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Synthesis and Characterisation of Biologically Potent Novel Chalcone Moieties

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ABSTRACT

As displaying a dominant biological interest of some amino chalcone derivatives which were synthesized by claisen-schmidt condensation reaction of amino acetophenone with aromatic aldehyde in presence of sodium hydroxide. These chalcones were screened for antifungal activity against *candida albicans* strain and also for antibacterial activity against *staphylococcus epidermidis* (G positive) and *pseudomonas aeruginosa* (G negative) strain by NCCLS method. The synthesized compounds were characterized by means of their FT-IR and ^{1}HNMR spectral study[14].

Keywords: Amino chalcone, Antifungal, Antibacterial.

INTRODUCTION

Chalcones are pharmacologically valuable moieties possessing 1,3diphenyl prop-2-ene-1-one (-CH=CH-CO-) as a core structure in which two aromatic rings are linked by first and third carbon of a α,β- unsaturated carbonyl skeleton. A number of chalcone derivatives have demonstrated wide spectrum of pharmacological activities which has drawn the attention of medicinal chemist and pharmacologists. Due to the extended conjugation, the complete delocalisation of π electrons on both the benzene rings makes whether from bioactivity aspect.

Isolation of Chalcone derivatives from nature requires a long and a far complicated procedure and comparable yield does not obtained. Chalcones and their derivatives are an interesting target class of compound which are extensively investigated due to their broad spectrum of various therapeutic activity such as antimicrobial[1], anti-inflammatory[2], antiulcerative[3], antiviral[4], antifungal[5], antimalarial[6,7], and anticancer[8]. Furthermore, chalcones are also known as the key intermediate in the synthesis of various biologically active heterocyclic compounds. In order to synthesize new therapeutic agents, this report illustrated the some novel amino chalcone derivatives and screening their activity against

candila albicans fungi, gram positive and gram negative bacterial species.

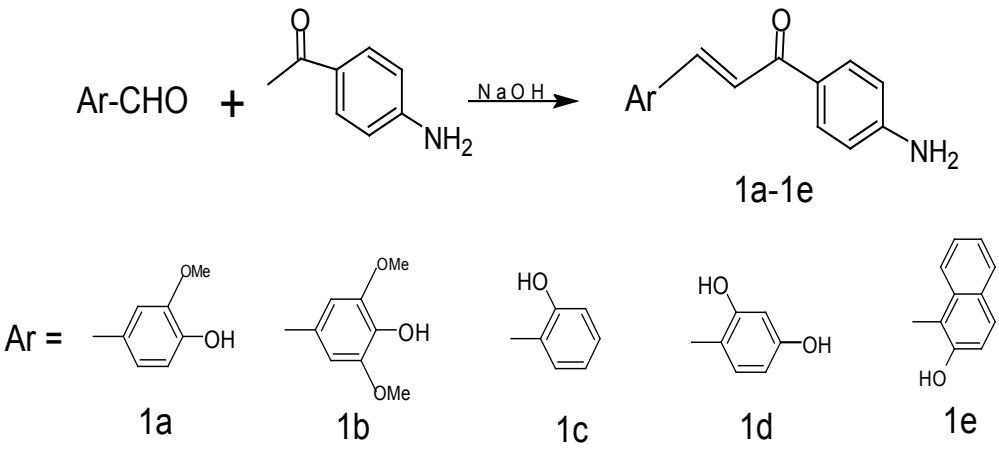
MATERIAL AND METHOD

General information

The all starting materials and solvents were purchased from sigma-Aldrich and SD Fine and used without further purification. Melting points were determined by conventional method and then by electro capillary apparatus and are uncorrected. All the synthesized compounds were inspected by thin layer chromatography on silica gel (E-Merck) and the spots were identified by UV lamp.IR spectra and proton NMR spectra in DMSO at 500 MHz were recorded at CSMCRI Bhavnagar.

General procedure of synthesis of chalcone

The synthesis of chalcone derivatives was conducted according to the procedure reported in the reference[10-12]. Acetophenone derivative (2.5milimole) and substituted benzaldehydes (2.5milimole) were dissolved in 30 ml methanol. To the solution, 10 ml NaOH(20%) solution was added drop wise and reaction mixture was stirred for 1-2 hour at room temperature by magnetic stirrer and kept for overnight. Subsequently, it was poured in ice water and neutralized. The solid precipitates was filtered off and recrystallized from methanol or ethyl acetate.



RESULT AND DISCUSSION

1a; **(2E)-1-(4-aminophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one**

Yellow solid, Yield 58.9 %. m.p. 105-107°C, Rf 0.71

FT-IR (ν, cm^{-1}): 3395(-OH), 3330, 3225 ($-NH_2$), 3063(aromatic C-H), 1649 (>C=O), 1590(-HC= CH-), 1277, 1305 (C-N str)

^{1}HNMR (500 MHz $CDCl_3$, Me_4Si): 3.50 (br, s, $-NH_2$), 3.85(s, $-OCH_3$), 6.027(s,1H, H_2), 6.62(d, $1H_\alpha$), 7.66 (d, $1H_\beta$),.

1b; **(2E)-1-(4-aminophenyl)-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-en-1-one**

Yellow solid, Yield 57.5 % . m.p. 98-100°C , Rf 0.66

FT-IR (ν, cm^{-1}): 3396(-OH), 3331, 3225($-NH_2$), 3064(aromatic C-H), 1648 (>C=O), 1590 (-HC= CH-), 1276, 1304 (C-N str)

^{1}HNMR (500 MHz DMSO, Me_4Si): 3.49(br, s, $-NH_2$), 3.71(s, $-OCH_3$), 3.82(s, $-OCH_3$), 6.028(s,1H, H_1,H_6), 6.58(d, $1H_\alpha$), 7.68 (d, $1H_\beta$).

1c: **(2E)-1-(4-aminophenyl)-3-(2-hydroxyphenyl) prop-2-en-1-one**

Pale Yellow solid, Yield 62.5% . m.p. 110-112°C , Rf 0.68

FT-IR (ν, cm^{-1}): 3570 (-OH), 3338, 3328 ($-NH_2$), 3050(aromatic C-H), 1676(>C=O), 1595(-HC =CH-), 1270,1364 (C-N str)

^{1}HNMR (500 MHz $CDCl_3$, Me_4Si): 3.47 (br, s, $-NH_2$),6.57(d, $1H_\alpha$), 7.51 (d, $1H_\beta$), 7.013 (m, H_2), 7.72 (m, H_3,H_4).

1d: (2E)-1-(4-aminophenyl)-3-(2,4-dihydroxy phenyl)prop-2-en-1-one

Yellow solid, Yield 87.0% . m.p. 98-100°C ,Rf 0.72

FT-IR (ν, cm^{-1}): 3680 (-OH), 3652 (-OH), 3370, 3325 ($-NH_2$), 3062(aromatic C-H), 1673 (>C=O), 1596 (-HC=CH-), 1270,1364 (C-N str)
^{1}HNMR (500 MHz $CDCl_3$, Me_4Si): 3.48(br, s, $-NH_2$),6.32(s,1H, H_2), 6.55(d, 1H_α), 7.48 (d, 1H_β), 7.55 (d, 1H, H_4), 7.67(d,1H, H_5).

1e: (2E)-1-(4-aminophenyl)-3-(2-hydroxynaphthalen-1-yl) prop-2-en-1-one

Brick Red solid, Yield 73.6%. m.p. 182-185°C, Rf 0.53

FT-IR (ν, cm^{-1}): 3652(-OH), 3322, 3335($-NH_2$), 3044(aromatic C-H), 1668 (>C=O), 1587(-HC=CH-), 1267,1349 (C-N str)
^{1}HNMR (500 MHz $CDCl_3$, Me_4Si): 3.49(br, s, $-NH_2$),6.58(d, 1H_α), 7.68 (d, 1H_β), 7.42 (m, C-H,), 7.85(d,1H, H_3),8.05(d,1H, H_2).

Antibacterial Study

Gram Positive* microorganism *[Staphylococcus epidermidis]

The antibacterial activity performed by antimicrobial susceptibility tests, NCCLS 1993,

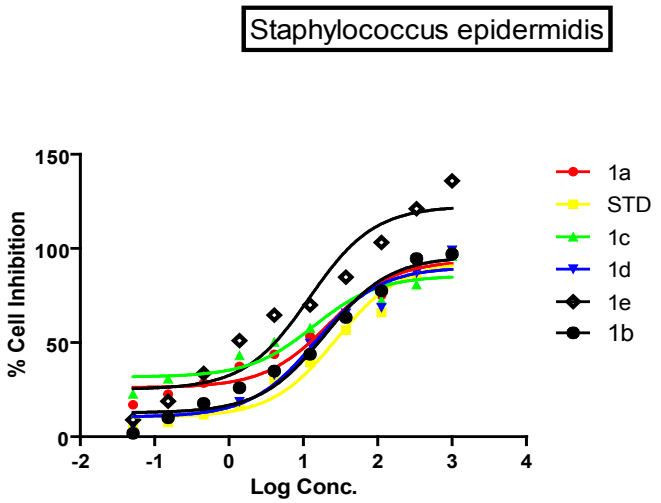


Fig. 1: Plot of log conc. (µg) v/s % cell inhibition of compounds against *Staphylococcus epidermidis*

Table 1: Percentage cell inhibition by compounds agains *Staphylococcus epidermidis* strain

Conc. (µg/ml)	Log Conc.	1a	1b	1c	1d	1e	STD
0.01	-2.29	1.023	12.23	1.08	11.02	7.16	10.12
0.02	-1.82	1.02	14.11	5.22	10.22	8.02	11.89
0.05	-1.34	4.05	17.02	7.13	14.74	9.11	13.98
0.14	-0.86	5.11	21.26	22.41	17.23	13.21	18.03
0.41	-0.39	11.23	26.17	30.27	28.21	15.42	28.49
1.23	0.09	14.52	32.20	32.36	27.62	18.85	33.26
3.70	0.57	25.34	39.19	42.87	40.33	25.63	42.13
11.11	1.05	29.78	52.36	48.16	63.11	40.17	49.65
33.33	1.52	37.41	68.23	49.20	74.42	67.32	70.32
100.00	2.00	67.28	74.12	54.14	93.12	87.24	84.97
IC50 µg/ml		7.69	5.67	0.30	7.60	21.61	7.625
R^2		0.9227	0.9760	0.9632	0.9773	0.9923	0.9507

Approved standard: M2-A5. Chemically synthesized compounds were taken for antibacterial activity. *P.aeruginosa (Gram negative), S.epidermidis (Gram positive)* strains were used for the antibacterial activity. Three-fold serial dilutions of the compounds (150µl) of each sample were made in sterile broth (nutrient broth). The specified amount of test organisms (50µl) was added to each dilution to give a final volume of 200µl. After incubation at 37°C for 18–24 h the plates were examined for growth of the organisms. Absorbance was read in a plate reader. The figures showed the plot of log concentration Vs % cell inhibition of compound against tested organisms. Test compounds show the dose-effect co-relation with maximum linearity in almost all cases within 0.8321 to 0.9863. The data analysis was accomplished using Graph Pad Prism version 5.00, Graph Pad Software Inc., San Diego California USA. IC_{50} values were obtained from regression lines with coefficient factors between R^2 = 0.52 and 0.99. Absorbance at 595nm between reading taken before and after incubation of the plates.

Results of gram positive organism inhibition study indicate followings compounds were found to be lid among others when it was compare IC_{50}

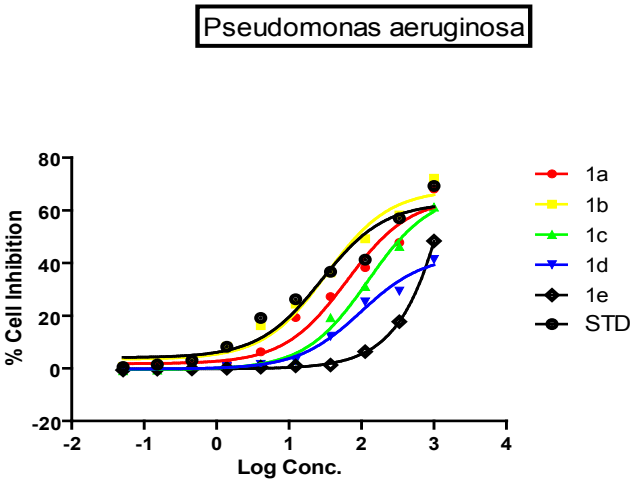


Fig. 2: Plot of log conc. (µg) v/s % cell inhibition of compounds against *Pseudomonas aeruginosa*

Table 2: Percentage cell inhibition by compounds against *Pseudomonas aeruginosa* strain

Conc. (µg/ml)	Log Conc.	1a	1b	1c	1d	1e	STD
0.01	-2.29	7.43	14.32	8.10	1.23	4.30	8.00
0.02	-1.82	10.22	15.26	12.42	2.52	7.12	12.94
0.05	-1.34	11.14	15.79	15.04	6.21	11.25	9.67
0.14	-0.86	17.16	20.64	22.16	5.11	13.02	13.41
0.41	-0.39	21.03	29.71	27.65	9.21	16.27	18.87
1.23	0.09	22.17	32.27	35.44	16.23	19.15	23.42
3.70	0.57	30.13	42.24	39.87	35.21	22.27	26.51
11.11	1.05	42.16	48.24	45.31	39.47	35.65	29.04
33.33	1.52	58.23	64.64	52.55	47.11	47.68	52.67
100.00	2.00	64.12	83.12	81.65	54.20	77.24	76.19
IC50 µg/ml		7.908	3.795	10.30	2.795	34.94	9.871
R^2		0.9737	0.9384	0.8675	0.9863	0.9643	0.9473

value obtained by *Streptomycin (7.625 µM/ml)* with standard drug inhibitory value.

1c (IC_{50} value; 0.3086 µM/ml, R^2= 0.9632)> 1b (IC_{50} value; 5.303µM/ml, R^2= 0.8821) >1d>1a

Results for gram negative microorganism, most effective compounds were arranged in following order when it was compare IC_{50} value obtained by Streptomycin (9.871 µM/ml) with standard drug inhibitory value:

1d (IC_{50} value; 2.795 µM/ml, R^2= 0.9863)>1b (IC_{50} value; 3.795 µM/ml, R^2= 0.9384)>1a(IC_{50} value; 7.908 µM/ml, R^2= 0.9737) >1c(IC_{50} value; 9.871 µM/ml, R^2= 0.9636)

Fluconazole and test compounds were tested against *Candida albican s*in dose dependent manner. Table showed that the high IC_{50} value of 1e was found against *Candida albicans* having (IC_{50}: 74.37µg/ml). Comparative lower IC_{50} value was found with compounds 1b against *candida albicans*(IC_{50}:

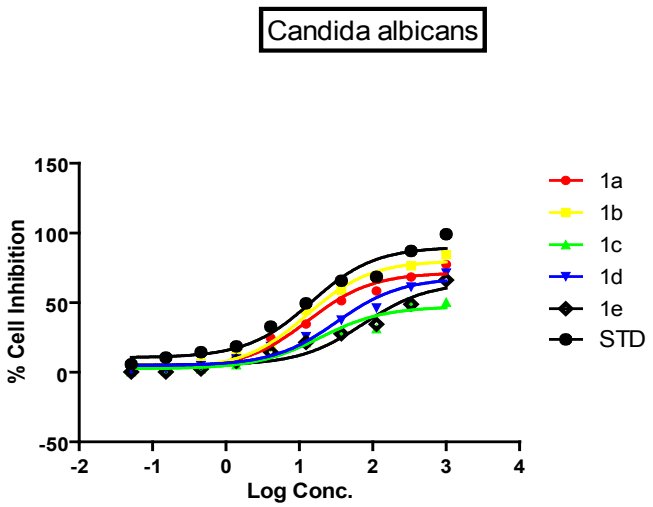


Fig. 3: Dose response curve of Test compounds against *Candida albicans* and Fluconazole

Table 3: Percentage growth inhibition of compounds against fungal strain and Fluconazole (Std.)

Conc. (µg/ml)	Log Conc.	1a	1b	1c	1d	1e	STD
0.05	-1.29	-0.02	0.35	0.36	-0.35	0.22	5.68
0.15	-0.82	0.032	2.36	0.89	2.35	0.156	10.64
0.46	-0.34	6.235	6.58	2.37	4.79	2.36	14.47
1.37	0.14	11.35	13.26	5.46	9.63	7.86	18.63
4.12	0.61	24.65	17.89	18.65	18.67	14.62	32.87
12.35	1.09	34.68	44.65	21.34	25.63	21.35	49.58
37.04	1.57	51.34	58.96	29.62	37.48	27.65	65.65
111.11	2.05	58.36	67.25	31.28	46.22	34.52	68.61
333.33	2.52	68.34	76.38	48.96	61.23	48.75	87.09
1000.00	3.00	77.35	84.36	50.30	71.22	66.22	99.08
IC50 µg/ml		**13.12**	**12.69**	**19.02**	**32.29**	**74.37**	**14.39**
R^2		**0.9809**	**0.9895**	**0.9358**	**0.9680**	**0.9394**	**0.9685**

12.6µg/ml).The figure showed the plot of log concentration vs. % cell inhibition of test compounds against *Candida albicans*. Test compounds show the dose-effect co-relation with maximum linearity (R^2value) with value being 0.9895 and comparatively lower linearity in case of *Candida albicans* at value being 0.9358. Activity order of compounds can be summarized as : *1b>1a>1c>1d.*

CONCLUSION

From above results we can conclude that compounds 1a, 1b and 1c are more effective in gram positive organism i.e. *Staphylococcus epidermidis*, While compounds like 1a, 1b and 1d are more effective against gram negative organism i.e. *Pseudomonas aeruginosa*.

Moreover, 1a and 1b both show good antifungal activity on *Candida albicans s*train, while 1c and 1d having comparable activity and compound 1e is less effective.

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