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Bio-screening of Chalcone and Aurone analogues as therapeutic agents

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Original Research Article

ABSTRACT

Chalcones and aurones are compounds having appealing pharmacological profile due to presence of carbonyl system. The bio-screening of 13 compounds was conducted and assessed against *S. aureus*, *C. albicans* and *E. coli* by agar well diffusion method. Chalcones analogues 1, 2, 3, 4, 5, 6, 7, and 8 were found to be inactive or insignificant against *E. coli*. Chalcone analogue 9 showed moderate activity against *E. coli*. Similarly, compounds, 1, 2, 3, 6, 7, 8 and 9 were found to be inactive or insignificant against *S. aureus*. Analogues 4 and 5 displayed moderate bioactivity against *S. aureus*. Similarly analogues 1, 2, 4, 7, 8 and 9 were found to be inactive or insignificant against *C. albicans*. Compound 3, 5, and 6 were found more effective against *C. albicans*. Among aurones 2, 3, and 4 showed insignificant activity while compound 1 showed significant activity against *E. coli*. Analogue 1 showed very effective acitivity against *S. aureus*. In a similar way, analogue 3 was found to be inactive, while analogues 1, 2 and 4 showed moderate activity against *C. albicans*. Overall, chalcone and aurone analogues have been effective against selected bacteria and fungi strains and are expected to be effective in other bioscreening studies.

Keywords: Chalcone, Aurone, *Escherichia coli, Staphylococcus aureus, Candida albicans,* Incubation

INTRODUCTION

Chalcones (1,3-diphenyl-2-propene-1-one) are widely found in various plants which are abundantly used as folk remedies. They are intermediate metabolites in the synthesis of flavonides, which perform many biological activities in plants. Two benzene rings are attached to α-β unsaturated carbonyl group in them. Chromophore (-CO-CH=CH-) presence renders these molecules as colored (Hasan *et al*., 2015). Chalcones demonstrate a wide range of numerous natural biological activities like cell reinforcement, antibacterial, mitigating and so forth. They have potential applications in the prescriptions and also different employments. On both rings of benzene chalcones have conjugated two fold bonds. Particles having such framework have generally low redox possibilities and have a more noteworthy likelihood of experiencing electron exchange responses (Rahman *et al*., 2007).

Aurones are represented by 2-benzylidenebenzofuran-3(2H)-ones and are naturally existing heterocyclic (Dubey *et al*., 2014) secondary metabolites that originate from flavonoid family (Haudecoeur & Boumendjel, 2012). In plants aurone synthesis occurs, by an enzyme aureusidine synthase, from chalcones through oxidation, cyclization and rearrangement (Nakayama *et al*., 2000). The separation of aurones is executed in form of methoxylated, hydroxylated and glycosylated derivatives (Koya *et al*., 2014). Aurones also known as anthochlor pigments and are found in mosses, algae, ferns, fruits, vegetables and flowers and are responsible for pigmentation in plants (Deepthi *et al*., 2003) to help them resist infections by acting as phytoalexins (Lee *et al*., 2010). Moreover, they are isomeric to flavones and impart sharp yellow color to plant parts. In the recent years, scientists have focused more on aurones to understand their biological, therapeutic and genetic importance (Zwergel *et al.,* 2012).

Aurones are found effective as anti-cancer (Lawrence *et al*., 2003), anti-malarial (Oliver *et al*., 2002), anti-microbial (Bandgar *et al*., 2010), anti-fungal, anti-bacterial, and anti-viral agents (Lawrence *et al*., 2003). They have proven effect against oxidant (Anastasia *et al*., 2009) and inflammatory condition (Shin *et al*., 2011). They have been reported as anti-plasmodial, vasorelaxant (Dong, 2009), anti-tumor, insect anti-feedant (Morimoto *et al*., 2007), anti-leukemic

Author's Contribution: **M.M.,** Conceived idea, designed and supervised the study; **Q.A.,** Provided the chalcones and aurones and helped in writing the manuscript; **U.F.D.,** Performed the experiments; **A.H.,** Analyzed the data of experiments; **M.T.,** Helped in review of literature and writing of manuscript

(Pandeya *et al*., 2005) activities and for therapy of thyroid disease (Okombi *et al*., 2006). They also act as agents to treat skin diseases (Okombi *et al*., 2006) and to inhibit soybean lipoxygenase (Anastasia *et al*, 2009). Their role as chemosensors (Chen *et al*., 2013) and herbicides has also been well documented (Zhang *et al*., 2012).

In the present study, the potential of diverse novel chalcones, aurones and their synthetic analogues against gram-positive, gram-negative bacteria and fungi was explored with the prime objective to develop these anti-microbial and anti-fungal agents for improving the quality of human life.

MATERIALS AND METHODS

The study undertaken was a preliminary one to determine whether the chalcone, aurone and their derivatives were biologically active or not. The synthesized chalcones, aurones and their novel analogues were obtained from Chemistry department of University of Education, Lahore. To test their pharmaceutical potential, these compounds were dissolved in methanol followed by blending with vortex. Two representative concentrations (0.2 µg/mL and 0.4 µg/mL) of these compounds were selected to test for biological activity by applying agar well diffusion strategy.

Agar well diffusion method

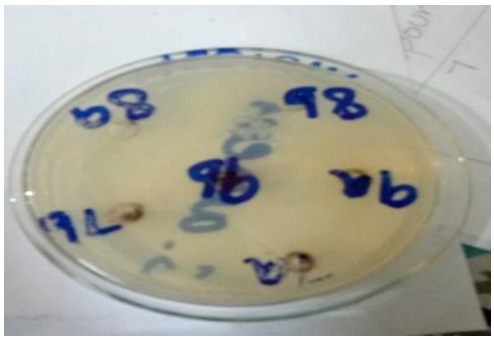
Sterile agar glass plates were prepared with 15ml agar nutrient medium. *E. coli*, *S. aureus,* and *C. albicans* were cultured on these plates. Briefly, the agar plates were inoculated with these microbes by spreading a small volume of inoculum (prepared and maintained in our lab) on the entire agar surface for each microorganism separately. Then 6 wells of 6mm size were punched with aseptic cork borer or sterile pasteur pipette in agar plates. 50 µl of two different concentrations, 0.2 µg/mL and 0.4 µg/mL of chalones, aurones and their analogues were introduced into each well. Antimicrobial agents diffuse in to the surrounding agar and inhibit the growth of microorganism tested. Following 24 hours of incubation, growth of microorganisms was observed with naked eye and estimated the width of zone of growth inhibition with the help of scale. The chalcone, aurone and their analogues (13) tested in this study have been given in Table 1 and Table 2.

RESULTS

Bioactivity of chalcone and aurone analogues against bacteria and fungi

Aurone and chalcone analogues (13 compounds) were administered in the wells of agar plates in two concentrations (0.2µg/ml & 0.4µg/ml) inoculated with *E. coli, S. aureus and C. albicans. The microorganisms were allowed to grow for 24 hours at 37C°. Figure 1 shows the bioactivity of desired compounds against microorganisms* by agar well diffusion technique.

(a)



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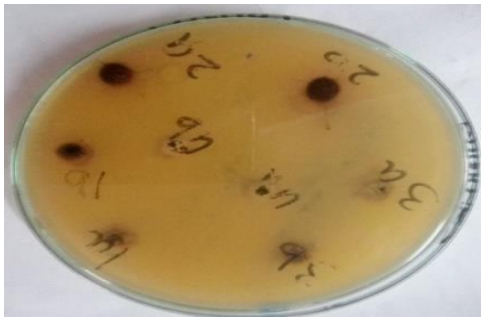

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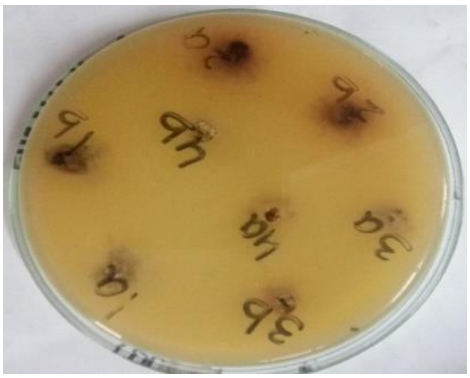

(f)

Fig. 1: Shows bioactivity of chalcones, aurones and their analogues. Chalcones and their analogues (0.2µg/ml & 0.4µg/ml) showed bioactivity after 24 hours incubation at *37C°* against *E. coli* (A), *S. aureus* (B) *C. albicans.* Aurones and their analogues showed bioactivity after 24 hours incubation at *37C°* against bacteria (D), (E) and fungi (F).

The results showed that the chalcone analogues 2 and 5 were inactive, whereas derivatives 1, 3, 4, 6, 7 and 8 showed insignificant activity and compound 9 showed moderate activities against *E. coli.* The zone of inhibition produced by chalcone derivatives after 24 hours became significantly large at higher concentrations *as* shown in Table 1 and Figure 2.

Table I: Zone of inhibition (mm) of chalcones after 24 hours of incubation at 37C° against *E. coli*

Sr. No.	Compound Name	Concentration	
		0.2 µg/mL	0.4 µg/mL
1)	(E)- chalcone	4	7
2)	(E)-3- (2-methoxyphenyl)-1-phenylprop -2-en-1-one	N.Z*	N.Z*
3)	(E)-3- (3-methoxyphenyl)-1-phenylprop -2-en-1-one	6	8
4)	(E)-3- (4-methoxyphenyl)-1-phenylprop -2-en-1- one	7	9
5)	(E)-3- (2,3-di methoxyphenyl)-1-phenylprop -2-en-1-one	N.Z*	N.Z*
6)	(E)-3- (3,4-di methoxyphenyl)-1-phenylprop -2-en-1-one	3	5
7)	(E)-1- phenyl-3-(2,3,4-di methoxyphenyl) prop-2-en-1-one	5	7
8)	(E)-3- (3-nitrophenyl)-1-phenylprop -2-en-1-one	5	9
9)	(E)-3-(3-chlorophenyl)-1-phenylprop -2-en-1-one	6	12

*N. Z denotes No Zone

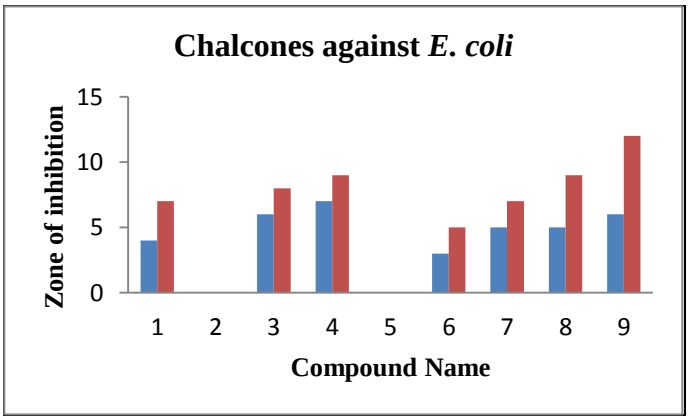

Fig. 2: Comparison of chalcones' bioactivity against *E. coli* at 0.2 µg/mL (blue bars) and 0.4 µg/mL (brown bars) after 24 hours of incubation at 37C°.

Among the aurone derivatives, compound 2, 3 and 4 showed insignificant zone of inhibition at both concentrations. The compound 1 emerged as the most effective antibacterial agent as the zone of growth inhibition was 15 and 18mm as shown (Table 2 and Figure 3).

Table II: Zone of inhibition (mm) of aurones after 24 hours of incubation at 37C° against *E. coli*

Sr. No.	Compound Name	Concentration	
		0.2 µg/mL	0.4 µg/mL
1)	(Z)-2-benzylidenebenzofuran-3 (2H)-one	15	18
2)	(Z)-2-(2-methoxybenzylidene) benzofuran-3(2H)-one	3	6
3)	(Z)-2-(3-methoxybenzylidene) benzofuran-3(2H)-one	2	3
4)	(Z)-2-(4-methoxybenzylidene) benzofuran-3(2H)-one	N.Z*	N.Z*

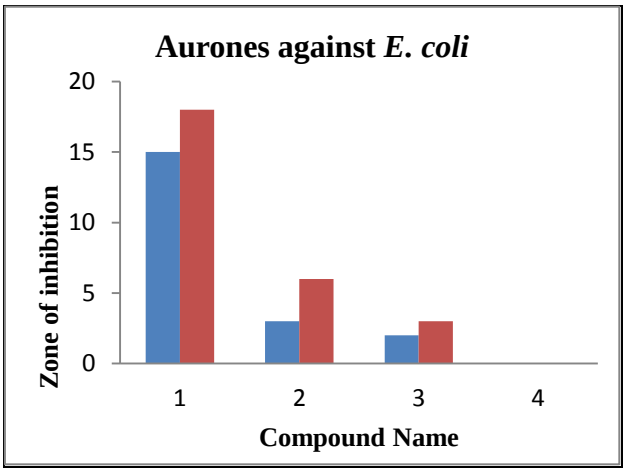

Fig. 3: Comparison of aurones' bioactivity against *E. coli* when incubated for 24 hours at 0.2 µg/mL (blue bars) and 0.4 µg/mL (brown bars).

Chalcone analogues were assayed for antimicrobial character against gram positive bacteria like *S. aureus* as shown in Table 3 and Figure 4.

The results revealed that analogues 2 and 9 were inactive as they could not produce any zone of growth inhibition. The derivatives such as 1, 2, 4, 7, 8 showed insignificant activity being unable to develop any wider zone of inhibition whereas the compounds 5 and 6 showed moderate activity at both concentrations.

Table III: Zone of inhibition of chalcones on 24 hours of incubation at 37C° against *S. aureus*
Zone of Inhibition (mm)

Sr. No.	Compound Name	Concentration	
		0.2 µL/mL	0.4 µL/mL
1)	E)- chalcone	5	8
2)	(E)-3- (2-methoxyphenyl)-1-phenylprop -2-en-1-one	N.Z*	N.Z*
3)	(E)-3- (3-methoxyphenyl)-1-phenylprop -2-en-1-one	4	5
4)	(E)-3- (4-methoxyphenyl)-1-phenylprop -2-en-1-one	6	10
5)	(E)-3- (2,3-di methoxyphenyl)-1-phenylprop -2-en-1-one	10	13
6)	(E)-3- (3,4-di methoxyphenyl)-1-phenylprop -2-en-1-one	10	14
7)	(E)-1- phenyl-3-(2,3,4-di methoxyphenyl) prop-2-en-1-one	4	6
8)	(E)-3- (3-nitrophenyl)-1-phenylprop -2-en-1-one	4	10
9)	(E)-3-(3-chlorophenyl)-1-phenylprop -2-en-1-one	N.Z*	N.Z*

*N. Z denotes No Zone

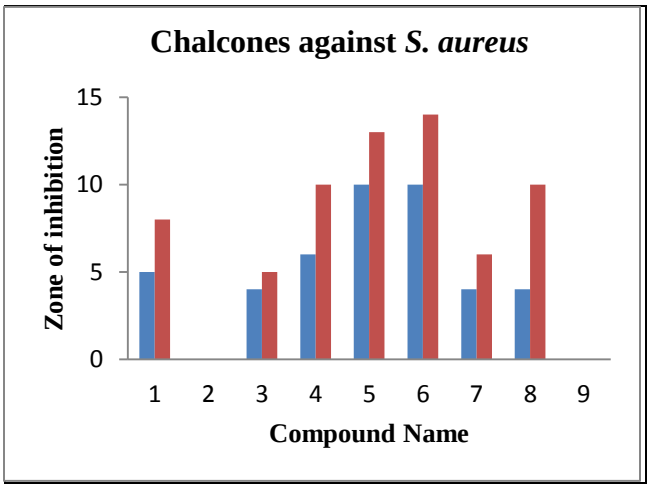

Fig. 4: Showing comparison of chalcones' bioactivity against *S. aureus* at 0.2 µg/mL (blue bars) and 0.4 µg/mL (brown bars).

When Aurone derivatives were tested for antimicrobial potential against *S. aureus,* the findings showed that compound 3 was inactive

being unable to produce any zone of inhibition. Compounds 2 and 4 showed moderate activity and compound 1 showed the most effective zone of inhibition as shown (Table 4 and Figure 5).

Table IV: Zone of inhibition of aurones on 24 hours of incubation at 37C° against *S. aureus*
Zone of Inhibition

Sr. No.	Compound Name	Concentration	
		0.2 µL/ mL	0.4 µL/mL
1)	(Z)-2-benzylidenebenzofuran-3(2H)-one	10	17
2)	(Z)-2-(2-methoxybenzylidene) benzofuran-3(2H)-one	8	10
3)	(Z)-2-(3-methoxybenzylidene) benzofuran-3(2H)-one	N.Z*	N.Z*
4)	(Z)-2-(4-methoxybenzylidene) benzofuran-3(2H)-one	5	7

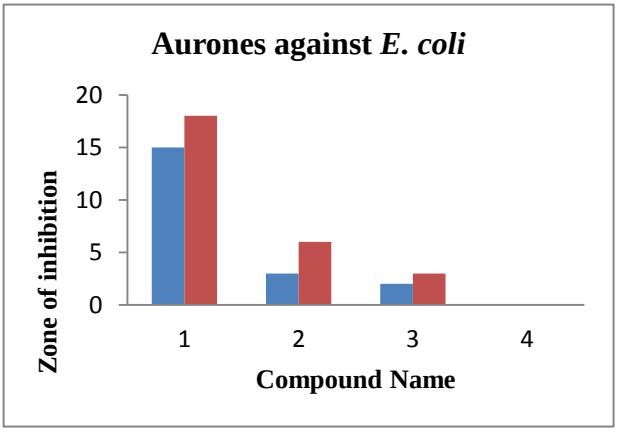

Fig. 5: Comparison of bioactivity of aurones on 24 hours of incubation at 37C° against *S. aureus* at 0.2 µg/mL (blue bars) and 0.4 µg/mL (brown bars).

Antifungal activity

Chalcone derivatives were also tested against fungus to assess antifungal potential. The results showed that compound 8 was inactive being unable to develop any zone of inhibition. The compounds 1, 2, 4, 5, 7 and 9 showed insignificant activity and compounds 3 and 6 reflected moderate activity against *C. albicans.* At higher concentration (0.4 µL/mL), compound 6 appeared the effective one as shown in Table 5 and Figure 6.

Table V: Zone of inhibition of chalcones on 24 hours of incubation at 37C° against *C. albicans*
Zone of Inhibition (mm)

Sr. No.	Compound Name	Concentration	
		0.2 µL/mL	0.4 µL/mL
1)	E)- chalcone	5	10
2)	(E)-3- (2-methoxyphenyl)-1-phenylprop -2-en-1-one	7	9
3)	(E)-3- (3-methoxyphenyl)-1-phenylprop -2-en-1-one	10	12
4)	(E)-3- (4-methoxyphenyl)-1-phenylprop -2-en-1- one	8	10
5)	(E)-3- (2,3-di methoxyphenyl)-1-phenylprop -2-en-1-one	9	11
6)	(E)-3- (3,4-di methoxyphenyl)-1-phenylprop -2-en-1-one	7	14
7)	(E)-1- phenyl-3-(2,3,4-di methoxyphenyl) prop-2-en-1-one	6	9
8)	(E)-3- (3-nitrophenyl)-1-phenylprop -2-en-1-one	N.Z	N.Z
9)	(E)-3-(3-chlorophenyl)-1-phenylprop -2-en-1-one	N.Z	4

***N. Z denotes No Zone**

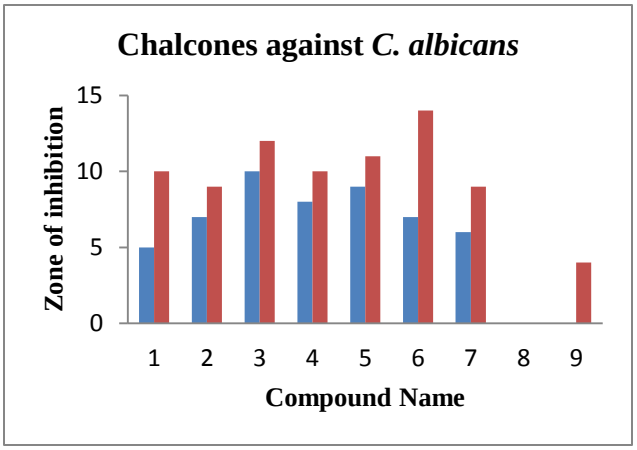

Fig. 6: Bioactivity chalcones on 24 hours of incubation at 37C° against *C. albicans* at 0.2 µg/mL (blue bars) and 0.4 µg/mL (brown bars).

Among the Aurone derivatives compound 2 was found inactive, while 1, 3 and 4 exhibited moderate activity against *C. albicans* (Table 6 and Figure 7).

Table VI: Zone of inhibition of aurones against *C. albicans*

Zone of Inhibition (mm)

Sr. No.	Compound Name	Concentration	
		0.2 µL/mL	0.4 µL/mL
1)	(Z)-2-benzylidenebenzofuran-3(2H)-one	6	9
2)	(Z)-2-(2-methoxybenzylidene) benzofuran-3(2H)-one	5	7
3)	(Z)-2-(3-methoxybenzylidene) benzofuran-3(2H)-one	N.Z*	N.Z*
4)	(Z)-2-(4-methoxybenzylidene) benzofuran-3(2H)-one	4	6

***N. Z denotes No Zone**

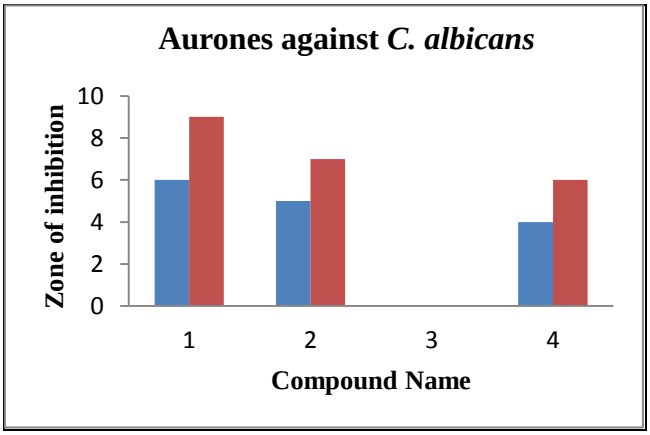

Fig. 7: Comparison of bioactivity of aurones on 24 hours of incubation at 37C° against *C. albicans* at 0.2 µg/mL (blue bars) and 0.4 µg/mL (brown bars).

DISCUSSION

Pharmacological potential of chalcones (and their analogues) & aurones (and their derivatives) have been explored against microorganisms on large scale to replace the traditional medicines (Prasad *et al*., 2008). The bioactivity of chalcones is largely attributed because of α, β-unsaturated ketone moiety. Aurones elong to a class of flavonoid possessing a chalcone-like molecule. The compounds of aurones showed a variety of therapeutic characteristics such as anti-cancers, insect anti-feedant and anti-microbial etc. (Morimoto *et al*., 2007).

Our study revealed that chalcone, aurone and their analogues showed antifungal activities as well. Chalcone derivatives having methoxy and chloro functionalities showed no activity against the bacteria tested in this study. Our findings are compatible to the report of Kenchappa *et al*. (2017) who described that some of the pyridine chalcones showed no activity against *E. coli* due to the presence of chloro group. It is also reported that amino chalcones showed insignificant effect against *S. aureus* and *E. coli* (Vazquez *et al*., 2015). Moreover, some of the chalcone derivatives containing aromatic amines exhibited no effect against gram positive and gram negative bacteria (Shakhatreh *et al*., 2016).

Some of the chalcone analogues reflected insignificant effect against *S. aureus* except compound 4 due to the presence of nitro group. Our results are in line with Bag *et al.* 2013 who reported that the chalcone having thiophene aromatic ring showed significant antibacterial activity. Some of the chalcone amine derivatives showed no activity and one derivative showed insignificant activity against *S. aureus*.

Chalcone derivative 5, 6 and 9 displayed moderate activity against both bacteria tested in this study. Some different results showed that quinolone derivatives containing pyrazole showed potent antibacterial activity (Siddiqui *et al*., 2011). It is also reported that chalcone with rhodanine-3 acetic acid showed strong antibacterial activity (Chen *et al*., 2013).

Similarly its compounds like 3 and 6 showed moderate activity against *C. albicans* because of the presence of methoxy group. Our findings are compatible to the report of Yin *et al*., (2014) who described that some of the homo isoflavanoids showed moderate zone of inhibition against microorganisms. Inamullah *et al*. (2017) also reported that novel chalcones derivatives such as Colucins and Colucones exhibited moderate toxicity on *C. albicans*. Similarly the analogues 8 and 9 exhibited no toxicity on *C. albicans* due to the presence of nitro- and chloro- groups.

Our results showed that the aurone derivatives 3 and 4 were inactive against *S. aureus, C. albicans* and *E. coli* respectively because of the

presence of methoxy group. Our findings are compatible to the report of Jagtap *et al*. (2016) who described that fluorinated aurones showed no toxicity on *S. aureus, E. coli* and *C. albicans*. It is also reported that some of the benzocumarines and benzochromone displayed no activity against the microbes (Kolancilar *et al*., 2008).

Some of the aurone derivatives such as 1 and 2 displayed moderate activity against *C. albicans* while derivative 2 was found against *S. aureus*. Our findings are compatible to the findings of Siddiqui *et al*., (2016) who reported that novel aurones which are produced by the oxidative cyclization of chalcones showed moderate toxicity on *E. coli*. It is also reported that some of the compounds of benzocumarines reflected moderate effect against *S. aureus* (Kolancilar *et al*., 2008). Konieczy *et al*., (2007) explained that aurone derivatives of axathioline joined chalcones showed moderate activity against *S. aureus*.

Aurone analogue 2 showed very significant activity against *S. aureus* and *E. coli*. Our findings are compatible to the report of Ashok *et al*., (2017) who described that aurone derivatives such as arylidine exhibited effective activity against *S. aureus, C. albicans* and *E. coli*. Compound (Z)-2-(2-methoxybenzylidene) benzofuran-3(2H)-one and (Z)-2-(3-methoxybenzylidene) benzofuran-3(2H)-one showed insignificant activity against *E. coli*.

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