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A Mild and Efficient Protocol For the Synthesis of Novel Series of Chalcones and Homoisflavonoids as Potential Antimicrobial Agents

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Abstract: A novel approach was adopted for the synthesis of series of new chalcones and dihydrochalcones under ultrasonication. The dihydrochalcones were then converted into homoisflavonoids under Vilsmeier-Haak reaction condition with excellent yield. This method offers significant advantages such as efficiency and mild reaction conditions with shorter reaction time. Structures of these compounds were established on the basis of IR, ¹H NMR, ¹³C NMR and mass spectral data. The title compounds were evaluated for their antimicrobial activity. Compounds 3c, 3e, 3f, 4c and 4e exhibited potent antimicrobial activity as that of standard drugs.

Keywords: Ultrasound, Chalcones, 2-Hydroxydihydrochalcones, Homoisflavonoids, Antimicrobial activity.

1. Introduction

Homoisflavonoids are an uncommon subclass of flavonoids, mainly found in the Fabaceae, Asparagaceae, Polygonaceae, Portulacaceae, Orchidaceae, and Gentianaceae families. Although reports on homoisflavonoids have dated back to the late 1960s [1], studies of this family of compounds were scant at the turn of the century, and the situation did not change until approximately 2002. Then, the interest in homoisflavonoids began to grow gradually, presumably because more and more

homoisflavonoids were isolated. Presently, approximately 240 naturally occurring homoisflavonoids have been identified despite their rare occurrence in nature [2,3], and a range of biological properties, including anti-inflammatory, antioxidant, antidiabetic, and antimicrobial activities, have been observed for various homoisflavonoids [2,3]. In connection with structural elucidations and investigations of the bioactivity of homoisflavonoids, many synthetic studies have also been performed [3]. They mainly include a chromanone, chromone, or chromane skeleton and are ubiquitous in

plants such as Ophiopogon [4], Polygonatum [5], Scilla [6], Eucomis [7], and Muscari [8]. Recently, several homoisoflavonoids have been successfully isolated from plants and evaluated for their bioactivities [9,10]. Also these compounds and their synthetic analogues have shown important biological properties such as anti-tuberculosis activity [11] and inhibition of protein tyrosine kinase (PTK) [12].

Chalcones have been the center of attention owing to their significant biological activities [13-17]. Besides they are the most important precursors for the formation of α,β -unsaturated carbonyl system in flavonoid classes. Homoisoflavonoids including chalcone system have shown selective biological activities [18]. The isolated natural homoisoflavonoids having 3-benzylidenechroman-4-one skeleton were found to be potent and selective MAO-B inhibitors. Compounds involving benzylidene chromanone have depicted significant medicinal properties such as antioxidant [19], anticancer [20], anti-inflammatory [21], anti-human-immune deficiency virus (HIV-I) activities [22]. Search for new methodologies for the synthesis of homoisoflavonoids continues to be of great interest for organic chemists due to the immense interest of this system from synthetic and biological standpoints. The two most popular pathways for the synthesis of homoisoflavonoids are the deoxybenzoin and the chalcone routes [23]. A few methods of synthesis have been reported in the literature for homoisoflavonoids and these were based on (i) the condensation of 4-chromanones with arylaldehydes in MeOH by passing HCl gas or by using piperidine as a base [24] or condensation using acetic anhydride [25] followed by isomerisation of the C=C bond using Pd/C at 250 ° and, (ii) hydrogenation of chalcones followed by one carbon extension using ethyl formate/Na [26] or methanesulfonyl chloride/DMF [27]. (iii) Condensation of 2-hydroxy-dihydrochalcones with dimethylaminodimethoxymethane, a one

carbon unit molecule [28]. Recently V. M. Rao et.al. reported synthesis of homoisoflavones by one carbon extension using triethylorthoformate and 70% perchloric acid followed by aqueous hydrolysis of the intermediate perchlorates [29] etc. However these methods are associated with many drawbacks, such as, formation of undesired side reactions, hazardous, toxic, expensive reagents and have moderate yields. Therefore, developing a milder and more general procedure for the synthesis of homoisoflavonoids is still highly desirable.

On the synthesis of bioactive heterocycles containing oxygen specially chalcones and homoisoflavonoids; herein, we focused on to design a series of novel substituted homoisoflavonoids (**Scheme 1**) by Vilsmeier reagent (DMF-POCl₃) with dihydrochalcones in moderate to high yields. Then, we evaluated their antimicrobial activities.

2. Results and discussion

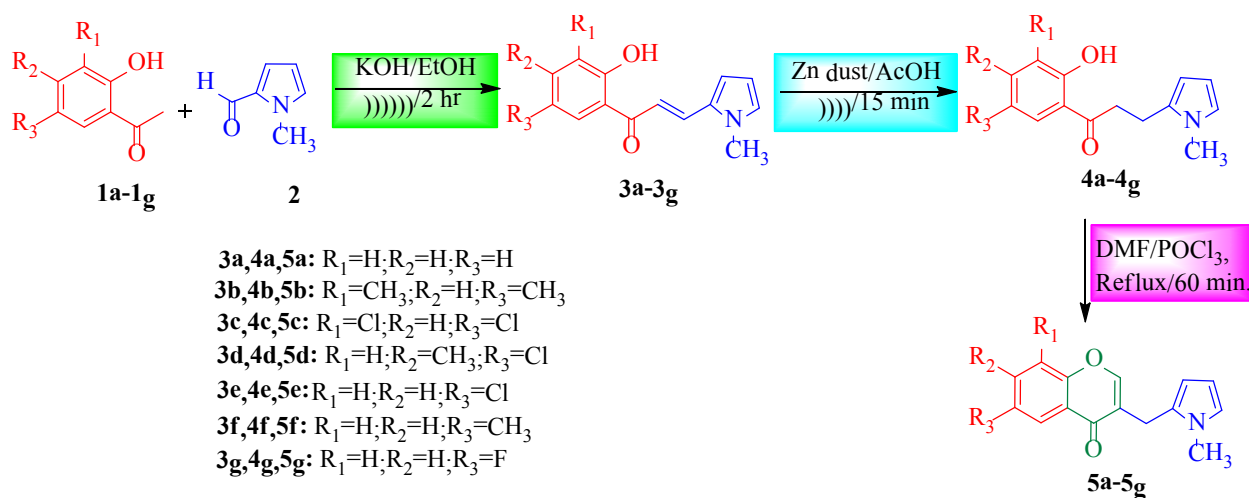
2.1 Chemistry.- As a part of our ongoing research in development of new biologically active chalcones and flavonoids [30,31] from readily available starting materials with our main strategy is to develop a efficient organic reaction enhancement method, which is relatively faster and cleaner than the reported methods. The strategies adopted for the synthesis of the intermediates and to target compounds are depicted in (**Scheme 1**). In order to obtain the key α,β -unsaturated intermediates as starting materials for the synthesis of the target products **5a-5g**, 3-((1-methyl-1*H*-pyrrol-3-yl)methyl)-4*H*-chromen-4-one derivatives, with high purity, **3a-3g** have been prepared by the Claisen-Schmidt condensation of commercially available 1-methyl-1*H*-pyrrole-2-carbaldehyde **2** was reacted with substituted *o*-hydroxy acetophenones **1a-1g** in EtOH under basic condition at room temperature under ultrasonic irradiation. This process afforded

the desired chalcones **3a-3g** with excellent yields. Then 1-(2-hydroxyphenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)propan-1-one **4a-4g** were synthesized by the chemoselective reduction of **3a-3g** using inexpensive and readily available Zn dust in AcOH under ultrasound irradiation at 60 °C within 15 min [32]. Under this reaction condition, C=O conjugated C=C bond in chalcones can be cleanly reduced C=C bond. The dihydrochalcones **4a-4g** was added to the Vilsmeier reagent (DMF-POCl₃) prepared by drop-wise addition of POCl₃ in ice cooled DMF. The mixture was heated to reflux for 60 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold H₂O, neutralized with NaHCO₃, the solid separated was filtered, washed with H₂O and crystallized from EtOH to obtain target molecules **5a-5g** in good yields (78–88%). Thus, our methodology added a new efficient procedure for the generation of **5a-5g** in excellent yields, to the existing reported methods.

2.2 Spectral data

The novel series of compounds **3a-3g**, **4a-4g** and **5a-5g** were fully characterized by spectroscopic

techniques such as IR, ¹H NMR, ¹³C NMR, EI-MS and elemental analysis, as summarized in the experimental section before being evaluated for *in vitro* antimicrobial activities. The [M + H]⁺ peak of all the compounds confirmed the respective molecular weights. The IR spectrum of **3a** showed a sharp and strong absorption band in the region of 1627–1635 cm⁻¹ which is due to C=O stretching of the formed chalcone. Another sharp and strongly absorption band at 3211–3220 cm⁻¹ was assigned to OH bond. The ¹H-NMR spectrum showed trans olefinic protons H_a and H_b as a doublets at δ 7.92 (*J* = 14.56 Hz) and δ 7.40 (*J* = 14.96 Hz) ppm, respectively. The value of spin–spin coupling constant *J*_{ab} in the range *J* > 15 Hz is indicative of the *E*-configuration of the chalcone. The MeN group of the *N*-methyl pyrrole moiety was apparent as a singlet at δ 3.79 ppm. The aromatic protons of the chalcones were present in the form of multiples. In the IR spectrum of **5a**, the C=O absorption band of homoisoflavonoid observed at 1661 cm⁻¹. The absorption bands at 1635 and 1555 cm⁻¹ were assigned to C=C and C–N groups of the pyrrole moiety, respectively. In the ¹H-NMR spectra of **5a**, showed one singlet in the region δ 6.91 ppm of chromone ring, these results supported the ring cyclization in the



Scheme 1. Synthesis of novel chalcones, dihydrochalcones and homoisoflavonoids.

products. The MeN group proton was present as sharp singlet at δ 3.65 ppm whereas protons of homoisoflavonoid CH_2 appeared at δ 3.46 ppm as another sharp singlet. Further evidence of the structure was given by mass spectrometry, which has given $[\text{M}]^+$ ion peak at 230.09 as base peak. Furthermore, all compounds showed signals due to aromatic, substituent protons in the expected region. Further confirmations of the structures were given by mass spectra and elemental analysis. The spectroscopic data of other compounds followed similar pattern.

3. Materials and methods

3.1 General

The melting points of all synthesized compounds were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Jasco FT-IR-4100, Japan, in KBr disc, ^1H NMR spectra were recorded on a Varian As 400 MHz spectrometer in $\text{CDCl}_3/\text{DMSO}-d_6$, chemical shift (δ) are in ppm relative to TMS and coupling constant (J) are expressed in hertz (Hz). Mass spectra were taken on a Macro mass spectrometer (Water) by electro-spray method (ES). Elemental analysis was performed on Perkin-Elmer EAL-240 elemental analyzer. Bandelin Sonorex (with a frequency of 35 kHz and a nominal power 200 W) ultrasonic bath was used for ultrasonic irradiation. Built-in heating, 30–80 °C thermostatically adjustable. The reaction vessel placed inside the ultrasonic bath containing water. The reactions were monitored by TLC on F254 silica-gel precoated sheets (Merck, Darmstadt, Germany) and the purified compounds each showed a single spot.

3.2 General procedure for the Synthesis of (E)-1-(2-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-ones 3a-3g

1-(5-Chloro-2-hydroxy-4-methylphenyl) ethanone (**1d**, 0.0027 mmol) in EtOH (10 ml) was added drop wise to a cooled 1-methyl-1H-

pyrrole-2-carbaldehyde (**2**, 0.0027 mmol) in 10% KOH (0.0081 mmol). Then the reaction mixture was sonicated at 20 kHz for 2 h at 25–30 °C. The progress of the reaction was monitored by thin layer chromatography by using ethyl acetate: pet ether (2:8) as eluent. After completion of the reaction, the mixture was poured into crushed ice and acidified with HCl (2N) till pH = 4. The solid was filtered under vacuum and crystallized from ethanol to give the title chalcone **3d**. The yield after crystallization of chalcones was 62–87%. In a similar fashion using general procedure we carried out the reactions of **1a-1c**, **1e-1g** with **2** to afford **3a-3c**, **3e-3g**. Their structures have been confirmed by ^1H -NMR, ^{13}C -NMR, Mass, IR spectra and elemental analysis.

(E)-1-(2-Hydroxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (3a): Yield: 88%, M.p. 88–90 °C. ^1H -NMR (400 MHz, CDCl_3): 3.79 (s, 1H, N- CH_3), 6.25 (dd, J = 3.28 and J = 7.9 Hz, 1H, Ar-H), 6.86 (d, 1H, Ar-H), 6.90 (m, 2H, Ar-H), 7.02 (m, 1H, Ar-H), 7.40 (d, J = 14.96 Hz, 1H, H_b), 7.45 (dd, J = 7.31 and J = 1.56 Hz, 1H, Ar-H), 7.87 (dd, J = 6.31 and J = 1.89 Hz, 1H, Ar-H), 7.92 (d, J = 14.56 Hz, 1H, H_a), 13.13 (s, 1H, OH). ^{13}C -NMR: 34.1, 109.2, 111.4, 123.4, 128.4, 130.4, 130.9, 131.2, 135.5, 137.4, 138.7, 190.3. MS: 228.12 $[\text{M}]^+$; IR (KBr) cm^{-1} : 3215 (OH), 1629 (C=O), 1530 (C-N). Elemental Analysis Calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: C, 73.99; H, 5.77; N, 6.16; Found: C, 74.02; H, 5.70; N, 6.22.

(E)-1-(2-Hydroxy-3,5-dimethylphenyl)-3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (3b): Yield: 83%, M.p. 115–117 °C. ^1H -NMR (400 MHz, CDCl_3): 2.17 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.76 (s, 3H, N- CH_3), 6.24 (dd, J = 3 Hz, 1H, Ar-H), 6.84 (d, J = 1.88 Hz, 1H, Ar-H), 6.91 (d, J = 2.72 Hz, 1H, Ar-H), 7.17 (d, J = 7.81 Hz, 1H, Ar-H), 7.37 (d, J = 8.2 Hz, 1H, Ar-H), 7.41 (d, J = 15.00 Hz, H_b), 7.86 (d, J = 14.96 Hz, H_a), 13.24 (s, 1H, -OH). ^{13}C -NMR: 25.3, 25.9, 34.3,

109.5, 111.7, 123.7, 128.9, 130.1, 130.4, 136.5, 137.1, 138.3, 139.4, 190.3. MS: 256.05 $[M]^+$; IR (KBr) cm^{-1} : 3211 (OH), 1631 (C=O), 1527 (C-N). Elemental Analysis Calcd. for $\text{C}_{15}\text{H}_{14}\text{Cl}_2\text{NO}_2$: C, 75.27; H, 6.71; N, 5.49; Found: C, 75.33; H, 6.65; N, 5.56.

(E)-1-(3,5-Dichloro-2-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (3c): Yield: 86%, M.p. 76-80 °C. ^1H -NMR (400 MHz, CDCl_3): 3.78 (s, 3H, N- CH_3), 6.25 (dd, $J = 3.83$ Hz, 1H, Ar-H), 6.88 (d, $J = 8.8$ Hz, 1H, Ar-H), 6.90 (dd, $J = 1.14$ Hz, 1H, Ar-H), 7.32 (d, 1H, Ar-H), 7.53 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.64 (d, $J = 14.92$ Hz, H_b), 7.89 (d, $J = 14.90$ Hz, H_a), 13.11 (s, 1H, -OH). ^{13}C -NMR: 34.4, 109.6, 111.8, 123.7, 128.6, 129.4, 129.9, 137.2, 137.5, 137.9, 141.7, 190.2. MS: 297.10 $[M]^+$ and 299.15 $[M]^+$; IR (KBr) cm^{-1} : 3215 (OH), 1634 (C=O), 1529 (C-N). Elemental Analysis Calcd. for $\text{C}_{14}\text{H}_{11}\text{Cl}_2\text{NO}_2$: C, 71.98; H, 4.32; N, 4.73; Found: C, 72.01; H, 4.42; N, 4.79.

(E)-1-(5-Chloro-2-hydroxy-4-methylphenyl)-3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (3d): Yield: 85%, M.p. 58-60 °C. ^1H -NMR (400 MHz, CDCl_3): 2.17 (s, 3H, CH_3), 3.79 (s, 3H, N- CH_3), 6.26 (dd, $J = 3$ Hz, 1H, Ar-H), 6.86 (dd, $J = 8.45$ Hz, 1H, Ar-H), 6.93 (dd, $J = 1.12$ Hz and $J = 7.5$ Hz, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 7.67 (d, $J = 14.98$ Hz, H_b), 7.80 (s, 1H, Ar-H), 7.91 (d, $J = 14.96$ Hz, H_a), 13.02 (s, 1H, -OH). ^{13}C -NMR: 16.3, 34.4, 109.6, 111.7, 123.8, 128.6, 130.1, 130.5, 131.6, 135.8, 137.3, 142.7, 190.9. MS: 276.13 $[M]^+$ and 277.12 $[M]^+$; IR (KBr) cm^{-1} : 3217 (OH), 1629 (C=O), 1522 (C-N). Elemental Analysis Calcd. for $\text{C}_{15}\text{H}_{14}\text{ClNO}_2$: C, 71.98; H, 4.32; N, 5.08; Found: C, 72.01; H, 4.42; N, 5.13.

(E)-1-(5-Chloro-2-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (3e): Yield: 80%, M.p. 55-57 °C. ^1H -NMR (400 MHz, CDCl_3): 3.79 (s, 3H, N- CH_3), 6.23 (dd, $J = 3.80$, 1H, Ar-H), 6.82 (dd, $J = 8.4$ Hz, 1H, Ar-H), 6.88

(dd, $J = 1.16$, 1H, Ar-H), 7.03 (d, 1H, Ar-H), 7.39 (dd, 1H, Ar-H), 7.53 (d, $J = 7.2$ Hz, 1H, Ar-H), 7.68 (d, $J = 14.90$, 1H, H_b), 7.89 (d, $J = 14.88$, 1H, H_a), 13.10 (s, 1H, OH). ^{13}C -NMR: 34.6, 110.2, 111.9, 123.7, 128.1, 129.3, 130.2, 130.8, 131.5, 135.2, 135.9, 140.7, 189.7. MS: 261.15 $[M]^+$; IR (KBr) cm^{-1} : 3214 (OH), 1635 (C=O), 1525 (C-N). Elemental Analysis Calcd. for $\text{C}_{14}\text{H}_{12}\text{ClNO}_2$: C, 71.98; H, 4.32; N, 5.35; Found: C, 72.01; H, 4.42; N, 5.41.

(E)-1-(2-Hydroxy-5-methylphenyl)-3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (3f): Yield: 75%, M.p. 96-98 °C. ^1H -NMR (400 MHz, CDCl_3): 3.76 (s, 3H, N- CH_3), 6.25 (dd, $J = 3.80$, 1H, Ar-H), 6.81 (dd, $J = 8.4$ Hz, 1H, Ar-H), 6.90 (dd, $J = 1.16$, 1H, Ar-H), 7.04 (d, $J = 6.8$ Hz, 1H, Ar-H), 7.41 (dd, $J = 7.2$ and $J = 1.6$ Hz, 1H, Ar-H), 7.56 (d, 1H, Ar-H), 7.64 (d, $J = 14.87$, 1H, H_b), 7.85 (d, $J = 14.84$, 1H, H_a), 13.12 (s, 1H, OH). ^{13}C -NMR: 25.7, 34.6, 109.1, 111.5, 123.6, 128.7, 130.3, 130.8, 136.9, 137.6, 138.7, 139.5, 190.8. MS: 242.3 $[M]^+$; IR (KBr) cm^{-1} : 3218 (OH), 1627 (C=O), 1520 (C-N). Elemental Analysis Calcd. for $\text{C}_{21}\text{H}_{15}\text{FO}_2\text{S}$: C, 71.98; H, 4.32; N, 5.81; Found: C, 72.01; H, 4.42; N, 5.88.

(E)-1-(5-Fluoro-2-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (3g): Yield: 73%, M.p. 130-132 °C. ^1H -NMR (400 MHz, CDCl_3): 3.79 (s, 3H, N- CH_3), 6.22 (dd, $J = 3.76$, 1H, Ar-H), 6.83 (dd, $J = 8.43$ Hz, 1H, Ar-H), 6.84 (dd, $J = 1.16$, 1H, Ar-H), 7.08 (d, $J = 1.8$ Hz, 1H, Ar-H), 7.45 (dd, 1H, Ar-H), 7.61 (d, $J = 7.4$ Hz, 1H, Ar-H), 7.65 (d, $J = 14.86$ Hz, 1H, H_b), 7.89 (d, $J = 14.91$, 1H, H_a), 13.09 (s, 1H, OH). ^{13}C -NMR: 34.6, 109.7, 111.1, 115.4, 122.4, 123.8, 126.3, 128.4, 131.4, 131.8, 135.5, 140.4, 164.7, 190.3. MS: 246.18 $[M]^+$; IR (KBr) cm^{-1} : 3214 (OH), 1633 (C=O), 1529 (C-N). Elemental Analysis Calcd. for $\text{C}_{21}\text{H}_{15}\text{FO}_2\text{S}$: C, 71.98; H, 4.32; N, 5.71; Found: C, 72.01; H, 4.42; N, 5.78.

3.3 General procedure for the preparation of 1-(2-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)propan-1-ones 4a-4g

Chalcone (**3a**, 0.0022 mmol) and Zn dust (0.0044 mmol) were well mixed in a round bottom flask and then AcOH (10 ml) was added. The reaction mixture was irradiated in ultrasonic at 65° for 28 min. After the completion of reaction monitor by TLC, the mixture was filtrated through filter paper and the filter cake was washed by EtOAc (10 ml) for three times. The filtrate was poured into H₂O (30 ml) and was adjusted to pH 5-6 with diluted NaOH aqueous solution, then extracted with EtOAc for three times. The combined organic layers were dried over anhydrous MgSO₄ and purified by column chromatography on silica gel eluted with mixture of petroleum ether/EtOAc (5:1) to afford **4a**. In a similar fashion using general procedure we carried out the reactions of **3b-3g** with Zn dust to afford **4b-4g**. The product obtained **4a-4g** was used for further reaction without any purification. Their structures have been confirmed by ¹H-NMR, Mass, IR spectra and elemental analysis.

1-(2-Hydroxyphenyl)-3-(1-methyl-1H-pyrrol-3-yl)propan-1-one (4a)s: Yield: 86%, M.p. 62-64 °C. ¹H-NMR (400 MHz, CDCl₃): 3.02 (*t*, *J* = 8.2 Hz, 2H, CH₂), 3.29 (*t*, *J* = 8.2 Hz, 2H, CH₂), 3.56 (*s*, 3H, N-CH₃), 6.20 (*dd*, 1H, Ar-H), 6.26 (*dd*, 1H, Ar-H), 6.48 (*dd*, 1H, Ar-H), 6.80 (*dd*, 1H, Ar-H), 7.28-7.87 (*m*, 3H, Ar-H), 12.11 (*s*, 1H, -OH). ¹³C-NMR: 23.3, 34.3, 46.4, 108.6, 109.7, 116.8, 122.3, 122.8, 123.5, 125.6, 131.1, 135.5, 161.6, 201.8. MS: 230.20 [M]⁺; IR (KBr) cm⁻¹: 3015 (OH), 2920, 2722 (CH₂), 1655 (C=O), 1591 (C=C). Elemental Analysis Calcd. for C₂₁H₁₅FO₂S: C: 73.34, H: 6.59, N: 6.11; Found: C: 73.30; H: 6.63; N: 6.15.

1-(2-Hydroxy-3,5-dimethylphenyl)-3-(1-methyl-1H-pyrrol-3-yl)propan-1-one (4b): Yield: 82%, M.p. 74-76 °C. ¹H-NMR (400 MHz, CDCl₃): 2.46 (*s*, 3H, CH₃), 2.59 (*s*, 3H,

CH₃), 3.03 (*t*, *J* = 8.4 Hz, 2H, CH₂), 3.26 (*t*, *J* = 8.4Hz, 2H, CH₂), 3.54 (*s*, 3H, N-CH₃), 6.23 (*dd*, 1H, Ar-H), 6.44 (*dd*, 2H, Ar-H), 6.89 (*d*, 1H, Ar-H), 7.67(*d*, 1H, Ar-H), 12.13 (*s*, 1H, -OH). ¹³C-NMR: 15.3, 23.6, 25.8, 34.7, 46.1, 108.2, 109.3, 122.6, 122.9, 123.6, 125.3, 128.3, 131.3, 137.5, 158.6, 201.3. MS: 258.16 [M]⁺; IR (KBr) cm⁻¹: 3010 (OH), 2918, 2726 (CH₂), 1658 (C=O), 1589 (C=C). Elemental Analysis Calcd. for C₂₁H₁₅FO₂S: C: 74.68, H: 7.44, N: 5.44; Found: C: 74.72; H: 7.49; N: 5.48.

1-(3,5-Dichloro-2-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-3-yl)propan-1-one (4c): Yield: 85%, M.p. 108-110 °C. ¹H-NMR (400 MHz, CDCl₃): 06 (*t*, *J* = 8.0 Hz, 2H, CH₂), 3.26 (*t*, *J* = 8.0 Hz, 2H, CH₂), 3.57 (*s*, 3H, N-CH₃), 6.20 (*dd*, 1H, Ar-H), 6.41 (*dd*, 2H, Ar-H), 6.86 (*d*, 1H, Ar-H), 7.57 (*d*, 1H, Ar-H), 12.10 (*s*, 1H, -OH). ¹³C-NMR: 23.6, 34.2, 46.7, 108.2, 109.4, 122.5, 122.7, 125.5, 125.8, 126.4, 129.1, 137.3, 158.6, 201.9. MS: 298.10 [M]⁺ and 300.13 (M+2) [M]⁺; IR (KBr) cm⁻¹: 3018 (OH), 2925, 2727 (CH₂), 1653 (C=O), 1586 (C=C), 765 (C-Cl). Elemental Analysis Calcd. for C₂₁H₁₅FO₂S: C: 56.39, H: 4.39, N: 4.70; Found: C: 56.34; H: 4.43; N: 4.73.

1-(5-Chloro-2-hydroxy-4-methylphenyl)-3-(1-methyl-1H-pyrrol-3-yl)propan-1-one (4d): Yield: 86%, M.p. 46-48 °C. ¹H-NMR (400 MHz, CDCl₃): 2.59 (*s*, 3H, CH₃), 3.05 (*t*, *J* = 8.1 Hz, 2H, CH₂), 3.29 (*t*, *J* = 8.1 Hz, 2H, CH₂), 3.52 (*s*, 3H, N-CH₃), 6.21 (*dd*, 1H, Ar-H), 6.48 (*d*, 1H, Ar-H), 6.80 (*d*, 1H, Ar-H), 7.28 (*s*, 1H, Ar-H), 7.63 (*s*, 1H, Ar-H), 12.10 (*s*, 1H, -OH). ¹³C-NMR: 16.4, 23.8, 34.9, 46.2, 108.7, 109.3, 117.3, 121.8, 123.3, 125.8, 127.5, 131.2, 142.5, 159.6, 201.4. MS: 278.15 [M]⁺ and 280.12 [M]⁺; IR (KBr) cm⁻¹: 3016 (OH), 2921, 2725 (CH₂), 1657 (C=O), 1590 (C=C), 762 (C-Cl). Elemental Analysis Calcd. for C₂₁H₁₅FO₂S: C: 64.87, H: 5.81, N: 5.04; Found: C: 64.91; H: 5.84; N: 5.00.

1-(5-Chloro-2-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-3-yl)propan-1-one (4e): Yield: 82%, M.p. 40-42 °C. ¹H-NMR (400 MHz, CDCl₃): 3.06 (t, *J* = 7.6 Hz, 2H, CH₂), 3.27 (t, *J* = 7.6 Hz, 2H, CH₂), 3.55 (s, 3H, N-CH₃), 6.26 (dd, 1H, Ar-H), 6.38 (d, 1H, Ar-H), 6.81 (d, 1H, Ar-H), 7.25 (d, 1H, Ar-H), 7.53 (dd, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 12.14 (s, 1H, -OH). ¹³C-NMR: 23.9, 34.3, 46.2, 108.4, 109.3, 118.8, 123.3, 124.8, 125.1, 127.6, 131.4, 135.3, 159.6, 201.3. MS: 263.5 [M]⁺ and 265.02 [M]⁺₂; IR (KBr) cm⁻¹: 3015 (OH), 2916, 2721 (CH₂), 1652 (C=O), 1592 (C=C), 763 (C-Cl). Elemental Analysis Calcd. for C₂₁H₁₅FO₂S: C: 63.76, H: 5.35, N: 5.31; Found: C: 63.72; H: 5.39; N: 5.36.

1-(2-Hydroxy-5-methylphenyl)-3-(1-methyl-1H-pyrrol-3-yl)propan-1-one (4f): Yield: 80%, M.p. 48-50 °C. ¹H-NMR (400 MHz, CDCl₃): 2.32 (s, 3H, CH₃), 3.05 (t, *J* = 7.6 Hz, 2H, CH₂), 3.26 (t, *J* = 7.6 Hz, 2H, CH₂), 3.54 (s, 3H, N-CH₃), 6.23 (dd, 1H, Ar-H), 6.40 (d, 1H, Ar-H), 6.80 (d, 1H, Ar-H), 7.31 (d, 1H, Ar-H), 7.49 (dd, 1H, Ar-H), 7.65 (d, 1H, Ar-H), 12.11 (s, 1H, -OH). ¹³C-NMR: 23.5, 25.3, 34.4, 46.6, 108.1, 109.2, 116.2, 122.5, 123.8, 125.2, 131.3, 131.5, 135.2, 158.6, 201.2. MS: 244.12 [M]⁺; IR (KBr) cm⁻¹: 3013 (OH), 2928, 2728 (CH₂), 1654 (C=O), 1591 (C=C). Elemental Analysis Calcd. for C₂₁H₁₅FO₂S: C: 74.05, H: 7.04, N: 5.76; Found: C: 74.11; H: 7.09; N: 5.71.

1-(5-Fluoro-2-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-3-yl)propan-1-one (4g): Yield: 83%, M.p. 72-74 °C. ¹H-NMR (400 MHz, CDCl₃): 3.07 (t, *J* = 7.2 Hz, 2H, CH₂), 3.26 (t, *J* = 7.2 Hz, 2H, CH₂), 3.50 (s, 3H, N-CH₃), 6.27 (dd, 1H, Ar-H), 6.42 (d, 1H, Ar-H), 6.84 (d, 1H, Ar-H), 7.36 (d, 1H, Ar-H), 7.56 (dd, 1H, Ar-H), 7.72 (d, 1H, Ar-H), 12.15 (s, 1H, -OH). ¹³C-NMR: 23.5, 34.8, 46.2, 108.8, 109.4, 116.2, 118.4, 122.0, 123.7, 125.2, 156.1, 157.5, 201.0. MS: 248.11 [M]⁺; IR (KBr) cm⁻¹: 3011 (OH), 2927, 2730 (CH₂), 1651 (C=O), 1588 (C=C). Elemental Analysis Calcd. for C₂₁H₁₅FO₂S: C:

68.00, H: 5.71, N: 5.66; Found: C: 68.05; H: 5.76; N: 5.70.

3.4 General procedure for the synthesis of various substituted 3-((1-methyl-1H-pyrrol-3-yl)methyl)-4H-chromen-4-one 5a-5g

1-(2-hydroxyphenyl)-3-(1-methyl-1H-pyrrol-2-yl)propan-1-one (**4a**, 0.0013 mmol) were added to the Vilsmeier reagent (DMF-POCl₃) prepared by drop-wise addition of POCl₃ (1.2 ml) in ice cooled DMF (10 ml). Then the reaction mixture was reflux at 80 °C for 60 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice cold H₂O, neutralized with NaHCO₃; the solid separated was filtered, washed with water and recrystallized from EtOH to obtain target molecules **5a** in good yield. In a similar fashion using general procedure we carried out the reactions of **4b-4g** with DMF/POCl₃ to afford **5b-5g**. Their structures have been confirmed by ¹H-NMR, ¹³C-NMR, Mass, IR spectra and elemental analysis.

3-((1-Methyl-1H-pyrrol-3-yl)methyl)-4H-chromen-4-one (5a): Yield: 76%, M.p. 208-210 °C. ¹H-NMR (400 MHz, CDCl₃): 3.46 (s, 2H, CH₂), 3.65 (s, 3H, N-CH₃), 6.00 (dd, 1H, Ar-H), 6.23 (d, 1H, Ar-H), 6.46 (d, 1H, Ar-H), 6.91 (s, 1H, Ar-H), 7.15-7.86 (m, 4H, Ar-H). ¹³C-NMR: 28.5, 35.1, 108.2, 109.7, 116.5, 118.0, 124.0, 124.6, 125.7, 125.9, 131.1, 136.5, 152.2, 158.3, 184.4. MS: 230.09 [M]⁺; IR (KBr) cm⁻¹: 1661 (C=O), 1632 & 1552 (C=C). Elemental Analysis Calcd. for C₁₅H₁₃NO₂: C, 75.30; H, 5.48; N, 5.85; Found: C, 75.27; H, 5.52; N, 5.80.

6,8-Dimethyl-3-((1-methyl-1H-pyrrol-3-yl)methyl)-4H-chromen-4-one (5b): Yield: 78%, M.p. 215-218 °C. ¹H-NMR (400 MHz, CDCl₃): 2.35 (s, 3H, Ar-CH₃), 2.52 (s, 3H, Ar-CH₃), 3.47 (s, 2H, CH₂), 3.65 (s, 3H, N-CH₃), 6.25 (dd, 1H, Ar-H), 6.27 (d, 1H, Ar-H), 6.31 (d, 1H, Ar-H), 6.93 (s, 1H, Ar-H), 7.16 (d, 1H, Ar-H), 7.56 (d,

1H, Ar-H). ^{13}C -NMR: 15.4, 25.6, 28.2, 35.3, 108.5, 109.2, 116.4, 123.4, 124.5, 125.6, 128.7, 128.9, 134.1, 138.5, 152.6, 155.3, 184.6. MS: 268.10 $[\text{M}]^+$; IR (KBr) cm^{-1} : 1667 (C=O), 1635 and 1555 (C=C). Elemental Analysis Calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}_2$ C, 76.38; H, 6.41; N, 5.24; Found: C, 76.34; H, 6.44; N, 5.28.

6,8-Dichloro-3-((1-methyl-1H-pyrrol-3-yl)methyl)-4H-chromen-4-one (5c): Yield: 80%, M.p. 110-113 °C. ^1H -NMR (400 MHz, CDCl_3): 3.51 (s, 2H, CH_2), 3.67 (s, 3H, N- CH_3), 6.24 (dd, 1H, Ar-H), 6.29 (d, 1H, Ar-H), 6.35 (d, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 7.26 (d, 1H, Ar-H), 7.60 (d, 1H, Ar-H). ^{13}C -NMR: 28.6, 35.5, 108.5, 109.9, 116.7, 123.8, 125.2, 127.9, 128.1, 129.1, 131.5, 151.2, 153.6, 184.8. MS: 307.02 $[\text{M}]^+$; IR (KBr) cm^{-1} : 1660 (C=O), 1631 and 1552 (C=C), 671 (C-Cl). Elemental Analysis Calcd. for $\text{C}_{15}\text{H}_{11}\text{Cl}_2\text{NO}_2$ C, 58.46; H, 3.60; N, 4.55; Found: C, 58.50; H, 3.65; N, 4.60.

6-Chloro-7-methyl-3-((1-methyl-1H-pyrrol-3-yl)methyl)-4H-chromen-4-one (5d): Yield: 79%, M.p. 155-157 °C. ^1H -NMR (400 MHz, CDCl_3): 2.55 (s, 3H, Ar- CH_3), 3.43 (s, 2H, CH_2), 3.69 (s, 3H, N- CH_3), 6.24 (dd, 1H, Ar-H), 6.25 (d, 1H, Ar-H), 6.26 (d, 1H, Ar-H), 6.90 (s, 1H, Ar-H), 7.17 (s, 1H, Ar-H), 7.86 (s, 1H, Ar-H). ^{13}C -NMR: 16.4, 28.7, 35.4, 108.6, 109.4, 116.1, 118.6, 123.3, 123.8, 125.0, 130.6, 131.7, 143.9, 152.1, 156.5, 184.7. MS: 288.07 $[\text{M}]^+$ and 290.12 $[\text{M}]^{+3}$; IR (KBr) cm^{-1} : 1665 (C=O), 1636 & 1550 (C=C), 675 (C-Cl). Elemental Analysis Calcd. for $\text{C}_{16}\text{H}_{14}\text{ClNO}_2$ C, 66.79; H, 4.90; N, 4.81; Found: C, 66.75; H, 4.88; N, 4.86.

6-Chloro-3-((1-methyl-1H-pyrrol-3-yl)methyl)-4H-chromen-4-one (5e): Yield: 72%, M.p. 220-222 °C. ^1H -NMR (400 MHz, CDCl_3): 3.49 (s, 2H, CH_2), 3.66 (s, 3H, N- CH_3), 6.21 (dd, 1H, Ar-H), 6.25 (d, 1H, Ar-H), 6.27 (d, 1H, Ar-H), 6.97 (s, 1H, Ar-H), 7.14 (d, 1H, Ar-H), 7.45 (dd, 1H, Ar-H), 7.68 (d, 1H, Ar-H). ^{13}C -NMR: 28.7, 35.5, 108.7, 109.2, 116.8, 120.0, 123.0,

125.3, 125.8, 130.9, 131.8, 136.5, 152.6, 154.3, 184.1. MS: 274.00 $[\text{M}]^+$; IR (KBr) cm^{-1} : 1667 (C=O), 1630 & 1558 (C=C), 670 (C-Cl). Elemental Analysis Calcd. for $\text{C}_{15}\text{H}_{12}\text{ClNO}_2$ C, 65.82; H, 4.42; N, 5.14; Found: C, 65.87; H, 4.46; N, 5.10.

6-Methyl-3-((1-methyl-1H-pyrrol-3-yl)methyl)-4H-chromen-4-one (5f): Yield: 70%, M.p. 228-230 °C. ^1H -NMR (400 MHz, CDCl_3): 3.51 (s, 2H, CH_2), 3.63 (s, 3H, N- CH_3), 6.25 (dd, 1H, Ar-H), 6.29 (d, 1H, Ar-H), 6.34 (d, 1H, Ar-H), 6.96 (s, 1H, Ar-H), 7.16 (d, 1H, Ar-H), 7.42 (dd, 1H, Ar-H), 7.71 (d, 1H, Ar-H). ^{13}C -NMR: 25.4, 28.1, 35.4, 108.9, 109.5, 116.2, 118.4, 123.2, 124.4, 124.8, 131.7, 134.9, 136.1, 136.5, 152.8, 155.3, 184.7. MS: 254.10 $[\text{M}]^+$; IR (KBr) cm^{-1} : 1660 (C=O), 1630 & 1557 (C=C). Analysis Calcd. for $\text{C}_{16}\text{H}_{15}\text{NO}_2$ C, 75.87; H, 5.97; N, 5.53; Found: C, 75.83; H, 6.01; N, 5.50.

6-Fluoro-3-((1-methyl-1H-pyrrol-3-yl)methyl)-4H-chromen-4-one (5g): Yield: 68%, M.p. 104-106 °C. ^1H -NMR (400 MHz, CDCl_3): 3.54 (s, 2H, CH_2), 3.65 (s, 3H, N- CH_3), 6.21 (dd, 1H, Ar-H), 6.25 (d, 1H, Ar-H), 6.30 (d, 1H, Ar-H), 7.00 (s, 1H, Ar-H), 7.18 (d, 1H, Ar-H), 7.47 (dd, 1H, Ar-H), 7.68 (d, 1H, Ar-H). ^{13}C -NMR: 28.7, 35.4, 108.5, 109.4, 116.2, 116.8, 120.1, 123.4, 124.3, 125.2, 126.9, 152.8, 154.3, 158.3, 184.8. MS: 258.09 $[\text{M}]^+$; IR (KBr) cm^{-1} : 1659 (C=O), 1632 & 1551 (C=C). Elemental Analysis Calcd. for $\text{C}_{15}\text{H}_{12}\text{FNO}_2$ C, 70.03; H, 4.70; N, 5.44; Found: C, 70.08; H, 4.74; N, 5.39.

3.5 Biological evaluation

The synthesized novel *N*-methyl pyrrole incorporated chalcones **3a-3g** and homoisoflavonoids **5a-5g** were then assayed for their *in vitro* antibacterial activity against Gram positive bacterial strain and Gram negative bacterial strain, and antifungal activity against all pathogenic fungal strains tested

using standardized agar well diffusion method for antibacterial [33] and antifungal activity [34]. The results were determined using the minimum inhibitory concentration (MIC) and the minimum inhibitory concentration (MIC) values that inhibited the growth of the tested microorganisms (MIC) and minimal bactericidal/fungicidal concentration were determined. The results have been reported in (Table 1, 2 and 3), along with those of standard drugs *Gentamicin* and *Nystatin*.

Antibacterial activity

The newly prepared compounds chalcones and homoisoflavonoids were tested for their *in vitro* antibacterial activity against two gram positive bacterial strain *Staphylococcus aureus* (ATCC No. 25923), *Bacillus subtilis* (ATCC 6633), and two gram negative bacterial strain, *Echerichia coil* (ATCC No, 25922) and *Pseudomonas aeruginosa* (ATCC No. 27853) (Table 1 and 2). The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. Standard antibiotics *Gentamicin* namely was used for comparison with antibacterial activity data shown by compounds **3a-3g** and **5a-5g**. All the compounds of the tested series possessed good antimicrobial activity. Four of these compounds **3d**, **3f**, **5d** and **5f** exhibited good antibacterial activity against Gram positive and Gram negative bacteria. In case of Gram positive bacteria compounds **3c**, **3f** and **5c** were found to be most effective against *Staphylococcus aureus* in the range of concentration 23 and 24 and compounds **3e** and **4e** were most effective against *Bacillus subtilis*, with the range of concentration between 23 and 24. However, in case of Gram-negative bacteria, compounds **3d**, **3f**, **5d** and **5f** were found to be most effective against *E. coil* and *P. aeruginosa* with zone of inhibition ranging between 18-20 (Table 1). Of the compound tested, compounds **3a** and **5f** expressed moderate to good activity against *S.*

aureus and compounds **3b**, **5a** and **5g** against *B. subtilis* whereas in case of Gram negative bacteria lowest MIC was found to be 58 µg/mL in case of *E. coil* by compounds **3a** and **5g** and 60 µg/mL in case of *P. aeruginosa* by compounds **5a** (Table 2).

Table 1. Antibacterial activity of compounds **3a-3g** and **5a-5g**

Compounds	Diameter of growth of inhibition zone (mm)			
	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Echerichia coil</i>	<i>Pseudomonas aeruginosa</i>
3a	10	13	12	15
3b	20	19	22	14
3c	23	20.5	20	22.6
3d	19	16	21	22
3e	23	20.2	20.5	21
3f	19	12	15	19
3g	20	21.6	20	19
5a	11	7	9	13
5b	19	18	17	13
5c	23	20	20.2	21.6
5d	18	17	19	16
5e	22	19	19	20
5f	14	13	17	15
5g	19	18	19	18.6
Gentamicin	24	22	21	23

Table 2. Minimum inhibitory concentration (MIC), (in µg/mL) of compounds **3a-3g** and **5a-5g**

Compounds	MIC (µg/mL) ^a			
	<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Echerichia coil</i>	<i>Pseudomonas aeruginosa</i>
3a	62	125	>125	>125
3b	30	62	>125	>125
3c	125	30	>125	>125
3d	62	125	125	>125
3e	125	14	>125	>125
3f	14	30	125	>125
3g	6	14	>125	>125
5a	62	6	125	>125

5b	6	6	60	62
5c	30	6	62	125
5d	14	6	125	>125
5e	125	62	62	>125
5f	62	125	>125	125
5g	14	58	125	62
Gentamicin	5	5	5	5

^aMean of three replicates

Antifungal activity

Antifungal activity was also done by all synthesized compounds. For assaying the antifungal activity two fungi *Candida albicans* and *Aspergillus niger* were tested *in vitro* for their antifungal activity. *Nystatin* was as standard drug used for comparison with antifungal activity shown by compounds **3a-3g** and **5a-5g**. A careful analysis revealed that almost all of the newly synthesized compounds **3a-3g** and **5a-5g** showed maximum potent inhibition against all the fungal strains as shown in (Table 3). Compounds **3e**, **3g**, **5e** and **5g** showed maximum inhibition against both of the fungi, *Candida albicans* and *Aspergillus niger*. Compounds **3c** and **5c** was found more effective against both fungi. Compounds **3b**, **3d**, **5d** and **5g** displayed moderate inhibition against both of the fungi.

Table 3. *In vitro* antifungal activity of compounds **3a-3g** and **5a-5g** by using agar well diffusion method.

Compounds	Diameter of growth of inhibition zone (mm)	
	<i>Candida albicans</i> ^a	<i>Aspergillus niger</i> ^a
3a	10	22
3b	16	10
3c	27	26
3d	20	18
3e	24	22
3f	08	22
3g	18	12
5a	08	16
5b	12	16
5c	28	28

5d	22	24
5e	21	20
5f	12	09
5g	20	24
Nystatin	30	30

^aZone of inhibition

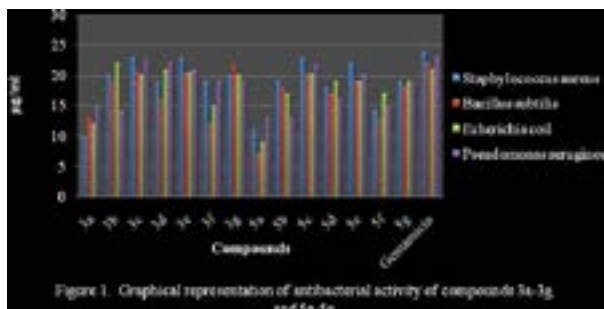


Figure 1. Graphical representation of antibacterial activity of compounds **3a-3g** and **5a-5g**

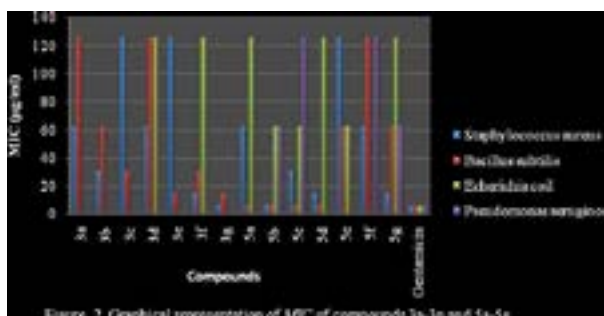


Figure 2. Graphical representation of MIC of compounds **3a-3g** and **5a-5g**

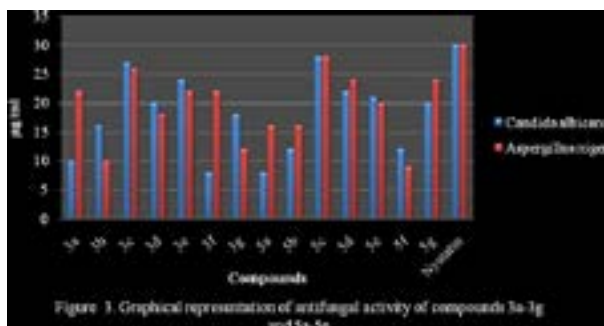


Figure 3. Graphical representation of antifungal activity of compounds **3a-3g** and **5a-5g**

It is interesting to note that different substituent's

moreover affect antibacterial and antifungal activity of compounds **3a-3g** and **5a-5g**. The presence of different substituents on phenyl ring i.e. chloro substitution in compounds influenced these molecules to exhibit inhibition to greater extent against the organisms tested. Methyl and Fluoro substitution present in compounds also increase the inhibitory effect of these compounds against the organism tested, which may be due to the electron withdrawing nature of this functional group. The presence of electron donating groups at ortho position or no substitution resulted with moderate activity.

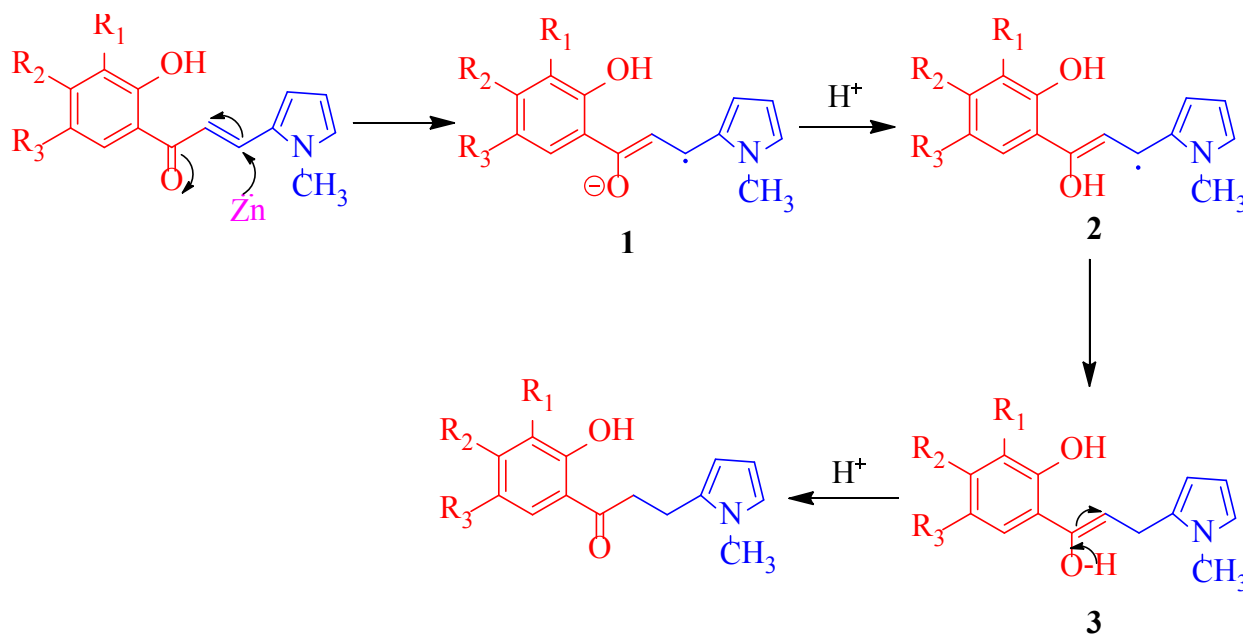
A possible mechanism was suggested in (Scheme 2); firstly, chalcone accepted electron from the zinc to form the anion free radical (1). Secondly, the anion free radical abstracted a proton from the solution of the reaction, then (2) was formed. Thirdly, (2) accepted an electron from the zinc to form the enol anion (3). Finally, the enol anion became the saturated alkane by passing a proton from acetic acid ion.

Conclusions

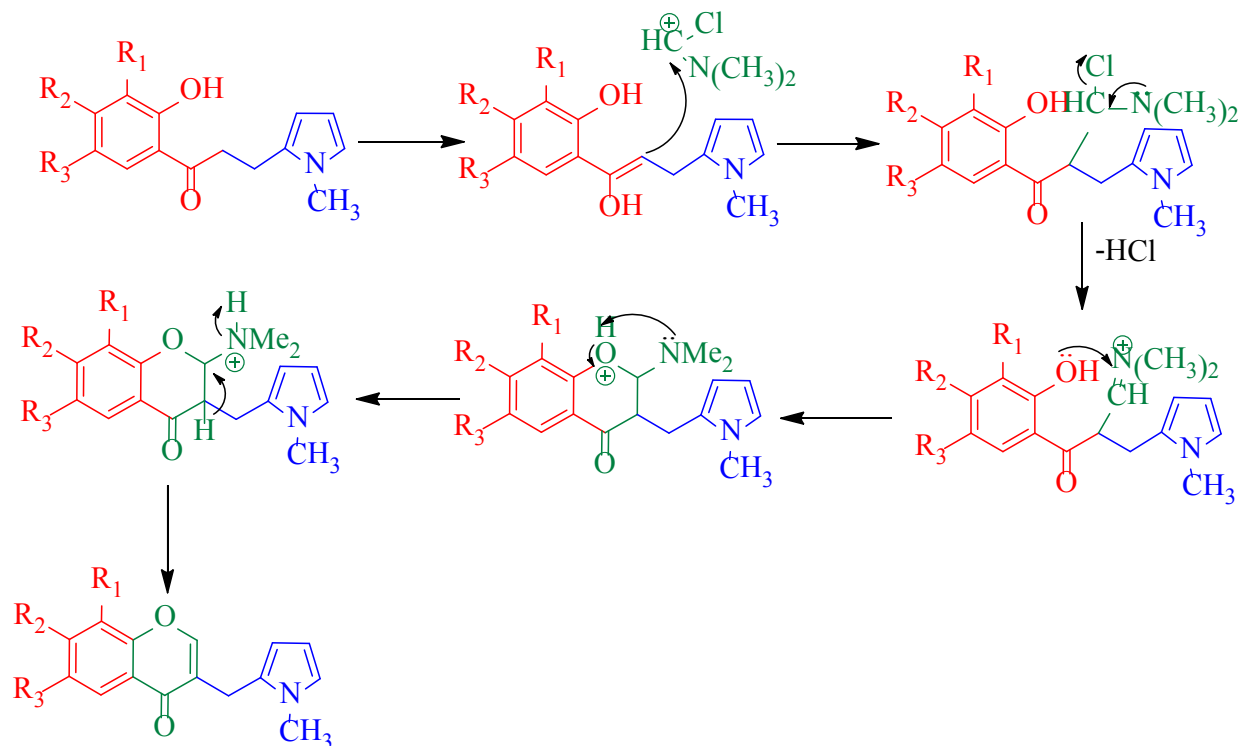
In summary, these studies should not only enable an extension of applicability of the ultrasound wave, but also introduce environmentally friendlier method for novel chalcones **3a-3g**, dihydrochalcones **4a-4g** and efficient protocol developed for homoisoflavonoid **5a-5g** and screened for their *in vitro* antimicrobial activity against four bacterial and two fungi. As a result, derivatives having electron withdrawing substituent's showed broad antimicrobial spectrum. Among the tested compounds, compounds **3c**, **3e**, **3f**, **4c**, **4e** and **5c** displayed good antimicrobial activity against all the tested strains and comp. **3c** and **5c** exhibited excellent antifungal activity against both fungi. We believed the insights gained in this study would be useful for the development of potential drug candidates derived from homoisoflavonoids.

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Scheme 2. Proposed mechanism for the formation of dihydrochalcone



Scheme 3. Proposed mechanism for the formation of homoisoflavonoid

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