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Synthesis and anti-bacterial, anti-fungal activity of some novel chalcone derivatives

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ABSTRACT

*Chalcone have displayed an impressive array of biological importance. A new series of chalcone have been synthesized by reacting 1-(4-isobutylphenyl) ethanone with different substituted aldehyde in turn clasien-schimidt condensation. All synthesized compounds have been evaluated for anti-bacterial and anti-fungal studies. Compound **11** showed promising anti-bacterial activities against staphylococcus aureus having MIC50 value of 2.10ug/ml and compound **2** also showed good anti-fungal activity against Candida krusei having MIC50 value of 2.12ug/ml.*

Keywords: Synthesis of Chalcone, derivatives of chalcone, 1-(4-Isobutylphenyl) ethanone, bioactive compounds.

INTRODUCTION

Chalcone is an aromatic ketone in which two aromatic ring joined by three-carbon alpha-beta-unsaturated carbonyl system. Studies reveled that compound with chalcone-based structure have an arry of pharmacological activities such as. Anti-inflammatory [1,2,3], Anti-malarial [4,5], induction of nitric oxide inhibition [6,7], anti-viral [8], anti-tuberculosis [9], anti-tumoral [10], Dule COX/5-LOX [11,12], inhibitory activities with these antibacterial, antiprotozoal, immunomodulantary, tyronas inhibition and cytotoxic activities [13], have been cited in literature. It is also useful intermediate in biosynthesis of flavonides, which are substances widespread in plant. As part of our continuing effort towards discovery of new class of compounds, here in report synthesis of new chalcone derivatives and evaluated for anti-bacterial and anti-fungal activity.

EXPERIMENTAL RESULTS

^{1}HNMR spectra were recorded on 300MHz Bruker FT-NMR (Avance DPX 300) spectrometer using tetramethylsilane as internal standard and chemical shifts are reported in

units. Mass spectra were recorded on either GCMS (fuscous GC with TSQ II mass analyzer and thermoelectron) with autosampler/direct injection (EI/CI) or LCMS (APCI/ESI; Bruker daltanoics Micro TOFQ). All chromatographic purifications were done on silica gel (100-200 mesh). Ethyl acetate and pet ether was used for purification. (Merck Kiesel 60 F254, 0.2mm thickness) sheet.

(E)-1-(4-isobutylphenyl)-3-(3, 4, 5-Trimethoxyphenyl) prop-2-en-1-one. (1)
Yield (71%). (1H NMR $CDCl_3$, 300Mz): δ 0.88 (d, 6H), 1.82-1.91 (m, 1H), 2.54 (d, 2H), 3.81(s, 3H), 3.91 (s, 6H), 6.89 (s, 2H), 7.43 (dd, *J* = 3,3 Hz 2H); 7.60 (d, *J* = 3, 1H); 7.93 (d, *J* =3 Hz, 1H); 8.02 (dd, *J* = 3,3 Hz, 2H).
Mass-(M/Z) :(m/z): 355.1(M+1).
Anal. Calcd. For $C_{22}H_{26}O_4$: C, 74.55; H, 7.39; O, 18.06.
Found C, 74.53; H, 7.39.

(E)-1-(4-isobutylphenyl)-3-(2, 4, 5-Trimethoxyphenyl) prop-2-en-1-one. (2)
Yield (78%). (1H NMR $CDCl_3$, 300Mz): δ 0.86 (d, 6H), 1.81-1.89 (m, 1H), 2.55 (d, 2H), 3.90 (s, 9H), 6.28 (s, 1H), 6.79 (s, 1H), 7.34 (d, *J* = 3 Hz, 1H), 7.56 (d, *J* = 3 Hz, 1H), 7.41 (dd, *J* = 3,3 Hz 2H), 8.03 (dd, *J* = 3,3 Hz, 2H).
Mass-(m/z): 355.1(M+1), 378.1(M+Na).
Anal. Calcd. For $C_{22}H_{26}O_4$: C, 74.55; H, 7.39; O, 18.06.
Found: C, 74.54; H, 7.39.

(**E)-1-(4-isobutylphenyl)-3-(2, 4-Dimethoxyphenyl) prop-2-en-1-one. (3)**
Yield (81%). (1H NMR $CDCl_3$, 300Mz): δ 0.86 (d, 6H), 1.81-1.90 (m, 1H), 2.57 (d, 2H), 3.91 (s, 6H), 6.58 (s, 1H), 6.89 (d, *J* = 6 Hz,1H), 7.32 (d, *J* = 6 Hz, 1H), 7.41 (d, *J* = 9, 2H), 7.56 (d, *J* = 6 Hz, 1H), 8.01 (d, *J* = 9 Hz, 2H), 8.08 (d, *J* = 6 Hz, 1H).
Mass (m/z): 325 (M+1).
Anal. Calcd. For $C_{21}H_{24}O_3$: C, 77.75; H, 7.46; O, 14.80.
Found: C, 77.73; H, 7.45.

(E)-1-(4-isobutylphenyl)-3-(2, 5-Dimethoxyphenyl) prop-2-en-1-one. (4)
Yield (90%). (1H NMR $CDCl_3$, 300Mz): δ 0.91 (d, 6H), 1.83-1.91 (m, 1H), 2.56 (d, 2H), 3.96 (s, 6H), 6.74(s, 1H), 6.81 (d, *J* = 3 Hz, 1H), 6.93 (d, *J* = 3 Hz, 1H), 7.39 (d, *J* = 3 Hz, 1H), 7.46 (d, *J* = 3,3 Hz, 2H), 7.49 (d, *J* = 3 Hz, 1H), 8.04 (d, *J* = 3,3 Hz, 2H).
Mass: (m/z): - 325(M+1).
Anal. Calcd. For $C_{21}H_{24}O_3$: C, 77.75; H, 7.46; O, 14.80.
Found: C, 77.73; H, 7.46.

(E)-1-(4-isobutylphenyl)-3-(4-Methoxyphenyl) prop-2-en-1-one. (5)
Yield (84%). 1H NMR ($CDCl_3$): δ 0.88 (d, 6H), 1.79-1.87 (m, 1H), 2.53 (d, 2H), 3.91 (s, 3H), 7.12 (d, *J* = 6 Hz, 2H), 7.18 (d, *J* = 6 Hz, 1H), 7.28 (d, *J* = 6 Hz, 2H), 7.31 (d, *J* = 3 Hz, 1H), 7.38 (dd, *J* = 9 Hz, 2H), 8.06 (d, *J* = 9 Hz, 2H).
Mass :(m/z): - 295.2(M+1), 317.
Anal. Calcd. For $C_{20}H_{22}O_2$: C, 81.60; H, 7.53; O, 10.87.
Found: C, 81.60; H, 7.51.

(E)-3-(4-chlorophenyl)-1-(4-Isobutyl phenyl) prop-2-en-1-one. (6)
Yield (75%). 1H NMR ($CDCl_3$): δ 0.93 (d, 6H), 1.82-1.89 (m, 1H), 2.54 (d, 2H), 7.19 (d, *J* = 3 Hz, 1H), 7.33 (d, *J* = 3 Hz, 1H), 7.36 (d, *J* = 6 Hz, 2H), 7.39 (d, *J* = 9 Hz, 2H), 7.68 (d, *J* = 6 Hz, 2H), 8.03 (d, *J* = 9 Hz, 2H).

Mass :(m/z): - 297(M-1).
Anal. Calcd. For $C_{19}H_{19}ClO$: C, 76.37; H, 6.41; Cl, 11.86; O, 5.35.
Found: C, 76.36; H, 6.39.

(E)-3-(3-fluoro-4-methoxyphenyl)-1-(4-isobutylphenyl) prop-2-en-1-one. (7)
Yield (78%). 1H NMR ($CDCl_3$): δ 0.89 (d, 6H), 1.79-1.87 (m, 1H), 2.56 (d, 2H), 3.96 (s, 3H), 6.83 (t, 1H), 6.94 (dd, J = 3,3 Hz, 1H), 7.08 (d, J = 6 Hz, 1H), 7.18 (d, *J* = 3 Hz, 1H), 7.29 (d, *J* = 3 Hz, 1H), 7.36 (dd, J = 3,3 Hz, 2H), 8.06 (dd, J = 3,3, 2H).
Mass :(m/z): 313.2(M+1) , 336.2(M+Na)
Anal. Calcd. For $C_{20}H_{21}FO_2$: C, 76.90; H, 6.78; F, 6.08; O, 10.24.
Found: - C, 76.90; H, 6.77.

(E)-3-(2-hydroxy-4methoxyphenyl)-1-(4-isobutylphenyl) prop-2-en-1-one. (8)
Yield (69%). 1H NMR (DMSO): δ 0.87 (s, 6H), 1.77-1.84 (m, 1H), 2.52 (d, 2H), 3.89 (s, 3H), 6.61(s, 1H), 6.84(d, *J* = 3 Hz, 1H), 7.39 (dd, *J* = 3,3 Hz, 2H), 7.36 (d, *J* = 3 Hz 1H), 7.56 (d, *J* = 3 Hz, 1H), 8.02 (dd, *J* = 3,3 Hz, 2H), 9.83(s, 1H).
Mass :(m/z): - 310(M+1).
Anal. Calcd. For $C_{20}H_{22}O_3$: C, 77.30; H, 7.14; O, 15.46.
Found: - C, 77.30; H, 7.13.
(E)-3-(2-hydroxy-5-methoxyphenyl)-1-(4-isobutylphenyl)prop-2-en-1-one. (9)
Yield (72%). 1H NMR (DMSO): δ 0.92 (d, 6H), 1.81-189 (m, 1H); 2.56 (d, 2H), 3.91 (s, 3H), 6.56 (d, *J* = 6Hz 1H), 6.68(s, 1H), 6.71 (d, *J* = 6 Hz, 1H), 7.34 (d, *J* = 6 Hz, 1H), 7.39 (d, *J* = 9 Hz, 2H), 7.58 (d, *J* = 6 Hz, 1H); 7.38 (d, *J* = 9 Hz, 2H), 8.04 (d, *J* = 9 Hz, 1H), 10.03(s, 1H).
Mass :(m/z): - 310(M+1).
Anal. Calcd. For $C_{20}H_{22}O_3$: C, 77.30; H, 7.14; O, 15.46.
Found: - C, 77.28; H, 7.14.

(E)-1-(4-isobutylphenyl)-3-(pyridin-2-yl)prop-2-en-1-one. (10)
Yield (68%). 1H NMR ($CDCl_3$): δ = 0.89 (d, 6H); 1.84-1.92 (m, 1H); 2.57 (d, 2H); 7.36 (d, *J* = 9 Hz, 2H); 7.38 (d, *J* = 6 Hz 1H); 7.43 (t, 1H); 7.46 (d, *J* = 6 Hz, 1H); 7.54 (d, *J* = 6 Hz, 1H); 7.68 (t, 1H); 8.08 (d, *J* = 9 Hz, 2H); 8.76 (d, *J* = 6 Hz,1H).
Mass:(m/z): - 264.1 (M-1),
Anal. calcd. For $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28; O, 6.03.
Found: - C, 81.46; H, 7.22; N, 5.28.

(E)-1-(4-isobutylphenyl)-3-(thiophen-3-yl)prop-2-en-1-one. (11)
Yield (71%). 1H NMR ($CDCl_3$): δ = 0.87 (d, 6H); 1.82-1.89 (m, 1H); 2.56 (d, 2H); 7.09 (d, *J* = 3 Hz, 1H); 7.16 (d, *J* = 3 Hz, 1H); 7.26 (d, *J* = 3 Hz, 1H); 7.31 (d, *J* = 3 Hz, 1H); 7.34 (s, 1H); 7.38 (d, *J* = 6 Hz, 2H); 8.06 (d, *J* = 6 Hz, 2H).
Mass:(m/z): 271.2(M+1), 294.2(M+Na)
Anal. calcd. for $C_{17}H_{18}OS$: C, 75.51; H, 6.71; O, 5.92; S, 11.86.
Found:- C, 75.49; H, 6.71.

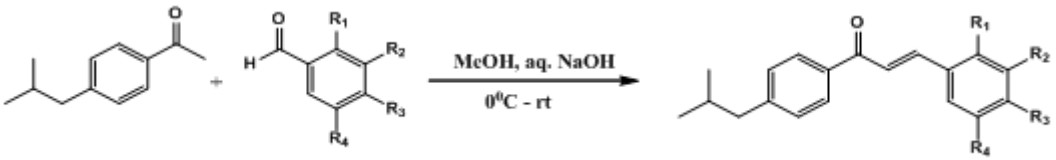
(E)-3-(furan-3-yl)-1-(4-Isobutylphenyl)prop-2-en-1-one. (12)
Yield (79%). 1H NMR ($CDCl_3$): δ = 0.91 (d, 6H); 1.80-1.88 (m, 1H); 2.48 (d, 2H); 6.38 (d, *J* = 3 Hz, 1H); 7.19 (d, *J* = 3 Hz, 1H); 7.26 (d, *J* = 3 Hz, 1H); 7.32 (d, *J* = 3 Hz, 1H); 7.49 (s, 1H); 7.39 (dd, *J* = 3, 3 Hz, 2H); 8.04 (dd, *J* = 3, 3 Hz, 2H).
Mass:(m/z):- 255.1(M+1).
Anal. calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13; O, 12.58.

Found: - C, 80.28; H, 7.12.

RESULTS AND DISCUSSION

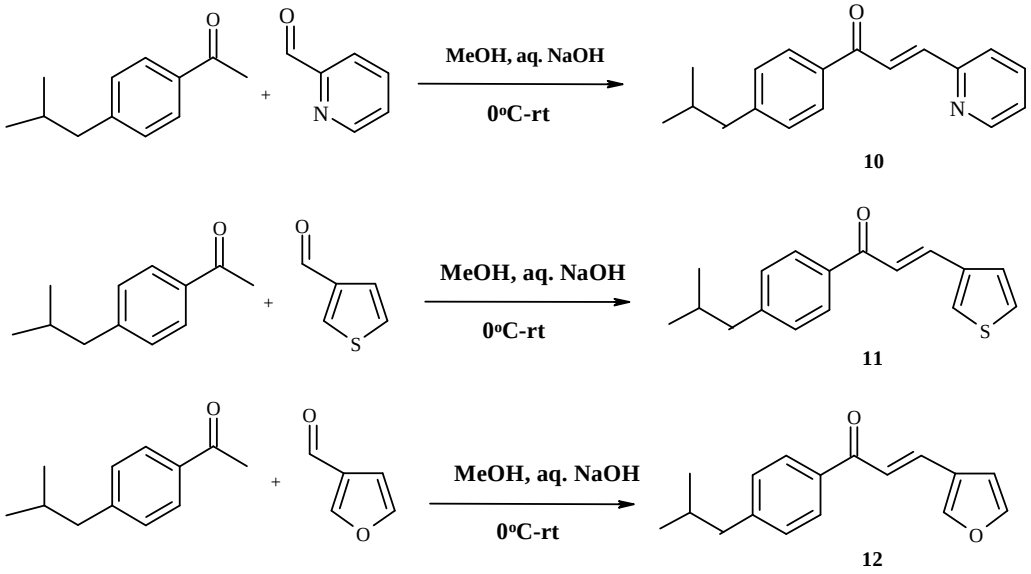
Chemistry:

Clasin-schmidt condensation the general synthetic method employed to synthesis of novel chalcone derivatives form commercially available 1-(4-isobutylphenyl) ethanone on treatment with different substituted aldehydes using aqueous sodium hydroxide and MeOH at 0^0C for 30 minute resulted in formation of proposed compounds **(1-9)** in 60-90% yield (Scheme-1).



1) R_1 = H, R_2 = OCH_3, R_3 = OCH_3, R_4 = OCH_3; **2)** R_1 = OCH_3, R_2 = H, R_3 = OCH_3, R_4 = OCH_3; **3)** R_1 = OCH_3, R_2 = H, R_3 = OCH_3, R_4 = H; **4)** R_1 = OCH_3, R_2 = H, R_3 = H, R_4 = OCH_3 ; **5)** R_1 = H, R_2 = H, R_3 = OCH_3, R_4 = H; **6)** R_1 = H, R_2 = H, R_3 = Cl, R_4 = H; **7)** R_1 = H, R_2 = F, R_3 = OCH_3, R_4 = H; **8)** R_1 = OH, R_2 = H, R_3 = OCH_3, R_4 = H; **9)** R_1 = OH, R_2 = H, R_3 = H, R_4 = OCH_3

Compounds 10, 11 and 12 were synthesized by using same base aqueous sodium hydroxide and MeOH for 11-12 hours in 40-55% yield (scheme-2)



and purification of these compounds was done by silica gel column chromatography but in case of compounds **(1-9)** purification was done by precipitations. Group like trimethoxy, dimethoxy chloro, fluoro attached to propenone moiety have antimalerial, anti-cancer, nitric oxide production activity and also TNF-alpha (VCAM) inhibition activity is reported in literature likewise pyridyl, thienyl and fural group have reported considerable COX / 5-LOX inhibitory activities. Standard Ciprofloxacin used for anti-bacterial screening and Flconazol used standard for anti-fungal screening. Piperazine linked ciprofloxacin dimmers are reported to be potent anti-bacterial agents against resistant strains a novel class of mixed D2/D4 receptor antagonists, duel calcium antagonist, anti-malarial agent and potential antipsychotic

agents recently, piperazin derivatives containing tetrazole nucleus have been reported as antifungal agent.

Biology

The synthesized compounds were tested for their anti-bacterial activity against **A**, Staphylococcus aurous; **B,** Eschericha coli; **C,** Proteus vulgaris; **D,** Klebsiella pneumoniae and **E**, Aspergiuus fumigates bacteria by adopting (CUP-plate method)* agar well diffusion technique, nutrient agar was poured on to the sterilized petridish (20-25Ml) each Petri dish. The poured material was allowed to set (1-2hours) and there after the CUPS' (10mm diameter) was made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar, into these CUPS the test compounds solutions was added with the help of sterile syringe, And the plates were incubated at 37^0C for 48hour and results were noted. A solvent control (10%DMSO in methanol) was also run to note the activity of blank (solvent) the results of anti-bacterial activity were summarized in table-1.

Table-1: Anti-bacterial activity data of chalcones

Entry	A	B	C	D	E
1	16	28	22	04	22
2	22	30	24	11	24
3	20	18	09	22	14
4	20	21	12	16	18
5	08	14	10	12	04
6	10	14	28	04	09
7	28	20	30	18	11
8	06	24	02	18	18
9	08	24	14	22	16
10	22	20	18	21	24
11	28	28	20	09	22
12	26	28	18	12	08
Ciprofloxacin	**24**	**26**	**26**	**26**	**26**

Zone of inhibition is expressed in mm at concentration level of 250ug/ml of chalcone.
***A,** staphylococcus aureus; **B,** Escherchia coli; **C,** Proteus vulgaris; **D,** Klebsiella phenumoniae; **E**, Aspergillus funigatus*

Form table-1 it is evident that compounds **7, 11** and **12** shows very good activity against staphycococcus aureus (*i.e.*26-28mm) compounds **1, 2, 11** and **12** also shows very good activity against Escherchia coli (*i.e.*28-30mm) compound **6, 7** showed activity against Proteus vulgaris while the remaining compound showed moderate anti-bacterial activity against micro-organism.

MIC50 are recorded as the minimum concentration of a compound that inhibits the 50%growth of tested micro-organisms. All of the compounds tested illustrated significant anti-bacterial activity compared to references drug Ciprofloxacin the MIC50 values are generally within the range of 2.10-100ug/ml against all evaluated strains.

While comparing MIC50 value with that of Ciprofloxacin, compound **7, 11** and **12** found to be effective against Staphylococcus aureus, (MIC50=2.10-3.64) also compound **1, 2, 11,** and **12** also shows good activity (MIC50=2.45-4.81) against Escherchia coli, compound **7** shows MIC50 of 2.38 against Proteus vulgari. And all other compound showed less or moderate

activity against the respective bacteria. All MIC 50 data of compounds are summarized in table-2

Table-2: MIC50 value (ug/ml) of chalcones

Entry	A	B	C	D	E
1	80	3.12	72	96	65
2	22.75	2.45	45	88	60
3	35.56	60.81	96	12.30	72
4	50	32.4 6	86	42.12	40
5	100	60	73	70.27	100
6	91	68	3.89	100	100
7	3.64	16.27	2.38	60	75
8	98	10.83	100	72.21	80.23
9	72.13	32.60	85	41.36	68.18
10	22.53	56	18	13.26	9.21
11	2.10	4.81	65.30	90	12.35
12	3.20	4.65	18.60	80	90
Ciprofloxacin	**100**	**100**	**100**	**100**	**100**

A, *staphylococcus aureus;* ***B,*** *Escherchia coli;* ***C,*** *Proteus vulgaris;* ***D,*** *Klebsiella phenumoniae;* ***E****, Aspergillus fmnigatus*

All compounds were also screened for their in vitro antifungal activity against **F**, Candida albicans; **G,** Candida Krusei; **H**, Candidaglabrata the antifungal activity of test compound were compared to that of slandered Fluconzole the activity result of all compound were summarized in Table-3

Table-3: Anti-bacterial activity data of chalcones

Entry	F	G	H
1	22	20	20
2	26	28	24
3	09	12	04
4	06	16	10
5	09	04	02
6	22	20	04
7	22	24	26
8	04	02	10
9	08	08	04
10	24	26	16
11	20	21	20
12	24	18	26
Fluconazole	**29**	**29**	**29**

Zone of inhibition is expressed in mm at concentration level of 250ug/ml of chalcone.
F, Candida albicans; G, Candida krusei; H, Candida glabrata.

Compound **2**, shows good inhibitory activity against all fungi having MIC50= 2.12-4.80 range, compound **7** shows activity against G, *Candida krusei* and **H**, *Candida glabrata* with MIC50=6.30-7.02, compound **10** shows inhibitory activity against **F**, *Candida albicans* and *Candida krusei* with MIC50=3.56-5.69 and also compound **12** shows activity against **F** *Candida albicans* and **H**, *Candida glabrata* with MIC50=4.18-4.97 and remaining

compounds shows less or moderate activity against fungi MIC50 value (ug/ml) of chalcones were summarized in table-4.

Table-4: MIC50 value (ug/ml) of chalcones

Entry	F	G	H
1	40.32	42.34	55.65
2	3.70	2.12	4.80
3	71.27	50	70
4	60.13	68.10	48.12
5	68.27	45.13	71.20
6	8.71	18.56	58.36
7	9.12	7.02	6.30
8	60	80.16	32.18
9	75	82.13	60
10	3.56	5.69	22.31
11	6.38	16.37	9.20
12	4.97	28.12	4.18
Fluconazole	**50**	**50**	**50**

F, Candida albicans; G, Candida krusei; H, Candida glabrata.

CONCLUSION

New series of chalcone have been synthesized by using simple clasin-smidt condensation reactions as potent antibacterial and anti-fungal agents it is observed that heterocyclic group (**10, 11 and 12**) attached to propenone moiety show good anti-bacterial and anti-fungal activity. Trimethoxy group at R_1, R_3, R_4 **(2)** positions is prefer rather than at position R_2, R_3, R_4 **(1)** for anti-bacterial activity against **B,** Escherchia coli and anti-fungal activity against all fungi, with also fluoro group ortho to methoxy at positions R_3 is prefer for activity against **A,** staphylococcus aureus and **C,** Proteus vulgaris; bacteria and **G**, Candida krusei; **H**, Candida glabrata fungi.

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