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Antimicrobial Activities of Some Synthetic Flavonoids

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Abstract: *In an attempt to study the biological activities of flavonoids, a flavone, flavanone and series of chalcones were synthesized and characterized by IR and ^1H NMR and elemental analysis. All the targeted compounds were screened for their antibacterial activity against Bacillus cereus, Enterococcus faecalis, Kleibsiella pneumonia and Pseudomonas aeroginosa and antifungal activity against Aspergillus fumigatus and Candida glabrata. Only 2'-hydroxy-4-chlorochalcone **(3)** and 2'-hydroxy-4-nitrochalcone **(4)** showed moderate antimicrobial activity against the Gram-positive bacteria with MIC 125 µg/ml and a very weak antifungal activity with MIC 250 µg/ml. All other compounds displayed very weak activities against all the tested microorganisms.*

Keywords: *Flavonoids, Chalcones, Flavone, Flavanone, antibacterial and antifungal.*

I. Introduction

Antimicrobial is a general term for natural or synthetic compounds which at certain concentrations inhibit the growth of or kill microorganisms completely. The term antimicrobials are collective for antiviral, antibacterial, antifungal and antiprotozoal. Due to the rapid development of microorganism's resistance to antimicrobial agents, it is necessary to discover compounds both naturally and synthetic of the new antimicrobial agents to help in the battle against pathogenic microorganisms. Much research has been carried out with the aim to discover the therapeutic values of flavonoid derivatives.

Flavonoids are poly-phenolic compounds that are ubiquitous in nature and have been reported to possess various biological activities some of which include; antimicrobial, antioxidant, antimalarial, cytotoxic, antidepressant, anti-inflammatory, anti HIV and anticancer [1–7]. Scientific studies involving pharmaceutical drug potencies of flavonoids are extensively examined in the past several years and are increasing [8]. Chalcones been the precursors of various biologically important heterocyclic compounds have a reactive α,β-unsaturated carbonyl group which was found to be responsible for their antimicrobial activities. The antimicrobial activities may be altered depending on the type and position of the substituent(s) on the aromatic rings [9]. Despite the successful report on the targeted compounds, their effect on the antibacterial and antifungal activities against the tested microorganisms has not been reported. However, this study focuses on the synthesis and biological evaluation of the compounds as antibacterial and antifungal agents and also the effect of the substituents on aromatic rings against the tested microorganisms.

II. Experimental

The melting points of the target compounds were measured and recorded using Leica Galen III Kofler micro melting points apparatus and were uncorrected. The ^1H (400 MHz) NMR experiments were recorded Chloroform ($CDCl_3$, purity 99.96%) on a Bruker Avance spectrometer with referenced against residual non-deuterated solvent [^1H NMR, $CDCl_3$ (7.27 ppm)]. Meanwhile, the Infrared (IR) was recorded on Perkin Elmer 1650 FTIR spectrophotometer as thin film KBr pellet for solid samples.

General Procedure for the preparation of Chalcones

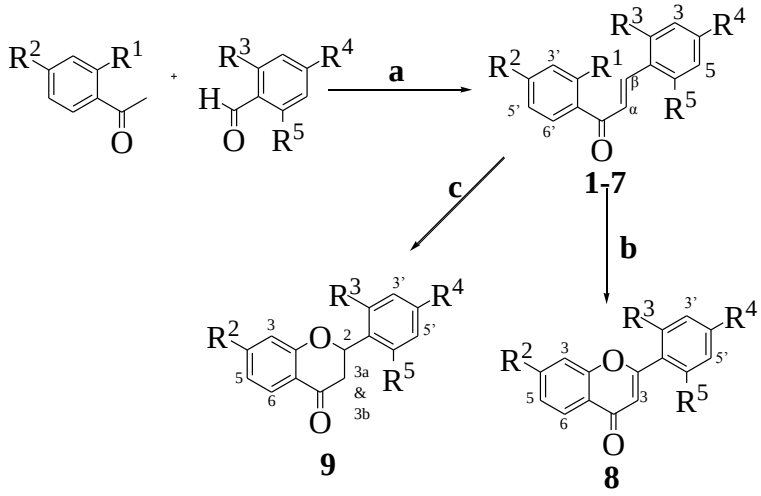
A mixture of substituted acetophenone (0.01mole) and substituted benzaldehyde (0.01mole) was stirred in ethanol and then sodium hydroxide solution (50%) was added till highly turbid solution was obtained. Completion of mixture was monitored by TLC. The mixture was kept overnight at room temperature and it was poured on crush ice and acidified with dilute hydrochloric acid. The precipitate obtained was washed with ethanol and purified by chromatographic technique and recrystallization from ethanol [10].

General Procedure for the preparation of Flavone

A mixture of substituted chalcone (0.01 mol) and I_2 (0.0078 mmol) in DMSO (6 ml) were refluxed for 45 mins and monitored using TLC. Water was added to cooled mixture and extracted with EtOAc. The organic extract was then washed with saturated NaS_2O_3 solution, followed by water and brine. It was then dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was then re-crystallized from ethanol to yield substituted flavone [11].

General Procedure for the preparation of Flavanone

A mixture of susbstituted chalcone (0.01 mol), MeOH (30 mL) and 10% HCl (5 ml) was refluxed for 60 mins. NaOAc was added to the mixture and further refluxed for 48 hrs. The progress of the reaction was monitored by TLC. Water was added to the cooled mixture and the organic layer was extracted with EtOAc, dried using $MgSO_4$, filtered and evaporated under reduced pressure. The residual yellow oil was purified using silica gel CC to afford substituted flavanone [12].



1. R^1= R^4H, R^2=OH, R^3=R^5=Cl **2.** R^1=OH, R^2=R^4=H, R^3=R^4=Cl **3.** R^1=OH, R^2=R^3=R^5=H, R^4=Cl
4. R^1=OH, R^2=R^3=R^5=H, R^4=NO_2 **5.** R^1=OH, R^2=R^3=R^5=H, R^4=NMe_2 **6.** R^1=OH, R^2=R^3=R^5=H, R^4=OMe
7. R^1=OH, R^2=*O*-prenyl, R^3=R^5=Cl, R^4=H **8.** R^2=R^4=H, R^3=R^5=Cl **9.** R^2=R^4=H, R^3=R^5=Cl

Scheme 1: Synthesis of chalcones, flavone and flavanone derivative. **(a):** NaOH, Eaton, stir 24 hrs; **(b)**: I_2, DMSO, reflux 2 hrs and **(c):** (i): 10% HCl, MeOH, reflux 60 mins; (ii): NaOAc, reflux 48 hrs.

Characterization of the Synthesized compounds

4′-Hydroxy-2,6-dichlorochalcone (1)

IR (ν cm^{-1}): 3340 (–OH), 1654 (C=O), 1613 (C=C alkene), 1599 and 1566 (C=C aromatic), 1226 (C-O) and 770 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (2H, d, *J*=8.4 Hz, H–3′ and H–5′), 7.23 (1H, t, *J*=8.0 Hz, H–4), 7.42 (2H, d, *J*=8.0 Hz, H–3 and H–5), 7.66 (1H, d, *J*=16.0 Hz, H–α), 7.85 (1H, d, *J*=16.0 Hz, H–β), 8.02 (2H, d, *J*=8.4 Hz, H–2′ and H–6′).

2′-Hydroxy-2,6-dichlorochalcone (2)

IR (ν cm^{-1}): 3435 (–OH), 1686 (C=O), 1645 (C=C alkene), 1580 and 1437 (C=C aromatic), 1307 (C–O) and 775 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (1H, ddd, *J*=2.0, 8.0 and 8.0 Hz, H–5′), 7.08 (1H, dd, *J*=2.0 and 8.0 Hz, H–3′), 7.26 (1H, dd, *J*=8.0 and 8.0 Hz, H–4), 7.43 (2H, d, *J*=8.0 Hz, H–3 and H–5), 7.55 (1H, ddd, *J*=2.0, 8.0 and 8.0 Hz, H–4′), 7.89 (1H, dd, *J*=2.0 and 8.0 Hz, H–6′), 7.85 (1H, d, *J*=16.0 Hz, H–α), 8.00 (1H, d, *J*=16.0 Hz, H–β), and 12.65 (1H, s, –OH).

2′-Hydroxy-4-chlorochalcone (3)

IR (ν cm^{-1}): 3446 (–OH), 1639 (C=O), 1579 (C=C alkene), 1564 and 1487 (C=C aromatic), 1205 (C–O alcohol) and 760 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (1H, ddd, *J*=1.6, 8 and 8 Hz, H–5′), 7.06 (1H, dd, *J*=1.6 and 8 Hz, H–3′), 7.45 (2H, d, *J*=8 Hz, H–3 and H–5), 7.54 (1H, ddd, *J*=1.6, 8 and 8 Hz, H–4′), 7.63 (2H, d, *J*=8 Hz, H–2 and H–6), 7.68 (1H, d, *J*=15.6 Hz, H–α), 8.00 (1H, d, *J*=15.6 Hz, H–β), 7.95 (1H, dd, *J*=1.6 and 8 Hz, H–6′) and 12.78 (1H, s, –OH).

2′-Hydroxy-4-nitrochalcone (4)

IR (ν cm^{-1}): 3447 (–OH), 1704 (C=O), 1645 (C=C alkene), 1607 and 1442 (C=C aromatic), 1541 and 1345 (N=O), 1197 (C–N) and 1104 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (1H, ddd, *J* = 1.6, 8.0 and 8.0 Hz, H–5′), 7.09 (1H, dd, *J*=1.6 and 8.0 Hz, H–3′), 7.58 (1H, ddd, *J*=1.6, 8.0 and 8.0 Hz, H–4′), 7.79 (1H, d, *J*=15.6 Hz, H–α), 7.85 (2H, d, *J*=8.0 Hz, H–2 and H–6), 7.94 (1H, d, *J*=15.6 Hz, H–β), 7.96 (1H, dd, *J*=1.6 and 8.0 Hz, H–6′), 8.32 (2H, d, *J*=8.0 Hz, H–3 and H–5), and 12.62 (1H, s, –OH).

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

IR (ν cm^{-1}): 3435 (–OH), 2919 (C-H sp^3), 1622 (C=O), 1599 (C=C alkene), 1520 and 1487 (C=C aromatic), 1177 (C–O) and 1035 (C–N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.09 (6H, s, 2 x CH_3), 6.74 (2H, d, *J*=8.8 Hz, H–3 and H–5), 6.95 (1H, ddd, *J*=1.6, 8.0 and 8.0 Hz, H–5’), 7.03 (1H, dd, *J*=1.6 and 8.0 Hz, H–3’), 7.47 (1H, ddd, *J*=1.6, 8.0 and 8.0 Hz, H–4’), 7.52 (1H, d, *J*=16.0, H–α), 7.62 (2H, d, *J*=8.8 Hz, H–2 and H–6), 7.93 (1H, d, *J*=16.0 Hz, H–β), 7.95 (1H, dd, *J*=1.6 and 8.0 Hz, H–6’), and 13.23 (1H, s, –OH).

2′-Hydroxy-4-methoxychalcone (6)
IR (ν cm^{-1}): 3422 (–OH), 1688 (C=O), 1622 (C=C alkene), 1623 and 1462 (C=C aromatic) and 1134 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (3H, s, OCH_3), 6.94 (1H, ddd, *J*=1.6, 8.0 and 8.0 Hz, H–4′), 6.97 (2H, d, *J*=8.8 Hz, H–3 and H–5), 7.03 (1H, dd, *J*=2.0 and 8.0 Hz, H–3′), 7.49 (1H, ddd, *J*=1.6, 8.0 and 8.0 Hz, H–5′), 7.56 (1H, d, *J*=15.2, H–α), 7.65 (2H, d, *J*=8.8 Hz, H–2 and H–6), 7.91 (1H, d, *J*=15.2 Hz, H–β), 7.94 (1H, dd, *J*= 2.0 and 8.0 Hz, H–6′) and 12.97 (1H, s, -OH).
2′-Hydroxy-4-O-prenyl-2,6-dichlorochalcone (7)
IR (ν cm^{-1}): 3445 (–OH), 3098 (C–H sp^2), 2952 (C–H sp^3), 1644 (C=O), 1598 (C=C alkene), 1506 and 1467 (C=C aromatic), 1232 (C–O) and 777 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (3H, s, H–4″), 1.83 (3H, s, H–5″), 4.58 (2H, d, *J*=6.8 Hz, H–1″), 5.48 (1H, t, *J*=6.8 Hz, H–2″), 6.50 (1H, d, *J*=2.4 and 8.8 Hz, H–5'), 6.52 (1H, d, *J*=2.4 Hz, H-3′), 7.22 (1H, dd, *J*=8.0 and 8.0 Hz, H–4), 7.41 (2H, d, *J*=8.0 Hz, H-3 and H–5), 7.76 (1H, d, *J*=8.8 Hz, H–6′), 7.79 (1H, d, *J*=15.6, H–α), 7.94 (1H, d, *J*=15.6 Hz, H–β) and 13.27 (1H, s, –OH).
2′,6′-Dichloroflavone (8)
IR (ν cm^{-1}): 1686 (C=O), 1645 (C=C alkene), 1681 and 1438 (C=C aromatic), 1311 (C–O) and 776 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (1H, s, H–3), 7.29 (1H, dd, *J*=1.6 and 8.0 Hz, H–3), 7.42 (2H, d, *J*=8.0 Hz, H–3′ and H–5′), 7.46 (1H, ddd, *J*=2.0, 8.0 and 8.0 Hz, H–5), 7.55 (1H, dd, *J*=8.0 and 8.0 Hz, H–4′), 7.73 (1H, ddd, *J*=2.0, 8.0 and 8.0 Hz, H–4) and 8.32 (1H, dd, *J*=1.6 and 8.0 Hz, H–6).
2',6'-dichloroflavanone (9)
IR (ν cm^{-1}): 2863 (C–H sp^3), 1693 (C=O), 1610 and 1463 (C=C aromatic), 1283 (C–O) and 762 (C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (1H, dd, *J*=2.4 and 12.8 Hz, vicinal H–2), 5.49 (1H, dd, *J*=2.4 and 15.6 Hz, geminal H–3a), 6.09 (1H, dd, *J*=12.8 and 15.6 Hz, geminal H–3b), 7.06 (1H, dd, *J*=1.6 and 8 Hz, H–3), 7.12 (1H, ddd, *J*=1.6, 8 and 8 Hz, H–5), 7.29 (1H, dd, *J*=8.0 and 8.0 Hz, H–4′), 7.43 (2H, d, *J*=8.0 Hz, H–3′ and H–5′), 7.57 (1H, ddd, *J*=1.6, 8.0 and 8.0 Hz, H–4) and 7.95 1H, dd, *J*=1.6 and 8.0Hz, H–6).

ANTIMICROBIAL ACTIVITY

Test Microorganism

For bacteria; *Bacillus cereus* (ATCC11778), *Enterococcus faecalis* (ATCC19433) (Gram-positive), *Kleibsiella pneumonia* (ATCC13883) and *Pseudomonas aeroginosa* (ATCC9027) (Gram-negative) and two fungi; *Aspergillus fumigatus* (ATCC204305) and *Candida glabrata* (ATCC2001) were purchased from Mutiara Scientific, Cheras, Kuala Lumpur, Malaysia. The strains were grown on nutrient agar (NA) (Oxoid, Italy) for the bacteria, and sabouraud dextrose agar (SDA) for fungi.

Disc diffusion

Antimicrobial activity of the chalcones, flavone and flavanone were determined by [13, 14]. The suspension (400 µL) of the test bacteria and fungi were spread on the nutrient agar (NA) and sabouraud dextrose agar (SDA) respectively. The disc (6 mm diameter) impregnated with 10 µL of the target compounds and DMSO (negative control) was placed on the inoculated agar, which was incubated for 24 h at 37°C (for bacteria) and 48 h at 30^0C (for fungi). Streptomycin sulfate (10 µg/mL) and nystatin (100 IU) were used as the positive controls for bacteria and fungi respectively. Clear inhibition zones around the discs indicated the presence of antimicrobial activity. All tests and analyses were carried out in triplicate and recorded.

Minimum inhibitory concentration (MIC)

The MIC was determined by the broth micro dilution method using 96-well micro-plates [13, 14]. The inoculate of the microbial strains was prepared from 24 h broth cultures and suspensions were adjusted to 0.5 McFarland standard turbidity. Each sample (1.0 mg) was dissolved in DMSO (1 mL) to obtain 1000 µg/mL stock solution. A number of wells were reserved in each plate for positive and negative controls. Sterile broth (100 µL) was added to the well from row B to H. The stock solutions of samples (100 µL) were added to the wells in rows A and B. Then, the mixture of samples and sterile broth (100 µL) in row B was transferred to each well in order to obtain a twofold serial dilution of the stock samples (concentration of 1000,500, 250, 125, 62.5, 31.3, 15.6 and 7.8 µg/mL). The inoculums (100 µL) were added to each well and a final volume 200 µL was obtained in each well. Streptomycin sulfate for bacteria and nystatin for fungi were used as positive controls. Plates were incubated at 37°C for 24 h. Microbial growth was indicated by the presence of turbidity and a pellet at the bottom of the well as shown in.

III. Results And Discussion

Chemistry

The synthetic approach to the targeted compounds was illustrated in scheme 1. A mixture of substituted acetophenone and substituted aromatic aldehyde was stirred in ethanol and then sodium hydroxide solution was added drop wise until a highly turbid solution is obtained. The mixture was kept overnight at room temperature and it was poured on crush ice and acidified with dilute hydrochloric acid yielded substituted chalcone. Furthermore, the flavone was obtained by cyclisation in the presence of iodine in DMSO as catalyst at room temperature while the flavanone was obtained using NaOAc in MeOH. The structures of the compounds **(1-9)** were ascertained by spectral parameters (IR and NMR) as well as the physical data which were recorded in **Table I**. Among the chalcones, compound **1** displayed higher percentage yield followed by compound **5, 4, 7, 3, 2** and **6.** This is probably due to the purification techniques employed as compounds **1**, **5** and **4** were purified by recrystallization technique using appropriate solvent while compounds **7**, **3**, **2** and **6** were purified by column chromatographic technique. The IR spectrum of 2'-hydroxy-2,6-dichlorochalcone **(2)** showed broad stretching band at 3435 cm^{-1} attributed to chelated –OH together with a strong stretching absorptions of C=O and C=C alkene at 1686 cm^{-1} and 1645 cm^{-1} respectively. The stretching absorptions at 1580 cm^{-1} and 1437 cm^{-1} were ascribed to the C=C aromatic, followed by the C–O alcohol absorption at 1307 cm^{-1}. The absorption band for C-Cl was observed at 775 cm^{-1}.The ^{1}H NMR spectra displayed the presence of two sets of doublet signals each resonated at δ 7.85 (1H, d, *J*=16 Hz), and 8.00 (1H, d, *J*=16 Hz) corresponding to two *trans*-coupled olefinic protons, H-α and H-β. This proved that condensation of 2-hydroxyacetophenone and 2,6-dichlorobenzaldehyde had successfully occurred. The ^{1}H NMR also showed the resonance of aromatic ring A protons at δ 6.96 (1H, ddd, *J*=2, 8 and 8 Hz), 7.08 (1H, dd, *J*=2 and 8 Hz), 7.55 (1H, ddd, *J*=2, 8 and 8 Hz), and 7.89 (1H, dd, *J*=1.6 and 8 Hz) corresponding to H–5', H–3', H–4', and H–6' respectively. The aromatic protons of ring B were also observed at δ 7.26 (1H, dd, *J*=8 and 8 Hz), 7.43 (2H, d, *J*=8 Hz) corresponding to H–4, H–3, and H–5 respectively. Moreover, a downfield signal at 12.65 (1H, s) corresponding to chelated OH.

Table I: Physical data of the synthesized chalcones, flavone and flavanone.

Compound Codes	M.P. (°C)	M.P. [Lit.]	Yield (%)	R_f value	Color
1	124-126	190-192 [8]	87.4	0.62	Yellow
2	66-68	68-70 [5]	62.1	0.79	Yellow
3	144-146	149-150 [15]	65.9	0.72	Yellow
4	102-104	104-106 [5]	75.1	0.81	Yellow
5	58-60	55 [16]	76.0	0.59	Orange
6	86-90	92-93 [17]	61.8	0.60	Yellow
7	96-98	101-102 [18]	74.5	0.83	Yellow
8	142-144	144-146 [19]	64.9	0.75	White
9	144-146	148-149 [20]	56.9	0.60	White

Antimicrobial Activity

All the targeted compounds were evaluated as antimicrobial agents against *Bacillus cereus*, *Enterococcus faecalis*, *Kleibsiella pneumonia*, *Pseudomonas aeroginosa* and antifungal activity against *Aspergillus fumigatus* and *Candida glabrata*. The compounds that showed positive activity were further tested using the minimum inhibitory concentration (MIC) to determine the concentration at which the compounds show higher activity. Among all the screened compounds, only compounds **(3)** and **(4)** displayed moderate activity against the Gram-positive bacteria producing a zone inhibition of 16 and 14 mm against *E. faecalis* and 12 and 12 mm against *B. cereus* respectively both with MIC 125 µg/ml as shown in **Table II**. Moreover, compounds **(3)** and **(4)** exhibited weak activity against the Gram-negative fungi each with 9 and 7 mm inhibition zone against *K. pneumoniae* and 7 and 8 mm against *P. aeroginosa* both with MIC of 500 µg/ml. Compounds **(1)**, **(2)**, **(7)**, **(8)** and **(9)** were inactive against all the tested microorganisms and their MIC results showed high turbidity at various concentrations justifying their inactivity. Compounds **(3)**, **(4)**, **(5)** and **(6)** showed very weak activity against *A. fumigatus* and *C. glabrata* with a very low zone of inhibition and high MIC compared to the standard control (Nystasin) as shown in **Table II**. A careful analysis of the data shows compounds with $–OCH_3$ group incorporated causes loss of activity [15]. Moreover, even though the α,β-unsaturated carbonyl group is found to be responsible for the antimicrobial activity [15], compounds with more than one electron withdrawing group such as chlorine atom on ring B of the chalcone skeleton causes loss of antimicrobial activity. The detail antimicrobial activities of the target compounds are recorded in **Table II.**

Table II: Zone inhibition and Minimum inhibitory concentration (MIC) of the synthesized compounds.

Cmpd	Assay	Antibacterial				Antifungal	
codes		*E.f.*	*B.s.*	*K.p.*	*P.a.*	*A.f.*	*C.g.*
1	DD	-	-	-	-	-	-
	MIC	-	-	-	-	-	-
2	DD	-	-	-	-	-	-
	MIC	-	-	-	-	-	-
3	DD	16±0.50	12±0.46	9±0	7±0.52	6±0	6±0.43
	MIC	125	125	500	500	250	250
4	DD	14±0.53	12±0.55	7±0.40	8±0.22	7±0.43	6±0.45
	MIC	125	125	500	500	250	250
5	DD	9±0	7±0.42	6±0.12	7±0	6±0.40	6±0.32
	MIC	300	300	500	>500	>500	>500
6	DD	8±0.43	8±0.45	6±0.42	8±0.43	6±0	7±0.21
	MIC	350	300	350	350	>500	350
7	DD	-	-	-	-	-	-
	MIC	-	-	-	-	-	-
8	DD	-	-	-	-	-	-
	MIC	-	-	-	-	-	-
9	DD	-	-	-	-	-	-
	MIC	-	-	-	-	-	-
SS	DD	24±0	22±0	24±0	26±0		
	MIC	7.8	7.8	7.8	7.8		
NS	DD					17±0	17±0
	MIC					15.6	15.6

Zone of inhibition measured in mm: *Enterococcus faecalis (E.f.), Bacillus cereus (B.s), Kleibsiella pneumonia (K.p.), Pseudomonas aeroginosa (P.a.), Aspergillus fumigatus (A.f.) and Candida glabrata (C.g.)*
SS: Streptomycin Sulfate, NS: Nystatin
-: No activity; result are means of three replicates. Diameter of the well (6mm)

IV. Conclusion

In the present work, a flavone, flavanone and a series of chalcones were successfully synthesized and characterized by spectral studies. All the synthesized compounds were evaluated for their antimicrobial activities against *B. cereus, E. faecalis, K. pneumonia, P. aeroginosa, A. fumigatus and C. glabrata* microorganisms by disc diffusion method. 2'-hydroxy-4-chlorochalcone **(3)** and 2'-hydroxy-4-nitrochalcone **(4)** showed moderate antimicrobial activity against the Gram positive bacteria with MIC 125 µg/ml and a very weak antifungal activity with MIC 250 µg/ml. Other compounds were weakly active or completely inactive against all the tested microorganisms with a very low zone of inhibition and high MIC compared to the standard control and their MIC results showed high turbidity at various concentrations justifying their inactivity.

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