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A Novel Method for Synthesis and their Antimicrobial Activity of 1*H*-Tetrazole Based Flavones and Flavanone Derivatives under Ultrasonic and Microwave Irradiation Methods

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A series of novel tetrazole scaffolds containing flavones and flavanones have been synthesized under conventional, ultrasonic and microwave irradiation methods. All the newly synthesized compounds were characterized by IR, NMR and Mass spectral analysis. Furthermore, the title compounds were screened *in vitro* antimicrobial activity against bacteria such as *Staphylococus aureus*, *Bacillus subtilis*, *Klebsiella pneumoniae* and *Escherichia coli* as well as fungi such as *Aspergillus niger, Aspergillus flavus* and *Fusarium oxysporum*. Some of the compounds showed good activity compared to standard drugs against all pathogenic bacteria and fungi.

Keywords: Flavones, Flavanones, Ultrasonication, Microwave irradiation, Antimicrobial activity.

INTRODUCTION

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Tetrazoles are a class of heterocyclic compounds containing four nitrogens, one carbon and one hydrogen atom in a five-membered ring. Tetrazoles are unknown in nature. Tetrazoles are found to possess various biological activities such as antibacterial [1], anticancer [2], antifungal [3], anticonvulsant [3], antitubercular [4], anti-inflammatory and antihypertensive activity [5,6]. Tetrazoles can act as pharmacophore for the carboxylate group, increasing their utility. Angiotensis II blocker often contain, used as Losartan [7] and candesartan [8]. Tetrazole is used in MTT assay to quantify the respiratory activity of live cells in cell culture, although it kills cells in the process [9]. The drugs pemirolast [10] and pranlukast [10] (Fig. 1) containing the NH unsubstituted tetrazole ring belong to new generation antihistaminic drugs, which effectively act on both H1 and H2 receptors of mast cells.

Flavones (2-phenylchromones) are abundant in numerous naturally occurring compounds including apigenin (4',5,7-trihydroxyflavone), tangeritin (4',5,6,7,8-pentamethoxyflavone) and chrysin (5,7-dihydroxyflavone). Flavones widely distributed in the plant kingdom as secondary metabolites [11] and has been the synthesis of flavones because of their various biological activities, such as anti-inflammatory [12], antiestrogenic [13], antioxidant, anticancer, anti-HIV, antihypertensive [14], antiantimicrobial [15], cardiovascular [16], antidiabetic [17], antiallergic [18] and chemo preventative activities [19]. Similarly, flavanone constitute a naturally occurring class of substances [20] which are classified as privileged structures [21], as compounds based on these scaffolds display a wide range of biological activities [22] including anxiolytic [23], anti-inflammatory, antiviral [24] and anticarcinogenic activities [25]. Flavanone, such as eriodictyol and pinocembrin are associated with reduced risk of certain chronic diseases [26]. Natural flavanones (chromen-4-ones) isolated from flowers of *Chromolaena odorata*, such as 4'-hydroxy-5,6,7-trimethoxy-flavanone are reported to have antimycobacterial activity [27] (Fig. 1).

Microwave irradiation is known to provide enhanced rate of reaction and improved product yield in organic synthesis and its application has been quite successful in the formation of a variety of carbon heteroatom bonds. In recent years, microwaves have been extensively applied to different chemical reactions as a useful non-conventional energy source [28]. The

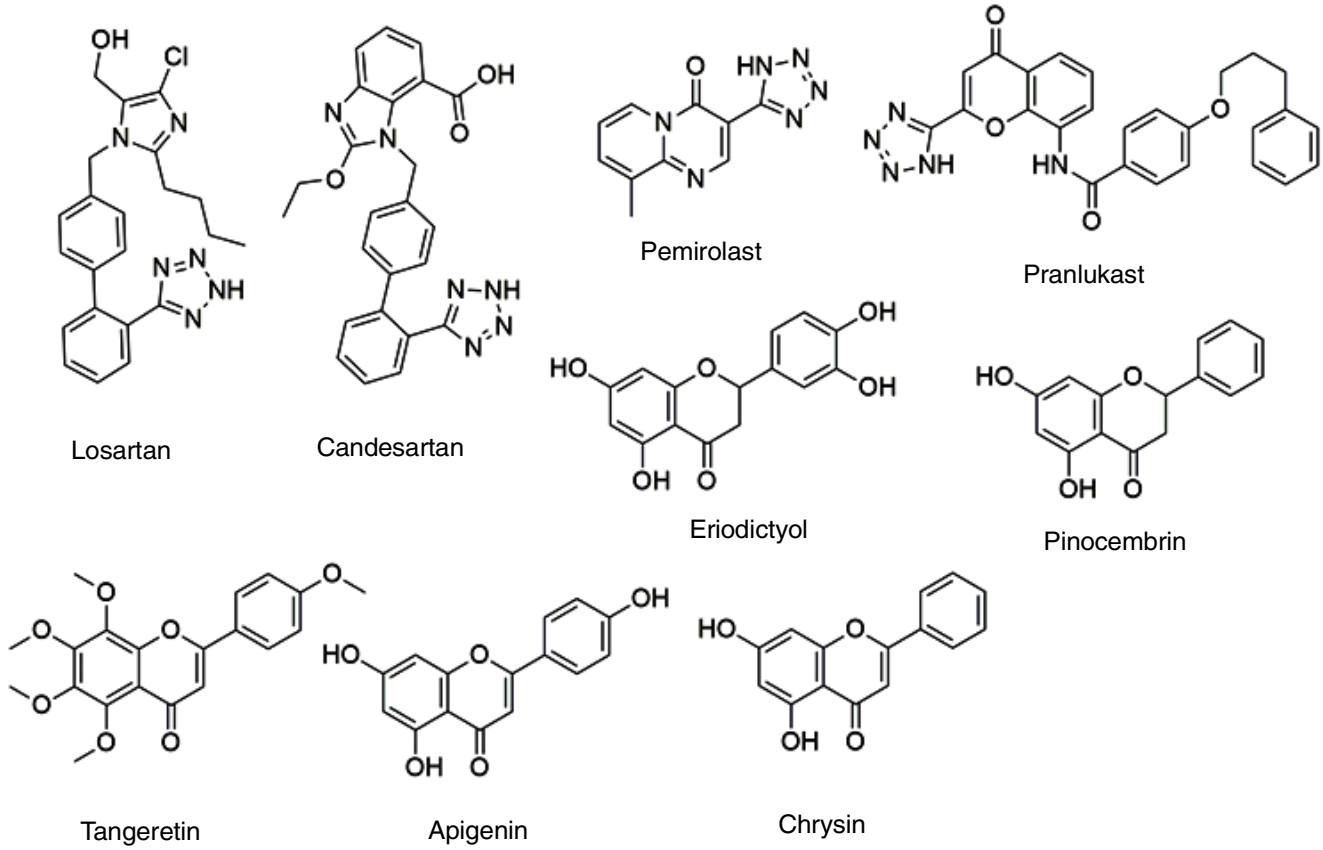


Fig. 1. Structures of some biologically active tetrazoles and flavanoids

ultrasound irradiation can lead to the apparent improvement of the reaction efficiency with increased yields and reduced reaction time. Ultrasound has increasingly been used in organic synthesis [29]. Similarly, both the advantages of ultrasound and microwave irradiation techniques include higher yields, shorter reaction times and milder reaction conditions as compared with conventional method. Our research group has made considerable efforts to design and put into practice innovative synthetic protocols adopting a more eco-sustainable approach.

The combination of two or more pharmacophores or chemical entities either linked with one another or fused together to create a new molecule is referred to as molecular hybridization. Owing to the interesting application of tetrazole and flavonoids, in present work, we have synthesized some new flavones (**4a-g**) and flavanones (**5a-g**) derivatives using conventional, ultrasound and microwave irradiation methods. In these techniques provides that highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of the product. All the synthesized compounds have been tested for their *in vitro* antimicrobial activity.

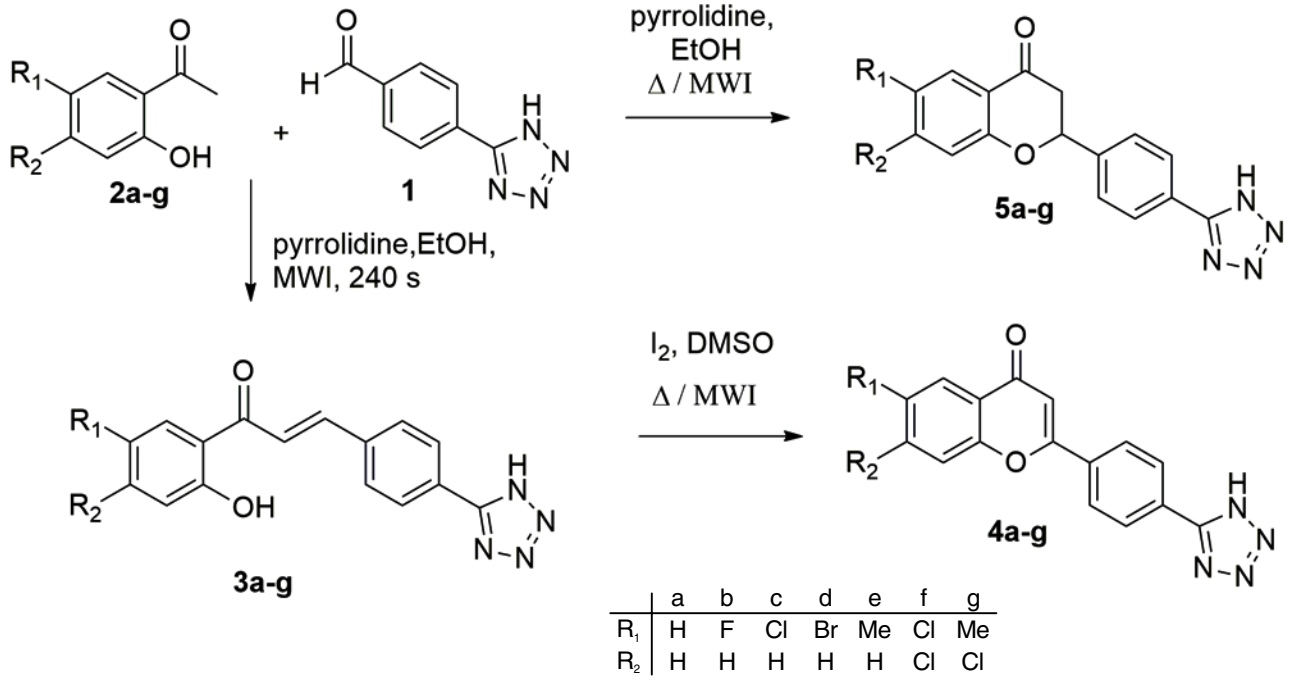
EXPERIMENTAL

All the reagents and solvents were purchased from Sigma-Aldrich or S.D. fine chemicals limited and used without further purification. Melting points were determined using a Cintex apparatus and were uncorrected. Elemental analysis was measured by means of Perkin Elmer 2400 CHN elemental analyzer. Purity of compounds was monitored by TLC on silica gel plates 60 F254 (Merck). Reactions under microwave irradiation were carried out in milestone multi SYNTH microwave system. IR (KBr) spectra were recorded on a Shimadzu FT-IR-8400S spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on Bruker Avance II 400 MHz spectrometer (TMS internal standard). Mass spectra were recorded on Shimadzu LCMS 2020 mass spectrometer.

The synthetic route to compounds (**4a-g**) and (**5a-g**) was shown in **Scheme-I**. Compound (**1**) was synthesized according to the literature [30]. The condensation of 2-hydroxy acetophenones (**2a–g**) with 4-(1*H*-tetrazol-5-yl)benzaldehyde (**1**) in the presence of pyrrolidine, under microwave irradiation gave substituted chalcone (**3a–g**). Subsequently, these chalcones (3**a–g**) on reaction with I_2 in DMSO (dimethyl sulfoxide) to obtained substituted 2-(4-(1*H*-tetrazol-5-yl)phenyl)-4*H*-chromen-4-one **(4a–g)** under ultrasound and microwave irradiation methods gave excellent yields. When 4-(1*H*-tetrazol-5-yl)benzaldehyde (**1**) was reacted with 2-hydroxy acetophenones (**2a–g**) in ethanol in the presence of pyrrolidine as base the expected corresponding 2'-hydroxychalcone could not be isolated. Instead, the isomeric cyclic product 2-(4-(1*H*-tetrazol-5-yl)phenyl)chroman-4-one (**5a-g**), *i.e.*, the corresponding flavanone, was obtained (**Scheme-I**).

General procedure for the synthesis of substituted 2-(4-(1*H*-tetrazol-5-yl)phenyl)-4*H*-chromen-4-one (4a-g)

Conventional method: To a stirred solution of iodine (20 mol %) in DMSO (20 mL) was added to substituted 2-hydroxy chalcone **(3a-g)** (10 mmol) at room temperature and refluxed at 130 °C for 8-9 h. After completion of reaction, the reaction



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

Scheme-I: Synthetic pathways of flavones (**4a-g**) and flavanones (**5a-g**) derivatives using conventional, microwave irradiation and ultrasound irradiation techniques

mixture was poured onto ice-cold water, extracted with dichloromethane and dried over Na_2SO_4. The obtained crude Purified by column chromatography using hexane:ethyl acetate (5:5 v/v).

Microwave irradiation method: A mixture of substituted 2-hydroxy chalcone **(3a-g)** (10 mmol) and iodine (20 mol %) in 20 mL of DMSO was taken in a quartz tube and inserted into a Teflon vial with screw capped and then it was subjected to microwave irradiation at 320 watts for 8-10 min with an every 30 s intervals. After completion of reaction (as indicated by TLC), the reaction mixture was poured onto ice-cold water, extracted with dichloromethane and dried over Na_2SO_4. The obtained crude purified by column chromatography using hexane:ethyl acetate (5:5 v/v).

Ultrasonic irradiation method: A mixture of 2-hydroxy chalcone **(3a-g)** (10 mmol) and iodine (20 mol %) in 2 mL of DMSO was loaded in a conical flask and it was subjected to ultrasound irradiation for 8-10 min at 60°C. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured onto ice-cold water, extracted with dichloromethane and dried over Na_2SO_4. The obtained crude Purified by column chromatography using hexane: ethyl acetate (5:5 v/v).

General procedure for the synthesis of substituted 2-(4-(1*H*-tetrazol-5-yl)phenyl)chroman-4-one (5a-g)

Conventional method: A mixture of 4-(1*H*-tetrazol-5-yl)benzaldehyde (**1**) (0.01 mol), 2-hydroxy acetophenones (**2a–g**) and pyrrolidine (0.01 mol) in ethanol (5 mL) was refluxed at 80 °C for 7-8 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured onto crushed ice and the separated solid was filtered off, washed with water and recrystallized from methanol to afford a pale-yellow crystalline product.

Microwave irradiation method: A mixture of 4-(1*H*-tetrazol-5-yl)benzaldehyde (**1**) (0.01 mol), 2-hydroxy acetophenones (**2a–g**) and pyrrolidine (0.01 mol) in ethanol (5 mL) was taken in a quartz tube, inserted into a screw-capped Teflon vial and subjected to microwave irradiation at 180 W for 6-8 min. After completion of the reaction (as indicated by TLC), the reaction mixture was poured onto crushed ice and the separated solid was filtered off, washed with water and recrystallized from methanol to afford a pale-yellow crystalline product.

Ultrasonic irradiation method: A mixture of 4-(1*H*-tetrazol-5-yl)benzaldehyde (**1**) (0.01 mol), 2-hydroxy acetophenones (**2a–g**) and pyrrolidine (0.01 mol) in ethanol (5 mL) was loaded in a conical flask and it was subjected to ultrasound irradiation for 6-8 h at 60 °C. Progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured onto crushed ice and the separated solid was filtered off, washed with water and recrystallized from methanol to afford a pale-yellow crystalline product.

Spectral data

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-4*H*-chromen-4-one (4a): Pale yellow coloured solid; m.p.: 258–260 °C; IR (KBr, ν_{max}, cm^{-1}): 3412 (NH), 1630 (C=O), 1585 (=CH); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.32 (d, 2H, *J* = 8.4 Hz, Ar–H), 8.21 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.50-7.55 (m, 2H, Ar–H), 7.14 (s, 1H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz): 177.6, 161.7, 154.5, 136.0, 135.8, 134.0, 130.8, 128.0, 127.8, 127.7, 124.6, 123.6, 118.9, 108.2; ESI–MS: 291 (M + H); Anal. calcd. (%) for $C_{16}H_{10}N_4O_2$: C, 66.20; H, 3.47; N, 19.30; Found (%): C, 66.24; H, 3.59; N, 19.42.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-fluoro-4*H*-chromen-4-one (4b): Pale yellow coloured solid; m.p.: 264–266 °C; IR (KBr, ν_{max}, cm^{-1}): 3419 (NH), 1645 (C=O), 1585 (=CH); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.27 (d, 2H, *J* = 8.4 Hz, Ar–H),

8.16 (d, 2H, *J* = 8.4 Hz, Ar–H), 7.80 (s, 1H, Ar–H), 7.68-7.61 (m, 2H, Ar–H), 7.10 (s, 1H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz): 179.6, 161.7, 155.5, 137.0, 136.8, 134.9, 131.8, 129.0, 128.8, 127.7, 126.6, 123.6, 119.0, 108.7; ESI–MS: 309 (M + H); Anal. calcd. (%) for $C_{16}H_9N_4O_2F$: C, 62.34; H, 2.94; F, 6.16; N, 18.17; Found (%): C, 62.34; H, 2.99; F, 6.19; N, 18.24.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-chloro-4*H*-chromen-4-one (4c): Pale yellow coloured solid; m.p.: 254–256 °C; IR (KBr, ν_{max}, cm^{-1}): 3422 (NH), 1640 (C=O), 1585 (=CH); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.28 (d, 2H, *J* = 8.8 Hz, Ar–H), 8.17 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.80 (s, 1H, Ar–H), 7.68-7.61 (m, 2H, Ar–H), 7.13 (s, 1H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz): 175.6, 163.7, 154.5, 136.0, 136.8, 134.8, 130.6, 128.4, 127.8, 127.8, 124.6, 123.8, 118.9, 108.4; ESI–MS: 325 (M + H); Anal. calcd. (%) for $C_{16}H_9N_4O_2Cl$: C, 59.18; H, 2.79; Cl, 10.92; N, 17.25; Found C, 59.28; H, 2.92; Cl, 10.97; N, 17.35.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-bromo-4*H*-chromen-4-one (4d): Pale yellow coloured solid; m.p.: 264–266 °C; IR (KBr, ν_{max}, cm^{-1}): 3420 (NH), 1652 (C=O), 1579 (=CH); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.27 (d, 2H, *J* = 8.8 Hz, Ar–H), 8.17 (d, 2H, *J* = 8.8 Hz, Ar–H), 7.80 (s, 1H, Ar–H), 7.68-7.61 (m, 2H, Ar–H), 7.13 (s, 1H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz): 177.4, 166.7, 161.3, 154.4, 135.8, 136.3, 133.9, 130.6, 127.6, 128.4, 124.4, 123.4, 118.8, 110.7; ESI–MS: 369 (M + H); Anal. calcd. (%) for $C_{16}H_9N_4O_2Br$: C, 52.05; H, 2.46; Br, 21.64; N, 15.18; Found (%): C, 52.14; H, 2.49; Br, 21.71; N, 15.21.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-methyl-4*H*-chromen-4-one (4e): Pale yellow coloured solid; m.p.: 260–262 °C; IR (KBr, ν_{max}, cm^{-1}): 3440 (NH), 1642 (C=O), 1584 (=CH); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.32 (d, 2H, *J* = 8.4 Hz, Ar–H), 8.21 (d, 2H, *J* = 8.4 Hz, Ar–H), 8.17 (s, 1H, Ar–H), 7.26-7.16 (m, 2H, Ar–H), 7.13 (s, 1H, Ar–H), 2.44 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): 177.0, 161.9, 153.9, 135.4, 135.2, 1334.4, 130.2, 127.4, 127.2, 127.1, 124.0, 123.0, 118.3, 107.5, 20.4; ESI–MS: 305 (M + H); Anal. calcd. (%) for $C_{17}H_{12}N_4O_2$: C, 67.10; H, 3.97; N, 18.41; Found (%): C, 67.14; H, 3.92; N, 18.46.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-7-chloro-6-methyl-4*H*-chromen-4-one (4f): Pale yellow coloured solid; m.p.: 254–256 °C; IR (KBr, ν_{max}, cm^{-1}): 3434 (NH), 1659 (C=O), 1590 (=CH); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.15 (d, 2H, *J* = 7.9 Hz, Ar–H), 8.01 (d, 2H, *J* = 7.9 Hz, Ar–H), 7.12-7.09 (m, 2H, Ar–H), 7.13 (s, 1H, Ar–H), 2.52 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): 177.0, 162.7, 156.9, 135.4, 134.2, 133.4, 131.2, 127.4, 127.8, 127.1, 124.8, 124.0, 118.7, 109.5, 22.4; ESI–MS: 339 (M + H); Anal. calcd. (%) for $C_{17}H_{11}N_4O_2Cl$: C, 60.28; H, 3.27; Cl, 10.47; N, 16.54; Found (%): C, 60.31; H, 3.29; Cl, 10.44; N, 16.59.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-5,7-dichloro-4*H*-chromen-4-one (4g): Pale yellow coloured solid; m.p.: 248–250 °C; IR (KBr, ν_{max}, cm^{-1}): 3432 (NH), 3045 (CH), 1656 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.20 (d, 2H, *J* = 8.2 Hz, Ar–H), 8.14 (d, 2H, *J* = 8.2 Hz, Ar–H), 7.77 (s, 1H, Ar–H), 7.50-7.48 (m, 2H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz): 177.2, 166.7, 161.3, 154.1, 135.6, 135.3, 133.6, 130.4, 127.6, 127.4, 124.2, 123.2, 118.3, 107.7;ESI–MS: 359 (M + H); Anal. calcd. (%) for $C_{16}H_8N_4O_2Cl_2$: C, 53.50; H, 2.25; Cl, 19.74; N, 15.60; Found (%): C, 53.52; H, 2.29; Cl, 19.82; N, 15.68.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)chroman-4-one (5a): Pale yellow coloured solid; m.p.: 260–262 °C; IR (KBr, ν_{max}, cm^{-1}): 3450 (NH), 3051 (CH) 1654 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.06 (d, 2H, *J* = 7.7 Hz, Ar–H), 7.56 (d, 2H, *J* = 7.7 Hz, Ar–H), 7.30 (d, 2H, *J* = 8.5 Hz, Ar–H), 6.89 (d, 2H, *J* = 8.5 Hz, Ar–H), 3.41-3.3.37 (dd, 1H, *J* =16.3 Hz, *J* = 3.5 Hz, CH), 3.17-3.08 (dd, 2H, *J* = 13.0 Hz, *J* = 16.3 Hz, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): 194.9, 184.7, 180.1, 175.0, 170.3, 162.8, 154.5, 151.3, 140.0, 112.1, 111.6, 105.0, 87.4, 69.3. ESI–MS: 293 (M + H). Anal. calcd. (%) for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17; Found (%): C, 65.79; H, 4.16; N, 19.20.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-fluorochrman-4-one (5b): Pale yellow coloured solid; m.p.: 256–258 °C; IR (KBr, ν_{max}, cm^{-1}): 3400 (NH), 3055 (CH) 1652 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): 7.92 (d, 2H, *J* = 8.3 Hz, Ar–H), 7.52 (d, 2H, *J* = 8.3 Hz, Ar–H), 7.19-7.09 (m, 3H, Ar–H), 3.73-3.66 (dd, 1H, *J* =14.3 Hz, *J* = 3.5 Hz, CH), 3.42-3.31 (dd, 2H, *J* = 12.6 Hz, *J* = 14.3 Hz, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): 192.3, 147.3, 138.7, 134.4, 133.5, 131.9, 127.2, 123.8, 112.8, 110.4, 77.8, 57.4. ESI–MS: 311 (M + H). Anal. calcd. (%) for $C_{16}H_{11}N_4O_2F$: C, 63.78; H, 3.85; F, 3.15; N, 18.60; Found (%): C, 63.81; H, 3.89; F, 3.20; N, 18.62

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-chlorochroman-4-one (5c): Pale yellow coloured solid; m.p.: 250–252 °C; IR (KBr, ν_{max}, cm^{-1}): 3412 (NH), 3041 (CH) 1650 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): 7.89 (d, 2H, *J* = 8.3 Hz, Ar–H), 7.58 (d, 2H, *J* = 8.3 Hz, Ar–H), 7.21-7.11 (m, 3H, Ar–H), 3.75-3.66 (dd, 1H, *J* =14.5 Hz, *J* = 3.1 Hz, CH), 3.18-3.28 (dd, 2H, *J* = 13.5 Hz, *J* = 14.5 Hz, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): 189.3, 150.3, 142.7, 135.4, 133.5, 131.9, 128.2, 125.8, 112.8, 111.4, 78.8, 58.4; ESI–MS: 327 (M + H). Anal. calcd. (%) for $C_{16}H_{11}N_4O_2Cl$: C, 58.82; H, 3.39; Cl, 10.85; N, 17.15; Found (%): C, 58.92; H, 3.46; Cl, 10.95; N, 17.19.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-bromochroman-4-one (5d): Pale yellow coloured solid; m.p.: 254–256 °C; IR (KBr, ν_{max}, cm^{-1}): 3409 (NH), 3020 (CH) 1640 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.09 (d, 2H, *J* = 8.53 Hz, Ar–H), 7.62 (d, 2H, *J* = 8.53 Hz, Ar–H), 7.23-7.12 (m, 3H, Ar–H), 3.79-3.64 (dd, 1H, *J* =13.5 Hz, *J* = 15.3 Hz, CH), 3.12-3.24 (dd, 2H, *J* = 11.3 Hz, *J* = 15.5 Hz, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): 191.3, 147.5, 137.7, 134.4, 133.5, 132.0, 128.2, 123.8, 112.8, 110.4, 79.8, 55.4; ESI–MS: 391 (M + H); Anal. calcd. (%) for $C_{16}H_{11}N_4O_2Br$: C, 51.77; H, 2.99; Br, 21.53; N, 15.09; Found (%): C, 51.79; H, 2.35; Br, 21.58; N, 15.19

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-6-methylchroman-4-one (5e): Pale yellow coloured solid; m.p.: 266–268 °C; IR (KBr, ν_{max}, cm^{-1}): 3412 (NH), 3040 (CH) 1660 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.0 (d, 2H, *J* = 8.53 Hz, Ar–H), 7.59 (d, 2H, *J* = 8.53 Hz, Ar–H), 7.26-7.16 (m, 3H, Ar–H), 4.01-3.94 (dd, 1H, *J* =15.3 Hz, *J* = 3.5 Hz, CH_2), 3.08-3.16 (dd, 2H, *J* = 12.5 Hz, *J* = 15.3 Hz, CH_2), 2.4 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): 191.9, 155.6, 147.0, 142.7, 141.9, 140.2, 135.6, 132.1, 128.8, 121.1, 118.7, 86.1, 65.7, 20.4; ESI–MS: 307 (M + H); Anal. calcd. (%) for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29; Found (%): C, 66.66; H, 4.61; N, 18.29

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-7-chloro-6-methylchroman-4-one (5f): Pale yellow coloured solid; m.p.: 261–263 °C; IR (KBr, ν_{max}, cm^{-1}): 3421 (NH), 3045 (CH) 1654

(C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): 7.9 (d, 2H, *J* = 8.33 Hz, Ar–H), 7.57 (d, 2H, *J* = 8.33 Hz, Ar–H), 7.24-7.18 (m, 2H, Ar–H), 4.07-3.95(dd, 1H, *J* =10.3 Hz, *J* = 3.3 Hz, CH), 3.02-3.15 (dd, 2H, *J* = 3.3 Hz, *J* = 10.3 Hz, CH_2), 2.4 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz): 192.5, 147.3, 142.7, 135.4, 133.5, 132.9, 127.2, 123.8, 111.8, 110.4, 79.8, 58.4; ESI–MS: 341 (M + H); Anal. calcd. (%) for $C_{17}H_{13}N_4O_2Cl$: C, 59.92; H, 3.85; Cl, 10.40; N, 16.44; Found (%): C, 59.98; H, 3.89; Cl, 10.44; N, 16.54.

2-(4-(1*H*-Tetrazol-5-yl)phenyl)-5,7-dichlorochroman-4-one (5g): Pale yellow coloured solid; m.p.: 262-264 °C; IR (KBr, ν_{max}, cm^{-1}): 3400 (NH), 3029 (CH) 1660 (C=O); ^{1}H NMR (DMSO-d_6, 400 MHz): 8.21 (d, 2H, *J* = 7.93 Hz, Ar–H), 7.59 (d, 2H, *J* = 7.93 Hz, Ar–H), 7.17-7.10 (m, 2H, Ar–H), 4.12-3.95 (dd, 1H, *J =15.3* Hz, *J = 3.2* Hz, CH), 3.05-3.18 (dd, 2H, *J* = 12.2 Hz, *J* = 15.3 Hz, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz): 189.3, 166.3, 152.7, 134.4, 132.5, 131.9, 129.2, 126.8, 112.8, 110.4, 79.8, 58.4; ESI–MS: 307 (M + H); Anal. calcd. (%) for $C_{16}H_{10}N_4O_2Cl_2$: C, 53.21; H, 2.79; Cl, 19.63; N, 15.51; Found (%): C, 53.24; H, 2.85; Cl, 19.62; N, 15.58.

RESULTS AND DISCUSSION

The synthesized compounds (**4a–g**) and (**5a–g**) was carried out under both the ultrasound and microwave irradiation methods produced a much higher reaction yield along with a significant decrease of the reaction time comparison with conventional heating (Table-1).

Antibacterial activity: All the synthesized compounds (**4a-g)** and (**5a-g)** were screened *in vitro* for their antibacterial activity against Gram-positive bacterial strains [*Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (ATCC 6633)] and Gram-negative bacterial strains [*Escherichia coli* (ATCC 25922), *Klebsiella pneumonia* (ATCC 13883)] using ciprofloxacin as the standard drug. The activity was determined using filter paper disc method by measuring the zone of inhibition in mm. The compounds were screened at the concentration of 20 and 40 µg/mL in DMSO. From the screening studies (Table-2), most of the compounds showed relatively better activity against Gram-positive bacterial strains and Gram-negative bacterial strains. Among all, compounds **4a**, **4b**, **5a** and **5b** were shown

TABLE-1
COMPARISON OF THE YIELD AND TIME OF THE SYNTHESIZED COMPOUNDS (**4a–g**) AND (**5a–g**)

Product	Time			Yield (%)		
	Conventional (h)	Microwave irradiation (min)	Ultrasound irradiation (min)	Conventional	Microwave irradiation	Ultrasound irradiation
4a	8	8	10	60	75	75
4b	9	9	9	65	77	74
4c	8	8	8	62	80	79
4d	9	10	9	63	79	79
4e	9	9	8	50	76	74
4g	8	10	7	62	80	79
5a	7	6	6	65	72	70
5b	8	7	7	69	75	74
5c	7	7	6	60	73	74
5d	6	8	7	63	73	73
5e	7	7	6	65	76	75
5g	7	8	8	60	73	73

TABLE-2
in vitro ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY RESULTS OF COMPOUNDS (**4a-g)** AND (**5a-g)**

Compounds	Inhibition zone (mm)										
	Gram-positive bacteria				Gram-negative bacteria				Fungi		
	S. aureus		*B. subtilis*		*K. pneumoniae*		*E. coli*		*A. niger*	*A. flavus*	*F. oxysporum*
Conc. (µg/mL)	20	40	20	40	20	40	20	40	50	50	50
4a	12	22	14	25	14	24	15	20	4.6	13.6	5.5
4b	12	24	09	17	19	26	16	22	14.5	4.9	17.0
4c	10	20	06	15	08	14	10	15	4.5	6.5	12.4
4d	10	20	09	15	06	14	07	18	2.6	6.4	4.5
4e	08	12	07	16	04	05	05	09	8.6	8.0	7.2
4f	07	15	04	12	05	07	05	10	8.4	11.2	4.5
4g	12	23	08	18	07	10	07	14	10.2	7.4	10.0
5a	13	23	12	26	20	22	14	24	8.1	8.4	9.0
5b	11	22	07	18	17	19	16	22	12.4	7.7	9.0
5c	11	22	10	14	09	14	08	15	8.4	6.1	8.3
5d	07	12	07	13	05	08	02	07	4.6	8.1	4.5
5e	11	20	08	14	08	12	08	11	7.8	4.9	7.9
5f	12	23	06	12	02	12	06	12	5.3	4.9	6.0
5g	10	17	10	16	09	14	05	12	2.5	12.8	5.6
Ciprofloxacin	15	28	16	30	23	35	18	35	–	–	–
Amphotericin-B	–	–	–	–	–	–	–	–	14.0	12.5	15.2

promising activity against Gram-positive bacterial strains and compounds **4c**, **4d**, **5c** and **5d** were shown moderate activity.

Antifungal activity: The antifungal activity of synthesized compounds (**4a-g**) and (**5a-g**) was tested against three pathogenic fungi, *Aspergillus niger*, *Aspergillus flavus* and *Fusarium oxysporum* using amphotericin-B as the standard drug. The activity was determined using the cup plate agar diffusion method by measuring the zone of inhibition in mm. The compounds were screened at a concentration of 50 µg/mL in DMSO. From the screening studies (Table-2). Among all compounds **4b**, **5b** with fluoro substitution on ring showed maximum activity against *A. niger* and *F. oxysporum*.

Conclusion

In conclusion, a series of novel compounds (**4a-e**) and (**5a-e**) derivatives were successfully synthesized by microwave and ultrasound irradiation methods to obtain excellent yields and shorter reaction time compared to conventional method. All the new compounds screened for antimicrobial activity, the synthesized compounds **4a**, **4b**, **5a** and **5b** showed good antibacterial activity against bacterial strains, where as the compounds **4b** and **5b** were more potent for pathogenic fungi compared to the standard drugs with their respective concentrations.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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