertained by spectralanalysis(IRandNMR)andidenticaltotheearlierreportedcompounds [10,11,12,15-17].Chalconeswere obtained as yellow or orange crystals with melting points ranging from 95^{O}C to 148^{O}C. Percentage yield and the physical properties of the synthesized chalcones is summarized in Table 1. Chalcone1 displayed the highest percentageyield(87.6%)followedby5(76.2%),4(75.4%),7(74.6*%),3(66.1%),2(62.4%)and6(62.1%).*

Table 1 Physical data of the synthesized chalcones,

Chalcone	m. p. (°C)	m. p. [Lit.]	Yield (%)	Rf	Color
1	124-126	190-192 [10]	87.4	0.62	Yellow
2	66-68	68-70 [11]	62.1	0.79	Yellow
3	144-146	149-150 [14]	65.9	0.72	Yellow
4	102-104	104-106 [10]	75.1	0.81	Yellow
5	58-60	55 [15]	76.0	0.59	Orange
6	86-90	92-93 [16]	61.8	0.60	Yellow
7	96-98	101-102 [17]	74.5	0.83	Yellow

Antifungal activity was carried out by using cup-plate method. [9] The synthesized compounds have no activity againstC.albicansandA.niger.Significantantifungalactivitywasshownbythesynthesizedcompoundsagainst M. gypseum, a dermatophyte. Synthesised chalcone chalcones 2′-Hydroxy-4-chlorochalcone and 2′-Hydroxy-4- nitrochalconeshowedstrongantifugalactivityandweresuperiortoketoconazole,usedasastandard

Table…2…Antifungal activity of chalcones synthesized

Chalcone	MIC (µg/ml)[a]	MIC(µg/ml)[b]	MIC (µg/ml)[c]
1	-	-	12.5
2	-	-	12.5
3	-	-	3.0
4	-	-	2.0
5	-	-	>50
6	-	-	>50
7	-	-	12.5
Keto*	12.5	6.25	6.25

*Ketoconazole used as a standard

a. Aspergillussniger

b. Candidaalbicans.

c. Micro sporumgypseum.

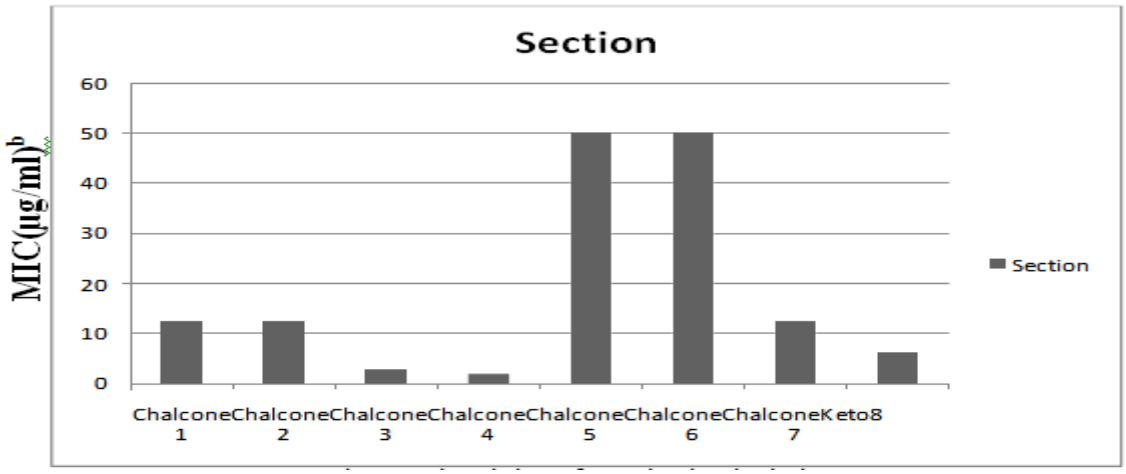


Figure: 1
Anti-Fungal activity of Synthesized Chalcones
Keto Ketoconazole used as standard
MIC= Minimum inhibitory concentration in µg/ml

Dermatophytes are a group of fungi, which normally infect the keratinized areas of the body and causes Dermatomycoses, which is difficult to eradicate. Of the seven synthesized chalcone, chalcones 2′-Hydroxy-4- chlorochalconeand2′-Hydroxy-4-nitrochalconederivativesshowedactivityagainstdermatophytes,andthusmay be a potential candidate to treatdermatomycoses.

Structure activity relationship

On studying the effect of the substituents on the activity, an interesting structure-activity relationship can be seen. An electron withdrawing group, that is, Cl and NO_2 group when placed in the para position as in the synthesized compound chalcones 2′-Hydroxy-4-chlorochalcone **and** 2′-Hydroxy-4-nitrochalcone **respectively** showed MIC betterthanketoconazoleindicatingbetterpotencythanketoconazole.ThepresenceofClgroupatorthopositionas inthesynthesizedcompound4′-Hydroxy-2,6-dichlorochalcone,2′-Hydroxy-2,6-dichlorochalconeand2′-Hydroxy- 4′-O-prenyl-2,6-dichlorochalcone has comparable potency. The presence of OCH_3 and NH_3group as in the synthesized compound 2′-Hydroxy-4-methoxychalcone and 2′-Hydroxy-4-(dimethyl) aminochalcone respectively showed a decrease in potency. On considering the relationship of the antifungal activity of substituted chalcone derivativeswiththeplanarityoftheirmolecules,itwasobservedthatassubstituentincreased,thatis,itturnedinto abulkygroup;activityofthechalconewasobservedtobelowerascomparedwiththelesssubstitutedchalcone. This shows that the steric hindrance may reduce the activity. [13]

IV. Conclusion

In the present work a series of chalcones were successfully synthesized and characterized by spectral studies. The synthesizedchalconesweretestedforantifungalactivitiesagainstthreefungalstrains.M.gypseumwasfoundtobe more sensitive to the two chalcones 3 and 4. Among the 7 compounds tested chalcone 3 and 4 were more effective than the clinical candidate ketoconazole. M. gypseumis a type of fungi which causes dermatomycoses, a type of infectiondifficulttotreat,hence,thestudiedcompounds,specifically,3and4couldbepromisingleadmoleculesfo r developmentofmorepotentandsaferantifungaldrugsforthetreatmentofdermatomycoses.

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