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Microwave Assisted One Pot Synthesis of Tetrazole Based 3-hydroxy-4*H*-chromen-4-ones by Modified Algar-Flynn-Oyamada Reaction and their Antimicrobial Activity

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Abstract. In the present work, we report the one pot synthesis of tetrazole based 3-hydroxy-4*H*-chromen-4-ones **3(a-g)** from 4-(1*H*-tetrazol-5-yl)benzaldehyde and 2-hydroxy acetophenone using KOH and H_2O_2 by modified Algar-Flynn-Oyamada reaction under conventional and microwave irradiation conditions. In this technique, flavonols are synthesized without isolating chalcones, in good yields. All the synthesized compounds were characterized by IR, NMR, MS and elemental analysis. All newly synthesized compounds were screened for their *in-vitro* antimicrobial activity against strains such as *Staphylococcus aurous, Bacillus subtilis, Klebsiella pneumonia, Escherichia coli*, *Aspergillus Niger*, *Aspergillus flavus*, and *Fusarium oxysporum*. The results of antimicrobial studies revealed that most of the compounds exhibit good activity.
Keywords: 2-hydroxy acetophenone; 4-(1*H*-tetrazol-5-yl) benzaldehyde; microwave irradiation; antimicrobial activity.

Resumen. En este trabajo se reporta la síntesis en un matraz (one-pot) de tetrazol basada en 3-hidroxi-4H-cromen-4-onas 3(a-g) a partir de 4-(1H-tetrazol-5-yl) benzaldehído y 2-hidroxi acetofenona utilizando KOH y H_2O_2 de acuerdo con la reacción de Algar-Flynn-Oyamada modificada bajo condiciones de reacción convencionales y de microondas. En esta técnica, se sintetizan flavonoles con buen rendimiento, sin aislar calconas. Todos los compuestos sintetizados se caracterizaron por IR, NMR, MS y análisis elemental. su La actividad antimicrobiana de todos los compuestos sintetizados por primera vez se probó *in vitro* contra cepas como *Staphylococcus aurous, Bacillus subtilis, Klebsiella pneumonia, Escherichia coli*, *Aspergillus Niger*, *Aspergillus flavus* y *Fusarium oxysporum*. Los resultados de los estudios antimicrobianos revelaron que la mayoría de los compuestos tienen una buena actividad.
Palabras clave: 2-hidroxiacetofenona; 4-(1*H*-tetrazol-5-yl) benzaldehído; irradiación microondas; actividad antimicrobiana.

Introduction

Heterocyclic compounds containing nitrogen and oxygen play an imperative role during the design of agrochemicals and pharmaceuticals. Flavonols (3-Hydroxyflavone) belongs to a class of flavonoids and their

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derivatives are known to possess various biological activities such as anticancer [1], antihypertensive [2], cytotoxic [3], antimicrobial [4], antioxidant [5], anti-inflammatory [6], free radical scavenging [7]. The synthesis of 3-hydroxy flavones was first described by Algar, Flynn and Oyamada [8,9] and was later modified by Murakami and Irie, Reichel and Steudel [10,11]. The original AFO reaction is a two-step process in which the first step involves the formation of 2-hydroxy chalcone intermediate which on subsequent cyclization in the second step in the presence of alkaline hydrogen peroxide affords the corresponding flavonols whereas the modified AFO reaction is a one-step process in which the flavonols derivatives were obtained without isolation of the intermediate 2-hydroxy chalcone in the presence of alkaline hydrogen peroxide.

Tetrazole is a key structural motif in heterocyclic chemistry that contains four nitrogens and one carbon atom in a five membered ring skeleton and has been successfully explored in the design of drug molecules [12]. Tetrazole can act as pharmacophore for carboxylate group. Tetrazole and their derivatives are known to possess broad range of biological activities such as antioxidant, antibacterial [13-15], anticancer [16], antihypertensive [17], antitubercular [18], antifungal [19] and anticonvulsant [20].

Throughout recent years, microwave method [21,22] is extensively used as a non-conventional source of energy to carry out various organic reactions because of the advantages of shorter reaction times, high yields, selectivity, consumption of a small amount of energy, low quantities of side products, and easier work up technique over conventional method.

Inspired by the biological activity of tetrazole, flavonol derivatives and also in continuation to our research work done earlier on the synthesis of flavonol derivatives, we devised the synthesis of novel hybrid molecules containing these active pharmacophore under conventional and microwave irradiation methods. All the synthesized compounds were screened *in vitro* for their antimicrobial activity.

Experimental

All the available reagent grade chemicals were purchased from Sigma Aldrich, and were used without further purification. Microwave reactions were carried out in Milestone multi SYNTH microwave system. The reactions were monitored by TLC on Merck Kieselgel 60 F524, by UV light and/or spraying a 5% H_2SO_4 in Ethanol followed by heating. Column chromatography was performed on Silica Gel 60 (60-120 mesh). Melting points were determined in open glass capillaries on a Stuart SMP30 apparatus and are uncorrected. Element analysis was carried out with Thermofinnigan CHNS analyzer. IR spectrum was recorded in KBr on a Shimadzu FTIR 8400S spectrophotometer. NMR spectra were recorded on a Bruker 400 NMR spectrometer in CDCl3 using TMS as internal standardand mass spectra were recorded by the Shimadzu mass spectrometer.

General procedure for the Synthesis of substituted 2-(4-(1*H*-tetrazol-5-yl)phenyl)-3-hydroxy-4*H*-chromen-4-ones 3(a-g)

Conventional heating method

To a well stirred solution of 4-(1*H*-tetrazol-5-yl) benzaldehyde (**1**) (1 mmol) and 2-hydroxyacetophenones 2(**a-g**) (1 mmol) in ethanol (20 ml), was added KOH (4 mmol in 10 mL of EtOH) at room temperature. The reaction mixture was further stirred for 8 h. After completion of the reactants (as indicated by TLC), the reaction mixture was dissolved in aqueous KOH (5 mmol in 5 mL), 3 mL of 30% H_2O_2 was added drop wise and continued the stirring for 6 h. After completion of reaction (as monitored by TLC), the resultant light yellow reaction mixture was poured on crushed ice and neutralized with dil. HCl. The light yellow solid obtained was filtered and dried. The crude product was purified by column chromatography using a mixture of EtOAc: hexane (7:3 *v*/*v*) to afford pure desired **3(a-g)** as the respective yields are shown in Table 1.

Microwave irradiation method

A mixture of 4-(1*H*-tetrazol-5-yl) benzaldehyde (**1**) (1 mmol) and 2-hydroxyacetophenones **2**(**a-g**) (1 mmol) in ethanol (20 ml), was added KOH (4 mmol in 10 mL of EtOH) was taken through a quartz tube and inserted into a teflon vial with screw capped and subjected to microwave irradiation at 180W for 6 min, with

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an interval of 30 sec. After consumption of the majority of reactants (as indicated by TLC), aqueous KOH (5 mmol in 5 mL), 3 mL of 30% H_2O_2 was added drop wise to the reaction mixture and continued the irradiation for 3 min. After completion of reaction (as monitored by TLC), the resulting light yellow reaction mixture was poured over crushed ice and neutralized with dil. HCl. The light yellow solid thus obtained was filtered, washed with water and dried. The crude product was purified by column chromatography on silica gel using EtOAc: hexane (7:3 *v*/*v*) as eluant to give the pure desired **3(a-g)** as the respective yields are shown in Table 1.

2-(4-(1*H*-tetrazol-5-yl)phenyl)-3-hydroxy-4*H*-chromen-4-one (3a)

A pale yellow solid: Yield 81%, mp 192-194°C; IR (KBr) νmax 3411 (OH), 3361 (NH), 1608 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.01-7.05 m (2H, Ar-H), 7.22 s (1H, OH), 7.59 t (1H, *J* = 7.02 Hz, Ar-H), 7.94–7.95 m (4H, Ar-H), 8.07 d (1H, *J* = 2.56 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 121.9, 123.5, 129.0, 132.5, 132.8, 134.4, 134.7, 139.3, 140.4, 141.0, 149.2, 158.2, 164.4, 178.2; ESI MS *m*/*z* (rel int): 307 $(M+H)^+$ (100). Anal. Calcd for $C_{16}H_{10}N_4O_3$: C 62.76; H 3.31; N 18.31. Found: C 62.74; H 3.29; N 18.29.

2-(4-(1*H*-tetrazol-5-yl)phenyl)-6-fluoro-3-hydroxy-4*H*-chromen-4-one (3b)

A pale yellow solid: Yield 79%, mp 171-173°C. IR (KBr) νmax 3522 (OH), 3363 (NH), 1606 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.85 d (1H, Ar-H), 7.03 s (1H, OH), 7.38–7.41 dd (1H, *J* = 8.80 Hz, *J* = 2.56 Hz, Ar-H), 7.94–7.95 m (4H, Ar-H), 8.07 d (1H, *J* = 2.56 Hz, Ar-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 122.3, 125.0, 127.9, 131.6, 133.5, 138.1, 139.2, 139.8, 143.7, 148.0, 157.0, 163.2, 170.7, 177.0; ESI MS *m*/*z* (rel int): 325 $(M+H)^+$ (100). Anal. Calcd for $C_{16}H_9FN_4O_3$: C 59.28; H 2.82; N 17.30. Found: C 59.26; H 2.80; N 17.28.

2-(4-(1*H*-tetrazol-5-yl)phenyl)-6-chloro-3-hydroxy-4*H*-chromen-4-one (3c)

A pale yellow solid: Yield 84%, mp 184-186°C. IR (KBr) νmax 3523 (OH), 3361 (NH), 1606 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.05 d (1H, *J* = 8.80 Hz, Ar-H), 7.23 s (1H, OH), 7.58–7.61 dd (1H, *J* = 8.80 Hz, *J* = 2.57 Hz, Ar-H), 8.14–8.15 m (4H, Ar-H), 8.27 d (1H, *J* = 2.57 Hz, Ar-H).^{13}C NMR (DMSO-d_6, 100 MHz) δ 122.9, 123.5, 126.2, 129.0, 132.5, 132.8, 134.4, 134.7, 140.4, 141.0, 144.9, 149.2, 158.2, 178.2; ESI MS *m*/*z* (rel int): 341 $(M+H)^+$ (100). Found: C 56.40; H 2.66; N 16.44.Anal. Calcd for $C_{16}H_9ClN_4O_3$: C 56.42; H 2.68; N 16.46.

2-(4-(1*H*-tetrazol-5-yl)phenyl)-6-bromo-3-hydroxy-4*H*-chromen-4-one (3d)

A pale yellow solid: Yield 82%, mp 172-173°C. IR (KBr) νmax 3523 (OH), 3424 (NH), 1620 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.82 d (1H, *J* = 8.80Hz, Ar-H), 7.00 s (1H, OH), 7.34–7.37 dd (1H, *J* = 8.80 Hz, *J* = 2.57 Hz, Ar-H), 7.90–7.91 m (4H, Ar-H), 8.03 d (1H, *J* = 2.57 Hz, Ar-H).^{13}C NMR (DMSO-d_6, 100 MHz) δ 122.0, 123.6, 126.2, 129.1, 132.6, 133.0, 134.5, 134.8, 138.4, 140.5, 143.4, 149.3, 158.3, 178.3; ESI MS *m*/*z* (rel int): 385 $(M+H)^+$ (100). Found: C 49.89; H 2.36; N 14.55.Anal. Calcd for $C_{16}H_9BrN_4O_3$: C 49.91; H 2.38; N 14.57.

2-(4-(1*H*-tetrazol-5-yl)phenyl)-3-hydroxy-6-methyl-4*H*-chromen-4-one (3e)

A pale yellow solid: Yield 79%, mp 161-163°C. IR (KBr) νmax 3522 (OH), 3363 (NH), 1606 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.34 s (3H, -CH_3), 6.92 d (1H, *J* = 8.43 Hz, Ar-H), 7.13 s (1H, OH), 7.41 d (1H, *J* = 8.43 Hz, Ar-H), 8.10–8.18 m (5H, Ar-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 20.2, 117.0, 118.5, 121.2, 124.1, 127.9, 129.7, 133.3, 134.4, 135.4, 136.1, 144.3, 153.2, 159.5, 173.3; ESI MS *m*/*z* (rel int): 321 $(M+H)^+$ (100). Found: C 63.75; H 3.78; N 17.49. Anal. Calcd for $C_{17}H_{12}N_4O_3$: C 63.77; H 3.80; N 17.51.

2-(4-(1H-tetrazol-5-yl)phenyl)-6,8-dichloro-3-hydroxy-4H-chromen-4-one (3f)

A pale yellow solid: Yield 83%, mp 155-157°C. IR (KBr) νmax 3523(OH), 3373 (NH), 1604 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.06 s (1H, Ar-H), 7.23 s (1H, OH), 8.14-8.15 m (4H, Ar-H), 8.27 s (1H, Ar-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 121.4, 123.4, 126.2, 129.1, 132.5, 132.9, 134.4, 134.7, 138.3, 140.4, 143.3, 149.2, 158.2, 178.2; ESI MS *m*/*z* (rel int): 375 $(M+H)^+$ (100). Found: C 51.22; H 2.15; N 14.93. Anal. Calcd for $C_{16}H_8Cl_2N_4O_3$: C 51.24; H 2.17; N 14.95.

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2-(4-(1*H*-tetrazol-5-yl)phenyl)-6-chloro-3-hydroxy-7-methyl-4*H*-chromen-4-one (3g)

A pale yellow solid: Yield 83%, mp 174-176°C. IR (KBr) νmax 3523 (OH), 3442 (NH), 1628 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.19 s (1H, Ar-H), 8.06–8.07 m (4H, Ar-H), 7.15 s (1H, OH), 6.99 s (1H, Ar-H), 2.43 s (3H, -CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.0, 161.2, 155.0, 146.0, 141.7, 137.8, 137.2, 136.1, 131.5, 129.6, 126.0, 123.0, 120.3, 118.7, 21.9; ESI MS *m/z* (rel int): 355 $(M+H)^+$ (100). Found: C 57.56; H 3.13; N 15.83. Anal. Calcd for $C_{17}H_{11}ClN_4O_3$: C 57.58; H 3.15; N 15.81.

Biological assay

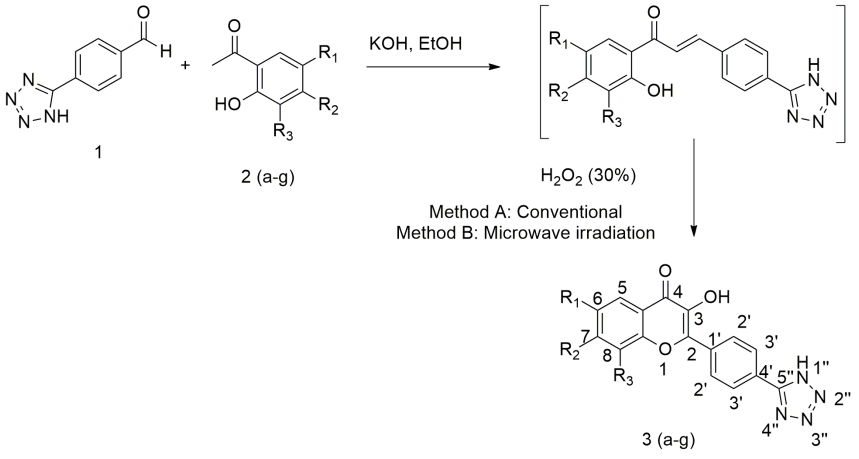
Antibacterial activity

The synthesized new compounds **3(a-g)** were screened for their Antibacterial activity against different types of bacterial strains such as Gram-negative bacterial strains of *Klebsiella pneumonia*, *Escherichia coli*, and Gram-positive bacterial strains of *Bacillus subtilis, Staphylococcus aeureus* at two different concentration of 10 and 20 µg/mL. The cultures were diluted with 5 % saline autoclaved, and the final volume was made with concentration approximately 10^5–10^6 CFU/mL. The synthesized compounds were diluted in DMSO for antibacterial biological assays. For agar disc diffusion method, the liquid form of test compound was soaked on to the disc and then allowed to air dry, such that the disc gets completely saturated with test compound. The saturated chemical discs were introduced onto the upper layer of the medium evenly flooded with the bacteria. The discs were dipped in different chemical samples, were placed over the evenly spread bacterial nutrient media, and incubated at 37°C for 24–48 h for better inhibition of bacteria. The zones of inhibition were measured after 24–48 h. All the experiments were carried out in triplicated and the results were expressed as zone of Inhibition in mm. The zones of inhibition of synthesized compounds **3(a-g)** were compared to the zone of inhibition of standard antibiotic concentrations of gatifloxacin (10 and 20 µg/mL).

Antifungal activity

The antifungal activity of synthesized compounds **3(a-g)** were tested against three pathogenic fungi, namely *Aspergillus niger, Aspergilus flavus* and *Fusarium oxysporum* by the poison plate technique at a concentration of 50 µg/mL. Three kinds of fungi were incubated in PDA at 25 ± 1 ^{0}C for 5 days to get new mycelium for antifungal assay, then a mycelium as discs of approximately 0.45 cm diameter cut from the culture medium were picked up with a sterilised inoculation needle and inoculated in the center of PDA plate. Test compounds were dissolved in DMSO (10 mL) after that added into the Potato Dextrose Agar medium (PDA, 90 mL). The final concentration of compounds into the medium was adjusted to 50µg/mL. The inoculated plates were incubated at 25 ± 1ºC for 5 days. Acetone was diluted with sterilised distilled water and used as control, while clotrimazole (50µg/mL) was used as standard control for each treatment three replicates of experiments were carried out. The radial growth of the fungal colonies was measured on the 5th day.

Results and discussion



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	a	b	c	d	e	f	g
R_1	H	F	Cl	Br	Me	Cl	Cl
R_2	H	H	H	H	H	H	Me
R_3	H	H	H	H	H	Cl	H

Scheme 1. Synthesis of 2-(4-(1*H*-tetrazol-5-yl)phenyl)-3-hydroxy-4*H*-chromen-4-one **3(a-g)** under conventional (Method A), Microwave irradiation (Method B) methods.

In the present investigation, some new substituted 2-(4-(1*H*-tetrazol-5-yl)phenyl)-3-hydroxy-4*H*-chromen-4-one **3(a-g)** have been effectively synthesised using both conventional and microwave irradiation methods. Substituted 2-hydroxyacetophenone **2(a-g)** was initially reacted with 4-(1*H*-tetrazol-5-yl) benzaldehyde [23] to give chalcone, later the reaction mixture was treated with catalytic amount of hydrogen peroxide (30 % H_2O_2) in alkaline medium at room temperature to give the corresponding flavonols (**3a-g**). As a model case, synthesis of derivative **3b** was carried out in both conventional and microwave irradiation method. In conventional method the **3b** was obtained with 61% yield in 10 h of stirring at RT, while in microwave irradiation [24] compound **3b** was obtained with 79% yield in 11 min. The comparisons of yields of the compounds **3(a-g)** in both the methods were depicted in Table 1.

Table 1. Reaction time and yields of the synthesized compounds **3(a-g)**

Comp. no	Conventional		MWI	
	Time, hr	Yield, %	Time, min	Yield, %
3a	14	64	9	81
3b	10	61	11	79
3c	11	68	10	84
3d	12	67	12	82
3e	14	61	9	79
3f	13	67	9	83
3g	14	68	10	83

The remaining compounds **3a, 3(c-g)** were synthesized in the similar way using both conventional and microwave conditions. We found that microwave irradiation provides much more faster conversion of the starting compounds and higher yields (reaction time 9–12 min, yields 79– 83%) than conventional heating (reaction time 10–14 h, yields 61–68%).

The title compound **3b** was characterized by detailed spectral analyses, including FT-IR, ^{1}H and ^{13}C NMR and mass spectral data as 2-(4-(1*H*-tetrazol-5-yl)phenyl)-6-fluoro-3-hydroxy-4*H*-chromen-4-one **3b**, that ruled out the formation of corresponding aurone and some other benzofuran derivatives, which were hypothetical to form as by-products in AFO reaction. This assumption of the reaction mechanism and cyclization of the chalcone were supported by literature [25].

In the IR spectrum of **3b**, the characteristic carbonyl absorption of flavonol observed at 1606 cm^{-1} (>C=O), -OH peak is observed at 3522 cm^{-1} and the –NH stretching peak appeared at 3363 cm^{-1}. In the ^{1}H NMR the -OH proton was appeared as a singlet at δ 7.03. H_7 proton appeared as doublet of doublet (J = 8.8 Hz and J = 2.56 Hz) at δ 7.40 and other adjacent proton of H_8 as doublet (J = 8.80 Hz) at δ 8.07 ppm. H_5 proton appeared at δ 8.07 as doublet (J = 2.56 Hz). The remaining proton signals are in the expected region and are in accord with the desired compound. In ^{13}C NMR spectrum of compound **3b,** the characteristic carbonyl carbon appeared at δ 176.7ppm. All the other carbon signals are in the expected region, which supports the formation of compound **3b**. In the ESI-MS mass spectrum of **3b** the base peak was observed at *m*/*z* 325 corresponding to $[M+H]^+$ ion, which further confirmed the structure of **3b**.

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Biological evaluation
Antibacterial activity

Table 2. Antibacterial activity of compounds **3(a-g)**

Compound	Zone of inhibition (mm)							
	Gram positive bacteria				Gram negative bacteria			
	S. aureus		*B. subtilis*		*K. pneumoniae*		*E. coli*	
	10 µg/mL	**20 µg/mL**	**10 µg/mL**	**20 µg/mL**	**10 µg/mL**	**20 µg/mL**	**10 µg/mL**	**20 µg/mL**
3a	9	15	7	16	10	16	11	18
3b	12	17	11	20	9	18	9	16
3c	11	16	10	18	8	9	8	7
3d	11	19	9	19	6	11	7	11
3e	9	15	6	15	10	18	10	16
3f	13	23	9	22	7	15	8	17
3g	10	17	8	15	11	19	12	17
Gatifloxacin	13	23	12	25	12	20	13	21

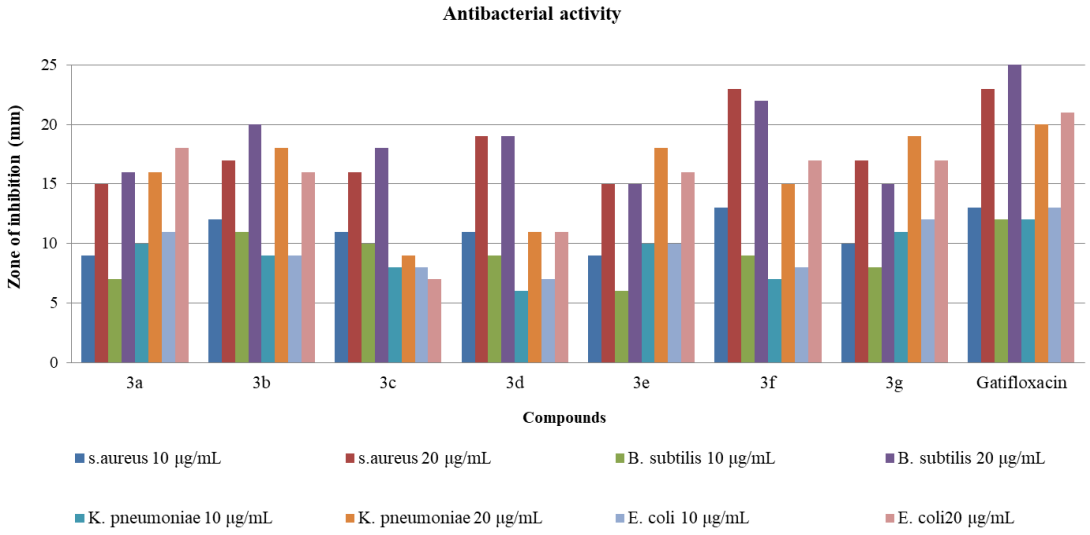

Fig. 1. Graphical representation antibacterial activity of synthesized compounds **3(a–g).**

The newly synthesized title compounds **3(a-g)** were evaluated for their *in-vitro* antibacterial activity against Gram-positive strains (such as *Bacillus subtilis* (MTCC 121), *Staphylococcus aureus* (MTCC 96)) and Gram-negative strains (such as *Escherichia coli*, (MTCC 43), *Klebsiella pneumonia* (MTCC 530)) at various concentration10µg/mL and 20µg/mL. The zone of inhibition was measured in mm and gatifloxacin was used as the standard drug and result shown (Table 2 and Fig. 1). Compounds **3b**, **3c**, **3d** and **3f** were of high potential against gram positive bacterial strains than gram negative bacterial strains. Compounds **3a**, **3e** and **3g** were moderately active against positive bacterial strains, and compounds **3a**, **3e**, and **3g** shown promise activity against gram-negative strains. The results also demonstrated that the activity of these compounds **3(a-g)** is influenced by their structures. In conclusion, **3b**, **3f**, and **3g** showed potential antibacterial activity against tested organisms.

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Antifungal activity

The synthesized compounds **3(a-g)** were screened for *in-vitro* antifungal activity against the fungal organisms such as *Aspergillus niger*, *Aspergillus flavus*, and *Fusarium oxysporum* at the concentration 50 µg/mL and the results were compared with clotrimazole as standard drug. Upon study of antifungal activity data (Table 3 and Fig. 2), it has been observed that, among all the synthesised compound **3b** and **3f** have shown better activity against three pathogenic fungi, compared to the standard drug. Compounds **3e** and **3g** were showed maximum activity against *Fusarium oxysporum*, compounds **3a** and **3d** were shown to promising activity against *Aspergillus niger* and the compound **3d** Shown better activity against *Aspergillus flavus.* Most of the compounds were shown good activity against the tested fungal strains.

Table 3. Antifungal activity of compounds **3(a-g)**

Compound	**Zone of Inhibition (mm)**		
Conc. (50µg/mL)	***A. niger***	***A. flavus***	***F. oxysporum***
3a	15.8	14.2	11.4
3b	17	16.7	18
3c	13.5	14	13
3d	16.4	15.8	12.5
3e	14	13.7	17.4
3f	16.8	16.5	17.8
3g	12.7	14.3	17
Clotrimazole	17.3	16.7	18.2

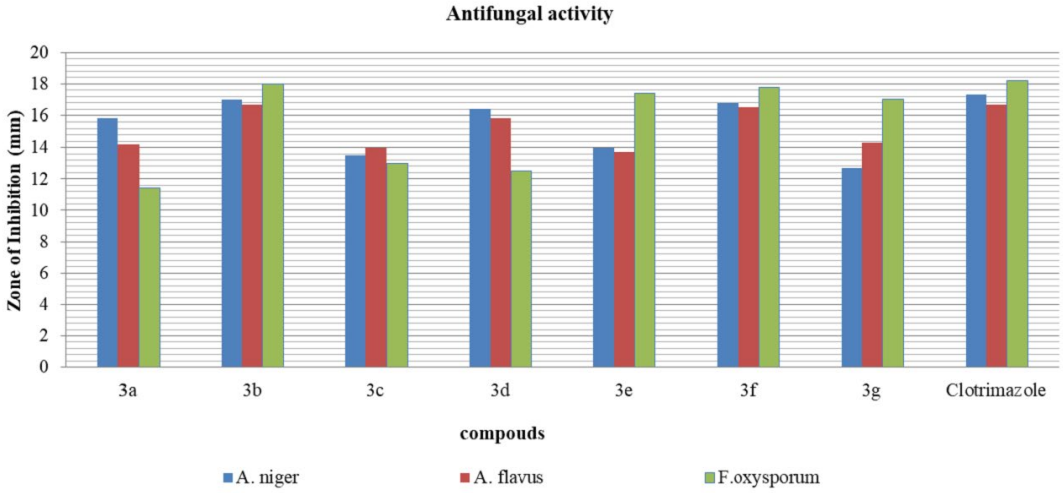

Fig. 2. Graphical representation antifungal activity of synthesized compounds **3(a-g)**.

In conclusion, we report a convenient, simple and high yielding route for the synthesis of new scaffold flavonol derivatives **3(a-g)** under microwave irradiation method in comparison to conventional method. These final compounds were evaluated for their *in vitro* antimicrobial activity. Compounds **3b**, **3f**, and **3g** exhibited promising antibacterial activity and compounds **3b** and **3f** were shows potential antifungal activity.

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