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MICROWAVE- ASSISTED SYNTHESIS OF NOVEL CHALCONE DERIVATIVES AND STUDYING OF SOME OF THEIR ANTIMICROBIAL ACTIVITIES

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ABSTRACT

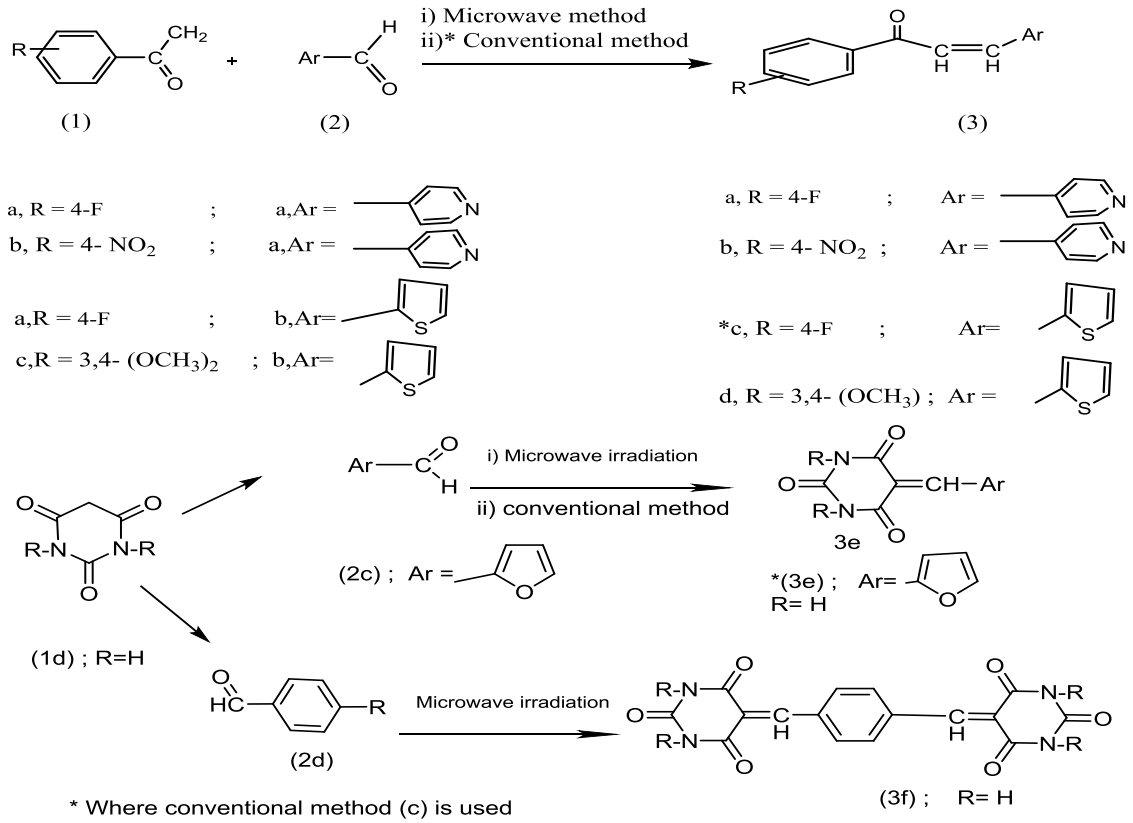
A novel approach for the synthesis of a series of chalcones (3a-f) by the reaction of acetophenones (1a-c) with different aromatic aldehydes (2a-c) as well as barbituric acid (1d) with terphthalaldehyde (2d) under thermal solvent-free conditions. All the synthesized compounds were characterized using elemental analysis and spectral data (IR,^{1}H-NMR, ^{13}C-NMR, and mass spectrometry). The synthesized compounds were tested for their antimicrobial activity by the disk diffusion assay against Gram-positive, Gram-negative strains of bacteria as well as fungi. The investigation of antimicrobial and antifungal screening revealed that most compounds showed potent antimicrobial and five antifungal activities respectively. Among the screened compounds (3a-c and 3f) showed more potent activity (IZ) nearly to that of standard antibiotics Chloramphenicol, Gentamycin, Sxt and Ketonazol.

KEYWORDS: Thermal solvent-free conditions, Green chemistry, Chalcones, Antimicrobial activity.

INTRODUCTION

The discovery of new antimicrobial agents with simpler structure and more effective mode of action remains the primary goal of medicinal chemistry scientists, for the treatment of many infections caused by microbes and fungi; since there is an increasing bacterial resistance caused by microorganisms to classical antimicrobial agents.[18] Chalcones or 1, 3-diaryl/heteroaryl-2-propen-1–ones consist of open–chain flavonoids in which the two aromatic rings are joined by a three carbon α,β-unsaturated carbonyl system. The presence of a reactive α,β- unsaturated keto function in chalcones is found to be responsible for their various pharmacological activities such as antioxidants,[25] anti- infective, anti-leishmanial,[23] anticancer,[17] anti-inflammatory,[5] anti-fungal,[16] and, anti-bacterial.[2] Chalcones isolated from natural products were known to possess several important activities,[8] recent reports indicated the importance of chalcones as anticancer,[11] antimitotic.[27] Encouraged by these findings **chalcones (3a-f)** were synthesized using both microwave irradiation method as a green approach and by conventional method then were screened against pathogenic microbes. Microwave heating offers several advantages over conventional techniques. Recently, microwave – assisted technique for organic synthesis is synonymous with green chemistry.[3,9,12,20]

Chalcones are readily synthesized by Claisen-Schmidt reaction in basic /or acidic medium in polar solvents either under thermal or cooling conditions. Due to the reactivity of the formyl group in heterocyclic aldehydes, as well as the versatile biological activity of barbituric acid,[1] herteroaryl chalcones (3a-f) were synthesized by the reaction of substituted acetophenones (1a-c) with heteroaryl aldehydes (2a, b), as well as barbituric acid (1d) with furaldehyde (2c), and /or terphalaldehyde (2d) under microwave, solvent- free irradiation or conventional heating as shown in Scheme 1.



Scheme 1: Synthesis protocol of target compounds (3a -f).

Chalcones' structure generates pharmacomolecules active agents and the presence of the α,β- unsaturated carbonyl chain allows for electronic delocalization of a free-radical position via extensive mesomeric effect and free radical stabilization through the so-called captodative effect, which is based on the fact that carbocations are stabilized by electron-donating substituents while carbanions are stabilized by electron-withdrawing substituents and radicals gain stability when flanked by a push-pull system.(Fig.1).

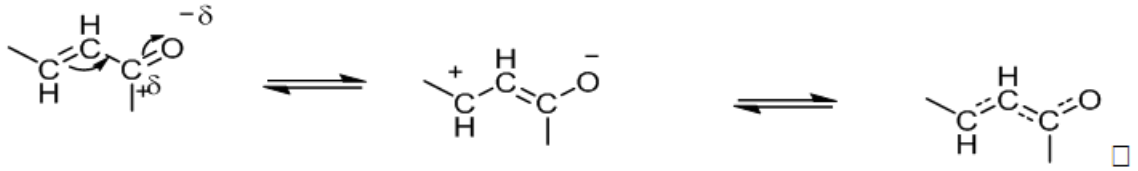


Fig. 1: Captodative effect of α, β- unsaturated carbonyl chain.

The present study is an attempt to investigate whether the substitution of various groups can change or improve the potency of the chalcone derivatives screened for their reactivity against a variety of Gram- positive or Gram negative as well as fungi.

1. Chemistry

Materials and Methods

Microwave synthesis was performed using Gem Microwave system. Melting points were determined on (Pyrex capillary tubes) Gallen Kamp apparatus and were uncorrected. Infrared spectra were recorded with a Thermo Nicolet Nexus 470FT-IR spectrometer in the range 4000-400 cm^{-1}, using potassium bromide disks. ^{1}H-NMR spectra and ^{13}C-NMR spectra were run on a Varian Gemini 400and 200MHz FT NMR spectrometer in DMSO-d_6; chemical shifts were recorded in δ (ppm) units. Mass spectra were run on a Shimadzu LCMS-QP 800-MS. Analytical data were obtained using Perkin-Elmer 2400II series CHN Analyzer. The reagents used were purchased from Aldrich and Merk and were used without further purification.

General procedure for the synthesis of 3- aryl- 1-(substituted aryl) propen-1- one derivatives (3a-f)

Microwave method (method A)

A mixture of 4- fluoro-acetophenone (1.4 g; 0.01 mol), or 4-nitro-acetophenone (1.7g; 0.01 mol) and/or 3,4-dimethoxy acetophenone (1.8 g; 0.01mol) and the aromatic aldehydes namely, isonicotinaldehyde (1.07g; 0.01mol) and/or thiosphene -2-aldehyde (1.1g; 0,01 mol) were dissolved in 2mL of absolute ethanol containing catalytic amount of sodium hydroxide (0.04g; 0.01mol), was irradiated for the appropriate time (Table1).

In a similar manner, equimolar mixture of barbituric acid (1d)(1.3g; 0.01mol) and furfural(2c)(0.96g; 0.01mol) in 2mL of absolute ethanol containing the catalytic amount of sodium hydroxide(0.04g; 0.01mol) was irradiated for the appropriate time (Table1).

Also, a mixture of barbituric acid (1d) (2.6g; 0.02mol) and terphthaldehyde (2d) (1.3g; 0.01mol) in 2mL of absolute ethanol containing the catalytic amount of sodium hydroxide (0.04g; 0.01mol) was irradiated for the appropriate time (Table1).

Conventional Method (Method B)

A mixture of the acetophenone derivatives(1a – 1c) namely, 4-fluoro-acetophenone (1.4g;0.01mol),4-nitro-acetophenone(1.7g;0.01mol) and 3,4-dimethoxy acetophenone (1.8g; 0.01mol) were dissolved in 30 mL of absolute ethanol, cooled and stirred well for 1hr then ethanolic aqueous solution of sodium hydroxide (5mL,10%) was added dropwise while stirring and cooling. Then a solution of the appropriate aldehydes namely, isonicotin aldehyde (2a) and/or thiophene-2-aldehyde (2b) (0.01mol) for each one dissolved in 5mL of absolute ethanol and added dropwise while stirring to the acetophenone derivatives. After addition, the reaction mixture was stirred for further 2hr, and then left to cool overnight. The product that separated was collected by filtration, washed well with dilute ethanol and recrystallized from the proper solvent as **3a-c** and d respectively (Table1).

Table 1: The differences in yield and time between the microwave and classical methods in synthesis of 3-aryl-1-(substituted aryl) propen-1-one (3a-f).

Entry	Product	Microwave		Conventional A		Conventional B	
		Time[a]	Yields[b] %	Time[a]	Yields[b] %	Time[a]	Yields[b] %
1	3a	3min	87	2hr	72%	-	-
2	3b	3min	89	2hr	76	-	-
3	3c	-	-	-	-	8hr	76
4	3d	3min	90	2hr	71	-	-
5	3e	-	-	-	-	8hr	69
6	3f	3min	90	-	-	-	-

[a] Reaction progress monitored by TLC

[b]All yields refer to recrystallized products

Conventional Method (Method C)

A mixture of the acetophenone derivative 4-fluoro-acetophenone(1a) (1.4g; 0.01mol) and thiosphene-2-aldehyde(2b) (1.1g ;0,01 mol) were dissolved in 30 mL of absolute ethanol containing catalytic amount of sodium hydroxide (0.04g; 0,01mol) dissolved in 5mL of water, and the mixture was refluxed for 8 hrs. The product was collected by filtration, washed well with dilute ethanol and recrystallized from the proper solvent as **(3c)** (Table1).

A mixture of barbituric acid (1d)(1.3g,0.01 mol) and 2-furaldehyde(2c)(0.9g,0.01 mol) in 30 mL of absolute ethanol containing 5mL (10%) aqueous sodium hydroxide was refluxed 8 hrs then filtered off, left to cool and the product that separated was collected, washed well with dilute ethanol and recrystallized as **(3e)**(Table1).

RESULTS AND DISCUSSION

A) Chemistry

3-(4-Pyridyl)-1-(4- fluorophenyl) propen-1-one (3a): M.p. 180°C; IR (KBr, cm^{-1}) γ 1674(C = O); γ 1615(C = N); γ 1597(C = C). ^{1}H-NMR (400MHz, DMSO-d_6): δ 4.21(d, 1H, CHα); δ2.38 (d, 1H, CHβ); δ 7.61- 7.78(m, 8H, Ar-H). ^{13}C-NMR (100MHz, DMSO-d_6): δ117.1(C3), 117.9(C5), 124.1(C`2), 132.1(C2), 132.3(C6), 129.9(CHα=), 134.1(C1- C), 145.3(CHβ), 144.5(C`1), 150.1(C`3), 190.1(C=O). LC-MS:m/z 225.55 for $M1^{+\cdot}$ Anal. Calcd. For: $C_{14}H_{10}ONF$(225); required C,74.66; H,4.44; N, 6.22; F,7.55 Found : C,74.64; H, 4.68; N, 6.22; F, 7.54%.

3-(4-Pyridyl)-1-(4- nitrophenyl) propen-1-one (3b): M.p. 210°C; IR (KBr, cm^{-1}) γ 1670(C = O); γ 1604(C = C). ^{1}H-NMR (400MHz, DMSO-d_6): δ4.39 (d, 1H, CHα); δ 3.64 (d, 1H, CHβ)); δ7.72- 7.77(m, 8H, Ar-H). ^{13}C-NMR (100MHz, DMSO-d_6):δ2x123.7(2xC`2), δ2x124.9(C2,C6),128.1(CHα), 2x131.8(C3,C5), 144.7(C4),145.1(CHβ),145.3(C`1), 2x149.9(C`3, C`5), 190.9(C=O). LC-MS:m/z254.61$M1^{+\cdot}$. Anal. Calcd. For: $C_{14}H_{10}O_3N_2$ (254): required C, 66.14; H, 3.39; N, 11.02, Found: C, 66.20; H, 3.94; N, 11.1%.

3-(2-Thienyl)-1-(4- fluorophenyl) propen-1-one (3c): M.P. 60°C; IR (KBr, cm^{-1}) γ 1673(C = O); γ1606(C=C). ^{1}H-NMR(400MHz,DMSO-d_6): δ4.23(d,1H,CHα); δ2.41(d,1H,CHβ); δ7.71-7.74 (m,8H,Ar-H). ^{13}C-NMR(100MHz,DMSO-d_6):δ2x116.6 (C3,C5), 128.1(CHα),128.7(C`4), 129.9(C`3), 131.1(C`5), 2x132.1 (C2,C6), 133.9 (C1), 135.1(CHβ), 141.1(C2), 190.7 (C=O). LC-MS: m/z 230 $M1^{+\cdot}$. Anal. Calcd. For: $C_{13}H_9SOF$(230): required C,67.82; H,3.91; S, 13.91; F,7.39 Found : C,67.90 ; H, 3.90; S, 13.92; F, 7.40%.

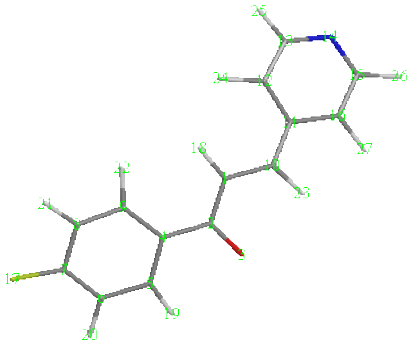
(E)-1-(3, 4-dimethoxyphenyl)-3-(thiophen-2-yl) prop-2-en-1-one (3d): M.p. 114°C: IR (KBr, cm^{-1}): γ1667 cm^{-1}(C=O), γ1606 cm^{-1}(C=C). ^{1}H-NMR (400MHz, DMSO-d_6): δ2x3.81(2xS, 2x3H,2xOCH_3), 7.17,7.2(m,2x1x1H, Ar-H), 7.61(d, 1H, CHα), 7.81(d,1H,CH-Ar), 7.91(d,1H,CH-Ar) 7.93(d, 1H,CHβ). ^{13}C-NMR

(100MHz, DMSO-d_6):δ2x56.3 (2xOCH_3), 108.3(C2), 112.9(C5), 124.1(C5), 124.6(C6), 127.9(CHα), 128.9(C3), 129.9(C2), 130.7(C5), 134.9(CHβ), 141.3(C1),2x152.6(2xCO)189.9(C=O).LCMS:m/z274.07$M1^{+\cdot}$.Anal.Calcd.For:$C_{15}H_{14}SO_3$ (274): required C, 65.67; H, 5.14; S, 11.69. Found C, 65.69; H, 5.20; S, 11.71%.

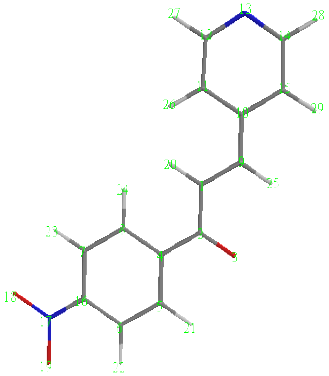
5-[(Furan -2-yl methylene)] pyrimidine- 2,4,6-(1H, 3H,5H)– trion(3e): M.p. 189°C; IR (KBr, cm^{-1}): γ NH 3331, 3251 cm^{-1}; γ 1678 cm^{-1} (C = O); γ 1604 (C = C). ^{1}H-NMR (400MHz, DMSO-d_6):δ 4.85 (s,1H,CHβ); δ 6.95- 8.29(m, 3H,Ar-H); δ 10.91, 11.11(2xs, 2x 1H, 2xNH)(D_2O exchangeable). ^{13}C-NMR (100MHz, DMSO-d_6): δ110.1 (CH3), 112.9 (CH4), 124.9(C5), 144.2(CH5), 148.3(CHβ), 150.1(C2), 151.7(C = O), 163.3 (C = O), 163.5(C = O). LC-MS: m/z 256.33 $M1^{+\cdot}$. Anal. Calcd. For: $C_9H_6O_4N_2$ (206): required C, 51.92; H, 2.91; N, 13.59 Found: C, 52.1; H, 2.90; N, 14%.

5,5`-(1,4-Phenylenebis(methaneylylidene) bis (pyrimidine-2,4,6-(1H,3H,5H)- trione(3f): M.p. 231°C; IR (KBr, cm^{-1}): γ NH 3337, 3241 cm^{-1}; γ 1679, 1653cm^{-1} (C = O); γ 1616,1605 (C = C). ^{1}H-NMR (400MHz, DMSO-d_6):δ 7.04, 7.051 (2xs,2x1H,2x CH=C); δ 7.31 - 8.59(m, 4H,Ar-H); δ 11.08, 11.09,11.29, 11.31(4xs, 4x 1H, 4xNH)(D_2O exchangeable). ^{13}C-NMR (100MHz, DMSO-d_6): δ117.9 (C = CH), 127.1, 127.9 (2xCH),136.1, 138.2(2xCH), 150.9(2xC= O),166.3(2xC= O), 168.9(2xC= O). LC-MS: m/z 354.66 $M1^{+\cdot}$. Anal. Calcd. For: $C_{16}H_{10}O_6N_4$ (354): required C, 54.23; H, 2.82; N, 15.81 Found: C, 54.1; H, 2.90; N, 15.91%.

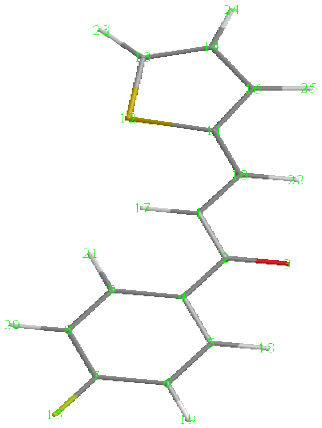
A study of data for the minimized geometry and the 3D geometrical structure of the synthesized **chalcones (3a-f)**; (Figs. 2) and Tables(2,3) showed that the atomic charges have been affected by the presence of the ring substituents, either in ring A or ring B in the chalcone moiety.



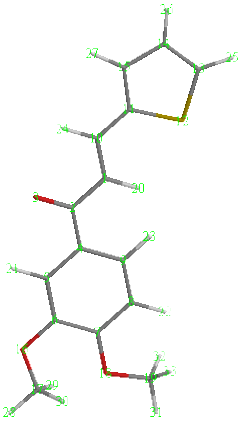
(3a)



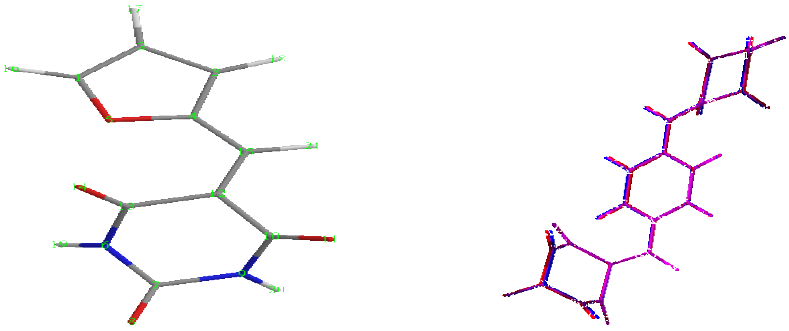
(3b)



(3c)



(3d)



(3e) **(3f)**

Fig. 2: The 3D structure of chalcones (3a-f).

Table 2: The atomic charges of chaconne (3a-f).

Entry	Atom	Charge(Huckel)	Atom	Charge(Huckel)	Atom	Charge(Huckel)
3a	C(1)	-0.0732985	C(11)	0.0634676	H (21)	0.0299269
	C(2)	0.402183	C(12)	-0.0397605	H(22)	0.0194725
	O(3)	-0.638068	C(13)	0.118991	H(23)	0.0176918
	C(4)	-0.00825099	N(14)	-0.180813	H(24)	0.00795132
	C(5)	-0.0107903	C(15)	0.131572	H(25)	-0.00168359
	C(6)	-0.080582	C(16)	-0.0228261	H(26)	-0.0256168
	C(7)	0.389787	F(17)	-0.173811	H(27)	-0.00149148
	C(8)	-0.0934564	H(18)	0.0320413		
	C(9)	-0.001161125	H(19)	0.034051		
	C(10)	0.0828019	H(20)	0.0216724		
3b	**Atom**	**Charge(Huckel)**	**Atom**	**Charge(Huckel)**	**Atom**	**Charge(Huckel)**
	C(1)	-0.0826042	C(11)	-0.0633248	H (21)	0.0214644
	C(2)	0.395976	C(12)	0.117686	H(22)	0.0229194
	O(3)	-0.611845	N(13)	-0.229133	H(23)	0.0227273
	C(4)	-0.063704	C(14)	0.119908	H(24)	0.0326923
	C(5)	-0.00785774	C(15)	-0.0522367	H(25)	0.0176152
	C(6)	-0.013975	C(16)	0.125954	H(26)	0.0334305
	C(7)	0.0131155	N(17)	1.27082	H(27)	0.00778754
	C(8)	-0.0173691	O(18)	-0.741364	H(28)	0.00793622
	C(9)	-0.0976233	O(19)	-0.741115	H(29)	0.0219889
	C(10)	0.0954468	H(20)	0.0440781		
3c	**Atom**	**Charge(Huckel)**	**Atom**	**Charge(Huckel)**	**Atom**	**Charge(Huckel)**
	C(1)	-0.174531	C(10)	0.0900975	H(19)	0.0290085
	C(2)	0.371517	C(11)	-0.0570805	H(20)	0.0288019
	O(3)	-0.710698	S(12)	0.732102	H (21)	0.0322684
	C(4)	-0.0313486	C(13)	-0.155255	H(22)	0.0200379
	C(5)	0.00057359	C(14)	-0.17338	H(23)	0.0274035
	C(6)	-0.130686	C(15)	-0.179897	H(24)	0.0248869
	C(7)	0.410549	F(16)	0.0935599	H(25)	0.022132
	C(8)	-0.132273	H(17)	0.037189		
	C(9)	-0.0089291	H(18)	0.021071		
3d	**Atom**	**Charge(Huckel)**	**Atom**	**Charge(Huckel)**	**Atom**	**Charge(Huckel)**
	C(1)	-0.17285	S(12)	0.730097	H (23)	0.0321764
	C(2)	0.365699	C(13)	-0.156377	H(24)	0.0200406
	O(3)	-0.713988	C(14)	-0.174043	H(25)	0.0274035
	C(4)	-0.0229533	C(15)	-0.181725	H(26)	0.0248872
	C(5)	-0.127854	O(16)	-0.204791	H(27)	0.022132
	C(6)	0.208267	C(17)	0.0901601	H(28)	0.0168028
	C(7)	0.22334	O(18)	-0.152374	H(29)	0.0258526
	C(8)	-0.140488	C(19)	0.0985477	H(30)	0.0258957
	C(9)	-0.0654033	H(20)	0.0371907	H(31)	0.0221311
	C(10)	0.0841657	H(21)	0.024958	H(32)	0.0246698
	C(11)	-0.0568598	H(22)	0.0406168	H(33)	0.0246716

	Atom	Charge(Huckel)	Atom	Charge(Huckel)		
3e	C(1)	0.0808841	C(12)	-0.053023		
	C(2)	-0.162005	C(13)	0.542037		
	C(3)	-0.199153	O(14)	-0.620236		
	C(4)	0.214226	C(15)	-0.0680084		
	O(5)	0.0447822	H(16)	0.0183287		
	N(6)	-0.0242878	H(17)	0.026882		
	C(7)	0.634761	H(18)	0.0247532		
	O(8)	-0.622503	H(19)	0.117755		
	N(9)	-0.022703	H(20)	0.117615		
	C(10)	0.534184	H (21)	0.0250171		
	O(11)	-0.609308				
3f	**Atom**	**Charge(Huckel)**	**Atom**	**Charge(Huckel)**	**Atom**	**Charge(Huckel)**
	N(1)	-0.0290273	N(13)	-0.0843862	C(25)	-0.0122437
	C(2)	0.634163	C(14)	0.521624	C(26)	-0.0852071
	O(3)	-0.62342	O(15)	-0.601079	H(27)	0.117738
	N(4)	-0.0349751	C(16)	-0.0129293	H(28)	0.117563
	C(5)	0.533123	C(17)	0.569528	H(29)	0.118478
	O(6)	-0.608164	O(18)	-0.593661	H(30)	0.118659
	C(7)	-0.0942202	C(19)	-0.0881339	H(31)	0.0285318
	C(8)	0.535783	C(20)	-0.0509236	H(32)	0.0207213
	O(9)	-0.586898	C(21)	-0.0475484	H(33)	0.0284316
	N(10)	0.103333	C(22)	-0.0872915	H(34)	0.0213709
	C(11)	0.63542	C(23)	0.0522989	H(35)	0.0275835
	O(12)	-0.622128	C(24)	0.0477488	H(36)	0.0301381

Table 3: The charge of the oxygen of the carbonyl group in chacones (3a- f).

Chalcone No.	Charge of the oxygen
3a	-0.638068
3b	-0.611845
3c	-0.710698
3d	-0.713988
3f	-0.62342

It is clear from the above data that the order of the (-) ve charge of the oxygen of the carbonyl group is as follows **3d > 3c > 3a>3f > 3b**.

B) Antimicrobial study

Materials and Methods

The newly synthesized compounds were screened for their anti-microbial properties against nine microbial strains, including Gram-positive (*Bacillus subtilus (ATCC 6051) (BS), Staphylococcus aureus (ATCC 29213) (SA), Methicillin resistance staphylococcus aureus(*Clinical isolate) as well as Gram-negative (*Escherichia coli (ATCC 25922) (EC), Salmonella typhimurium* RCMB015(1) NRRL B-543, bacteria, and the fungal strains (*Aspergillus niger 16404, Candida albicans ATCC* 10231, *Aspergillus fumigatus(RCMB002008), Croptococcus neoformasRCMB0049001*); all tested strains are included in the microbial collection of the Regional Center for Mycology and Biotechnology, Al-Azhar University, Cairo, Egypt and R& D sector of Vacsera Cairo, Egypt. Chloramphenicol 30mcg, SXT 26 (trimethoprim 1.25mcg / sulphamethoxazole 23075mcg), Ketoconazole (100ug/mL) and Gentamycin (5 ug/mL) were used as reference standards. The tests were carried out on the bacterial strains by applying the disk diffusion method.[6,7] A standard inoculums (1-2 x 10^7 c.f.u/ml 0.5 McFarland standards) was introduced on the surface of sterile agar plates, and a sterile glad spreader was used for even distribution of the inoculums. The disks measuring 6mm in diameter were prepared from Whatman no.1 filter paper and sterilized by dry heat at 140°C for 1 hr. The sterile disks of the tested compounds **(3a, 3b, 3c, 3d and 3f)** previously soaked at the concentration level of 0.1g/mL of the test compounds were placed in Trypticase soya agar medium (Oxoid Laboratories, Corporate, UK) for bacteria and Sabouraud dextrose agar (Oxoid Laboratories, Corporate, UK) for fungi. Solvent and growth controls were kept. Ketoconazole (30µg) were used as positive control for the fungi and the Gentamycin (30µg) were used as positive control for the Gram-positive bacteria and Gram-negative bacteria, while the disk soaked in DMSO was used as negative control. The tested organisms were sub-cultured on Trypticase soya agar medium (Oxoid Laboratories, Corporate, UK) for bacteria and Sabouraud dextrose agar (Oxoid Laboratories, Corporate, UK) for fungi and DMSO was used as solvent control. All tests were done in triplicate and average zone of inhibition was calculated. Bacterial cultures were incubated at 37°C

for 24 h while the other fungal cultures were incubated at (25–30°C) for 3–5 days for maximum bacterial and fungal growth, respectively. Antibacterial and antifungal activities were evaluated by measuring the diameter (mm) of the inhibition zones.

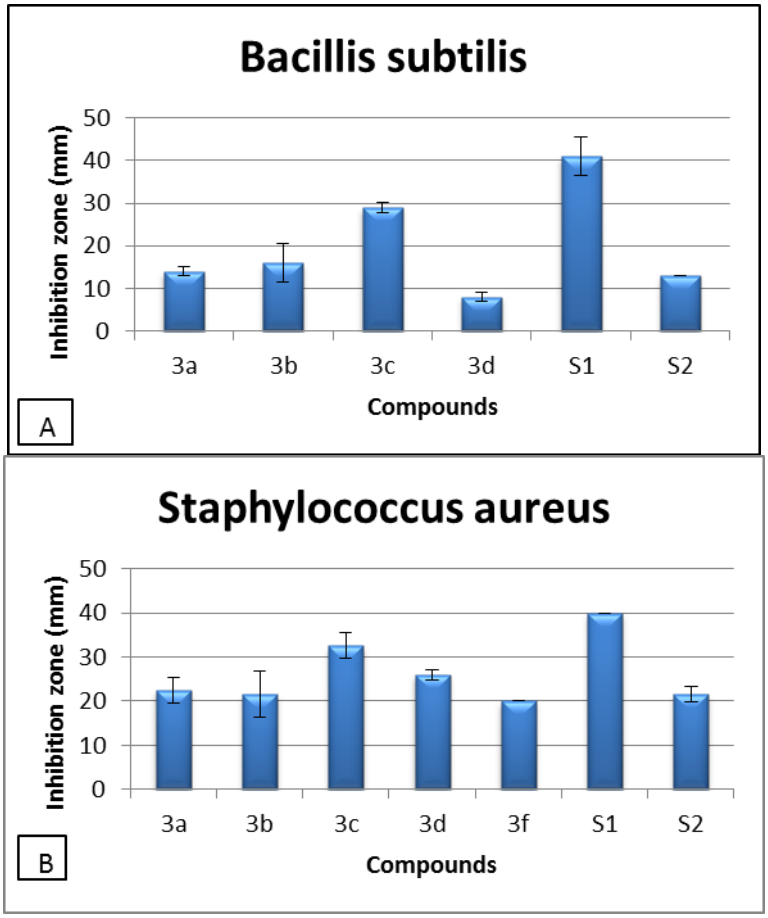
Antimicrobial Results

The results of the qualitative screening of the antimicrobial activity of the obtained compounds are presented in Figures (3-6).

Figure (3A, B) revealed that **chalcone 3c** was the most potent chalcone against Gram + bacterial strains and was more potent than SXT. Although **compounds 3a** and **3b** were effective in inhibiting the growth of *Bacillis subtilis*, and showed higher potency than SXT, while **compound 3d** showed low potency compared to the S1 and SXT. The antibacterial activity of **compound 3c** on *Staphylococcus aureus* not only was greater than **compounds 3a, 3b, 3d and 3f**, but also was more potent than SXT and very close in potency to Chloramphenicol. As regard to *E. coli* (Figure 3C), the tested chalcones showed moderate inhibitory activity in the order **compounds 3f>3a>3c**. When **chalcone 3a** (0.1g/mL) was tested against the tested bacterial strains (*Methicillin resistance Staphylococcus aureus* MRSA and *Salmonella typhimurium)* with regard to Gentamycin (30µg) as a reference drug, it showed moderate potency against MRSA compared to the standard drug and showed higher potency against *Salmonella typhimurium* with respect to Gentamycin(Fig4). The tested **chalcone 3a** showed moderate antibacterial activity against *MRSA*, however, it has higher activity than *Salmonella typhimurium* as compared to Gentamycin (Figure4).

As for the antifungal activity of the tested chalcones, the qualitative assay indicated that compounds 3a and 3b as the most active, exhibiting the largest spectrum of antifungal activity including *Asprigullus niger* and even more potent than the standard Ketoconazole. For *Candida albicans*, it was found that **compounds 3c>3d>3f>3a>3b** in this order and compound 3c was even more potent than the reference standard (Figure 5A, B).

As regard to **chalcone 3a**, it possessed moderate antifungal activity against *Croptococcus neoformas* and *Aspergillus fumigatus*, respectively, compared to its reference drug. (Fig.6).



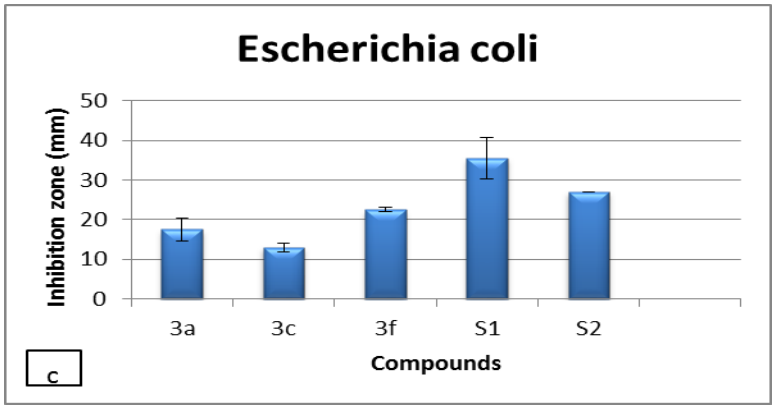


Figure 3: Anti-bacterial activity of the chalcone (0.1g/ml) against the tested bacterial strains (G +: A and B, G -: C) with regard to S1 chloramphenicol (30 mcg) and S2sxt (1.25mcg/23075mcg) as reference standards.

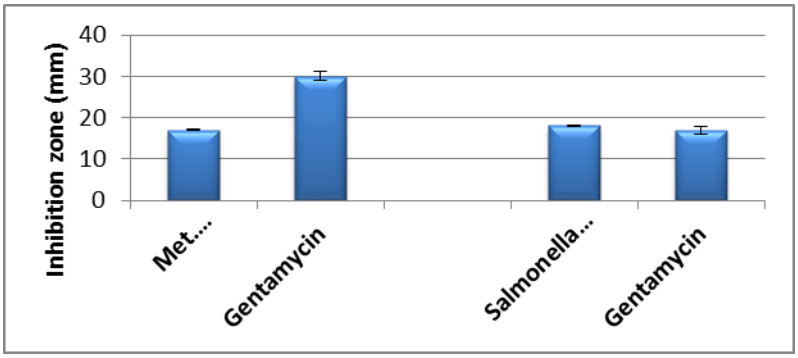


Figure 4: Anti-bacterial activity of chalcone 3a (0.1g/mL) against the tested bacterial strains (Methicillin resistance *staphylococcus aureus* and *Salmonella typhimurium*) with regard to Gentamycin (5 ug/mL) as a reference drug.

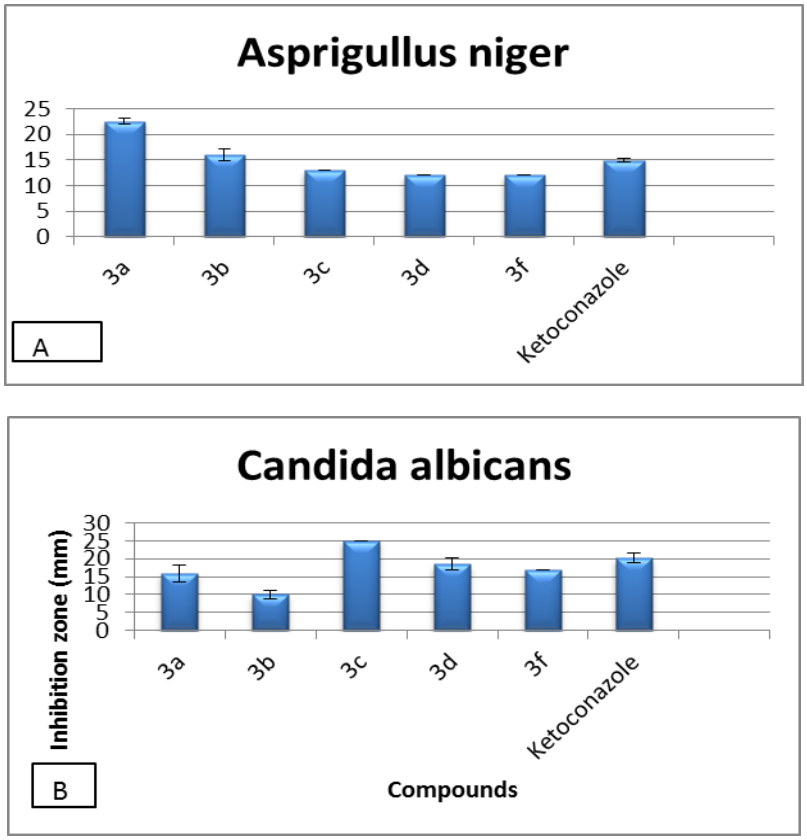


Figure 5: Anti-fungal activity of the chalcone (0.1g/mL) against the tested fungal strains (*Asprigullus niger*: A, *Candida albicans*: B) with regard to Ketoconazole (100 ug/ml) as reference drug.

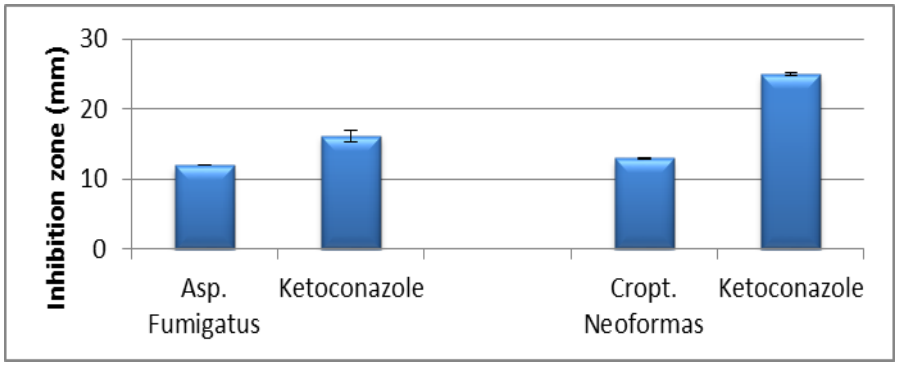


Figure 6: Anti-fungal activity of chalcone 3a (0.1g/mL) against the tested fungal strains (*Aspergillus fumigatus*, *Croptococcus neoformas*) with regard to Ketoconazole (100 ug/mL) as reference drug.

Infections account for a major cause of death throughout the developing world mainly due to the appearance of antimicrobial resistance.[14] More than 70% of the hospital-related bacterial isolates are resistant to most of the antibiotics.[22] Therefore, there is a growing demand for new antibiotics.

Chalcones are open-chain flavonoids with α, β-unsaturated carbonyl groups and posse a wide variety of pharmacological activities. Earlier research proved that chalcones have antibacterial as reported[13,19] and antifungal activities.[24]

The results of this study showed that **chalcone 3c** was almost the most potent against Gram + bacterial strains, besides it was more potent than SXT 26. In addition, **chalcones 3a and 3b** were effective in inhibiting the growth of Bacillis subtilis more than SXT but less effective than Chloramphenicol. On the other hand, when **chalcone 3a**(0.1g/mL)against the tested bacterial strains (*Methicillin resistance Staphylococcus aureus* MRSA and *Salmonella typhimurium)* with regard to Gentamycin (30µg) as a reference drug, it showed moderate potency against MRSA compared to the standard drug and showed higher potency against *Salmonella typhimurium* with respect to Gentamycin(Fig.4). The tested **chalcone 3a** showed moderate antibacterial activity against *Methicillin resistance staphylococcus aureus*, however, it has higher activity than *Salmonella typhimurium* as compared to Gentamycin (Fig.4).

These results agree with those of the previous reports[4,15] who observed that most of the chalcone derivatives showed antibacterial activity when tested against Gram positive and Gram-negative bacteria. The antibacterial activities of tested chalcones may be related to their ability to affect the permeability of bacterial cell wall through interacting with the peptidoglycan layer.

The results of anti-bacterial activity of some chalcone derivatives on Gram –ve bacteria revealed moderate effect on *E. coli* and was in the order **3f>3a>3c**, but they still less effective than the standard drugs.

The qualitative assay indicated that chalcone 3a as most active, exhibiting large spectrum of antimicrobial activity including Gram –ve bacteria, *Salmonella typhimurium*, compared to gentamycin.

The previous reports[10] revealed that positive contribution of molecular weight (MW) with activity against E. coli. in addition, chalcones with higher MW showed higher antibacterial activity, these reports explain the present result of **chalcone 3f** which had the highest Mwt.[22]

Outer membrane of the bacteria comprises of glycolipid and lipopolysaccharide which are hydrophilic and they act as a barrier for hydrophobic molecules. Permeability is high for charged or polar low molecular weight compounds through the outer membrane.[26] As these synthesized chalcones here, act by disturbing the cell membrane, compounds with charge exhibit high activity.

In the case of fungi, **chalcones 3a and 3c** were found to be more effective against *Asprigullus niger* and *Candida albicans*, respectively. In addition, chalcone 3a possesses mild to moderate antifungal activity against *Croptococcus neoformas* and *Aspergillus fumigatus*. These results are in agreement with a previous study in which the tested chalcones showed moderate to good antibacterial and antifungal activities.[15]

The previous investigation reported that increasing the polarizability will result in highly active antibacterial and antifungal agents.[21]

These results suggested that the chalcone derivatives have excellent scope for further development as commercial antimicrobial agents. Further experiments were needed to elucidate their mechanism of action.

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