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Synthesis, characterization and antibacterial activity of new series of prenyloxy chalcones and prenyloxy flavanones

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ABSTRACT

The prenyloxy chalcones and prenyloxy flavanones were synthesized and tested for antibacterial effects against E.coli, S.aureus. The synthesized compounds were characterized using IR, ¹H NMR, and MS data. The antibacterial screening of the synthesized compounds were performed in vitro by the filter paper disc diffusion method.

Keywords: synthesis of prenyloxy chalcones, prenyloxy flavanones, characterization, antibacterial activity.

INTRODUCTION

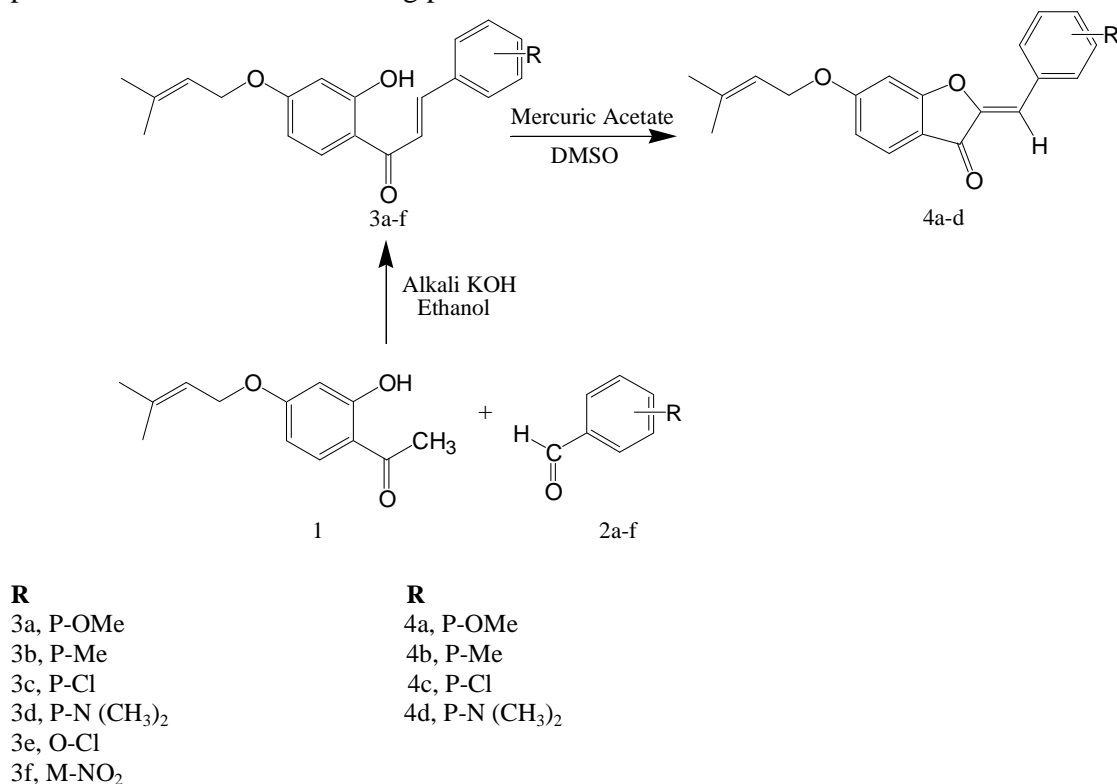
Chalcones and flavanones are widespread components in all parts of the plants and are important as flower pigments, growth regulators, phytoalexins, animal toxins [1, 2]. The growing interest of the synthesis of chalcones and flavanones for the last few years may be easily explained by their pharmacological activities Viz., Anti - bacterial [3], Antiulcer [4], Antifungal [5], Anticoagulating [6], Vasodilatory [7], Anti-pepticulcer [8], Anti mitotic [9], Narcosis Potentiation [10] and Antileishmanial [11] activities. Anti - psychotics actions, Monoamine oxidase inhibition, Anti-tubercular. It was reported that one phenolic group and certain degree of lipophilicity are required for the activity of the flavonoids [12]. Substitution of the flavonoid ring system with prenyl groups would increase their lipophilicity and consequently enhance their interaction with cellular membranes [13].

In the Claisen-Schmidt condensation of chalcones synthesis, 2'-hydroxyl functional group may cyclise to the corresponding flavanones under higher concentration of alkali, also, side reactions such as multiple condensation polymerizations and rearrangements are common, these undesirable side reactions decrease the yields of the target adduct and render their purification difficult [14] so, it was planned to use a weaker base like piperidine instead of using strong base to enhance the better yields.

In present communication, we report piperidine mediated synthesis of new prenyloxy chalcones **3** from 4-prenyloxy, 2-hydroxyl acetophenone and aromatic aldehyde and flavanones were cyclised from prenyloxy chalcones **3** under higher concentration of alkali sodium acetate. The structures of the compounds **3** and **4** have been established on the basis of elemental (C, H, and O) analysis, IR, ^1H NMR, MS spectral data and they were screened for antibacterial activities against *E. coli*, *S. aureus* by the filter paper disc diffusion method.

EXPERIMENTAL SECTION

Melting points were determined in open capillary tubes and were not corrected. IR spectra (KBr, λ_{max} in cm^{-1}) were recorded on a Bruker IFS 66 V spectrometer, ^1H NMR spectra (chemical shifts in δ , Ppm) on a Gemini - 400 MHz spectrometer in CDCl_3 using tetramethylsilane as the internal standard and MS spectra on a VG 70 70H spectrometer. The purity of the compounds was verified by TLC (benzene/ethyl acetate, 9:1), using Merck brand Silica Gel - G plates and spotting was done using iodine. The compound **1** was prepared from adopting the published procedure with the same melting point.



Scheme-1

General procedure for synthesis of 4'-prenyloxy, 2'-hydroxyacetophenone 1.

A solution of β -resacetophenone (0.5 g) in acetone (10 mL) was refluxed with prenyl bromide (0.4 mL) and anhydrous potassium carbonate (2 g) for 3h. The product crystallized from light petroleum ether at low temperature as colorless thick needles (0.5 g), mp. 45 - 47 °C, red ferric reaction; R_F 0.30 (solvent benzene - light petroleum 1: 1); V_{max} 1640 cm^{-1} .

General procedure for synthesis of 4'-prenyloxy, 2'-hydroxy chalcones 3.

To a mixture of 4'-prenyloxy, 2'-hydroxyacetophenone **1** (0.01 mol) and aromatic aldehyde **2** (0.01 mol) were dissolved in EtOH (50 mL). piperidine (1 mL) was added and refluxed. After the completion of reaction, which was monitored by TLC, ethanol was distilled off and residue was poured on ice water (100 mL). It was kept overnight in the refrigerator. The resulting solid was collected by filtration, washed with distilled water and crystallized from methanol to give corresponding chalcones **3**.

Synthesis of 1-[2-hydroxy-4-(3-methyl-but-2-enyloxy)-phenyl]-3-(4-methoxy-phenyl)-proenone 3a.

Yellow solid (0.69 g, 43.5%); mp. 87 °C; ir (KBr): 3420 (ν_{OH}), 1630 ($\nu_{C=O}$), 1130 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$); 1.75 (s, 6H, =C (CH_3)₂), 3.82 (s, 3H, -OCH₃), 4.61 (d, 2H, =CH-CH₂-), 5.46 (t, 1H, =CH-CH₂-), 7.95 (d, 1H, 6' - H), 6.34 (d, 1H, 5' - H), 6.54 (s, 1H, 3' - H), 7.92 (d, 1H, C_α H, $J = 15.3$ Hz), 8.12 (d, 1H, C_β H, $J = 15.3$ Hz), 13.62 (s, 1H, 2' - OH), 7.33 (m, 2H, 3, 5 - H), 7.46 (m, 2H, 2, 6 - H); ms m/z 338; Anal. Calcd for $C_{21}H_{22}O_4$; C, 74.71; H, 6.65; O, 18.98. Found: C, 74.52; H, 6.56; O, 18.90.

Synthesis of 1-[2-Hydroxy-4-(3-methyl-but-2-enyloxy)-phenyl]-3-p-tolyl-proenone 3b.

Yellow solid (0.61 g, 42.6%); mp. 91 °C; ir (KBr, cm^{-1}): 3440(ν_{OH}), 1640($\nu_{C=O}$), 1160(ν_{CH-O}); 1H nmr (400 MHz, $CDCl_3$); 1.72 (s, 6H, =C (CH_3)₂), 2.40 (s, 3H, -CH₃), 4.58 (d, 2H, =CH-CH₂-), 5.46 (t, 1H, =CH-CH₂-), 7.68 (d, 1H, 6' - H), 6.42 (d, 1H, 5' - H), 6.52 (s, 1H, 3' - H), 6.92 (d, 1H, C_α H, $J = 15.3$ Hz), 7.82 (d, 1H, C_β H, $J = 15.3$ Hz), 13.54 (s, 1H, 2' - OH), 7.13 (m, 2H, 3, 5 - H), 7.26 (m, 2H, 2, 6 - H); ms m/z 322; Anal. Calcd for $C_{21}H_{22}O_3$ (322.16); C, 78.48; H, 6.98; O, 14.98. Found: C, 78.23; H, 6.84; O, 14.88.

Synthesis of 1-[2-hydroxy-4-(3-methyl-but-2-enyloxy)-phenyl]-3-(4-chloro-phenyl)-proenone 3c.

Light yellow solid (0.53 g, 40.8%); mp. 185 °C; IR (KBr, cm^{-1}): 3500(ν_{OH}), 1650($\nu_{C=O}$), 1210(ν_{CH-O}); 1H nmr (400 MHz, $CDCl_3$); 1.75 (s, 6H, =C (CH_3)₂), 4.52 (d, 2H, =CH-CH₂-), 5.45 (t, 1H, =CH-CH₂-), 7.65 (d, 1H, 6'-H), 6.52 (d, 1H, 5'-H), 6.65 (s, 1H, 3'-H), 6.82 (d, 1H, C_α H, $J = 15.3$ Hz), 7.64 (d, 1H, C_β H, $J = 15.3$ Hz), 13.70 (s, 1H, 2'-OH), 7.03 (m, 2H, 3, 5-H), 7.29 (m, 2H, 2, 6-H); Ms M/z 342; Anal. Calcd for $C_{20}H_{19}ClO_3$ (342.); C, 70.11; H, 5.95; O, 14.18. Found: C, 70.07; H, 5.57; O, 14.04.

Synthesis of 3-(4-dimethylamino-phenyl)-1-[2-hydroxy-4-(3-methyl-but-2-enyloxy)-phenyl]-propenone 3d.

Dork red solid (0.38 g, 24.6%); mp. 95 °C; ir (KBr, cm^{-1}): 3420(ν_{OH}), 1630($\nu_{C=O}$), 1130(ν_{CH-O}); 1H nmr (400 MHz, $CDCl_3$); 1.78 (s, 6H, =C (CH_3)₂), 2.83 (s, 6H, -N(CH_3)₂), 4.58 (d, 2H, =CH-CH₂-), 5.46 (t, 1H, =CH-CH₂-), 7.90 (d, 1H, 6'-H), 6.34 (d, 1H, 5'-H), 6.54 (s, 1H, 3'-H), 6.92 (d, 1H, C_α H, $J = 15.3$ Hz), 7.82 (d, 1H, C_β H, $J = 15.3$ Hz), 13.48 (s, 1H, 2'-OH), 7.13 (m, 2H, 3, 5-H), 7.26 (m, 2H, 2, 6-H); Ms M/z 351; Anal. Calcd for $C_{22}H_{25}NO_3$ (351); C, 75.19; H, 7.17; O, 13.66, N, 3.99. Found: C, 75.10; H, 6.95; O, 13.76, N; 3.87.

Synthesis of 1-[2-hydroxy-4-(3-methyl-but-2-enyloxy)-phenyl]-3-(2-chloro-phenyl)-proenone 3e.

Yellow solid (0.54 g, 41.6%); mp. 89 °C; IR (KBr, cm^{-1}): 3420(ν_{OH}), 1630($\nu_{\text{C=O}}$), 1130($\nu_{\text{=CH-O}}$); ^1H nmr (400 MHz, CDCl_3); 1.78 (s, 6H, =C (CH_3)₂), 4.50 (d, 2H, =CH- CH_2 -), 5.42 (t, 1H, =CH- CH_2 -), 7.83 (d, 1H, 6'-H), 6.85 (d, 1H, 5'-H), 6.95 (s, 1H, 3'-H), 7.02 (d, 1H, C_α H, $J = 15.3$ Hz), 7.62 (d, 1H, C_β H, $J = 15.3$ Hz), 13.50 (s, 1H, 2'-OH), 7.03 (m, 2H, 3, 5-H), 7.28 (m, 2H, 4, 6-H); Ms M/z 323; Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{ClO}_3$ (342); C, 70.11; H, 5.65; O, 14.28. Found: C, 70.09; H, 5.58; O, 14.01.

Synthesis of 1-[2-hydroxy-4-(3-methyl-but-2-enyloxy)-phenyl]-3-(3-nitro-phenyl)-proenone 3f.

Light yellow solid (0.45 g, 36.6%); mp. 103 °C; ir (KBr, cm^{-1}): 3420(ν_{OH}), 1630($\nu_{\text{C=O}}$), 1130($\nu_{\text{=CH-O}}$); ^1H nmr (400 MHz, CDCl_3); 1.78 (s, 6H, =C (CH_3)₂), 4.58 (d, 2H, =CH- CH_2 -), 5.46 (t, 1H, =CH- CH_2 -), 7.76 (d, 1H, 6'-H), 6.40 (d, 1H, 5'-H), 6.52 (s, 1H, 3'-H), 6.92 (d, 1H, C_α H, $J = 15.3$ Hz), 7.82 (d, 1H, C_β H, $J = 15.3$ Hz), 13.45 (s, 1H, 2'-OH), 7.13 (m, 2H, 4, 5-H), 7.26 (m, 2H, 2, 6-H); Ms M/z 353; Anal. Calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_5$ (353): C, 67.98; H, 5.45; O, 22.69 N, 3.96. Found: C, 67.85; H, 5.42; O, 22.54; N, 3.86.

General procedure for synthesis of 4'-prenyloxy flavanone 4.

To the prenyloxy chalcone **3** (800 mg) in ethanol (30 mL), Sodium acetate (6.0 g) was added. The mixture was maintained at 60 - 70 °C for 3 - 4 hrs and then left at room temperature for three days. The product which was a mixture of the chalcone and flavanone was subjected to column chromatography over silica-gel. The flavanone was obtained as a yellow liquid on elution with pet- ether- acetone (45: 5), which on keeping solidified. Yield (520 mg) (42.5 %) mp. 185 -187 °C; ir: 1660, 1600 cm^{-1}

Synthesis of 2-(4-methoxy-phenyl)-7-(3-methyl-but-2-enyloxy)chroman-4-one 4a.

Yellow solid (0.520 g, 39.3%); mp. 129-131 °C; ir (KBr, cm^{-1}): 1630 ($\nu_{\text{C=O}}$), 1510 ($\nu_{>\text{C=C}}$); 1130 ($\nu_{\text{=CH-O}}$); ^1H nmr (400 MHz, CDCl_3); 1.78 (s, 6H, =C(CH_3)₂), 4.58 (d, 2H, =CH- CH_2 -), 5.46 (t, 1H, =CH- CH_2 -), 3.82 (s, 3H, - OCH_3), 2.78 (dd, 1H, $J = 17.4$ Hz and $J = 3.3$ Hz, H-3a), 3.20 (1H, dd, $J = 17.4$ and $J = 12.9$, H-3b), 5.62 (dd, 1H, $J = 10.0$ Hz and $J = .0$ Hz, H-2), 7.95 (d, 1H, 6-H), 6.34 (d, 1H, 5-H), 6.54 (s, 1H, 3-H), 7.13 (m, 2H, 3, 5-H), 7.26 (m, 2H, 2, 6-H); Ms M/z 338; Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{O}_4$ (338): C, 74.54; H, 6.55; O, 18.99. Found: C, 74.35; H, 6.41; O, 18.87.

Synthesis of 2-(4-methyl-phenyl)-7-(3-methyl-but-2-enyloxy)-chroman-4-one 4b.

Dark yellow solid (0.46 g, 38.9 %); mp. 167 °C; ir (KBr, cm^{-1}): 1650($\nu_{\text{C=O}}$), 1540($\nu_{>\text{C=C}}$); 1120($\nu_{\text{=CH-O}}$); ^1H nmr (400 MHz, CDCl_3); 1.73(s, 6H, =C (CH_3)₂), 4.61(d, 2H, =CH- CH_2 -), 5.43 (t, 1H, =CH- CH_2 -), 2.40 (s, 3H, - CH_3), 2.82 (dd, 1H, $J = 17.4$ Hz and $J = 3.3$ Hz, H-3a), 3.25 (1H, dd, $J = 17.4$ and $J = 12.9$, H-3b), 5.68 (dd, 1H, $J = 10.0$ Hz and $J = 4.0$ Hz, H-2), 7.82 (d, 1H, 6-H), 6.40 (d, 1H, 5-H), 6.64 (s, 1H, 3-H), 7.10 (m, 2H, 3, 5-H), 7.28 (m, 2H, 2, 6-H); Ms M/z 322; Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{O}_3$ (322): C, 78.71; H, 6.88; O, 14.99. Found: C, 78.25; H, 6.78; O, 14.87.

Synthesis of 2-(4-chloro-phenyl)-7-(3-methyl-but-2-enyloxy)chroman-4-one 4c.

Light yellow solid (0.47 g, 40.5%); mp. 183 °C; ir (KBr, cm^{-1}): 1645($\nu_{\text{C=O}}$), 1535($\nu_{>\text{C=C}}$); 1080($\nu_{\text{=CH-O}}$); ^1H nmr (400 MHz, CDCl_3); 1.76 (s, 6H, =C (CH_3)₂), 4.58 (d, 2H, =CH- CH_2 -), 5.46 (t, 1H, =CH- CH_2 -), 2.62 (dd, 1H, $J = 17.4$ Hz and $J = 3.3$ Hz, H-3a), 3.15 (1H, dd, $J = 17.4$ and $J = 12.9$, H-3b), 5.68 (dd, 1H, $J = 10.0$ Hz and $J = 4.0$ Hz, H-2), 7.95 (d, 1H, 6-H), 6.34 (d,

1H, 5-H), 6.54 (s, 1H, 3-H), 7.13 (m, 2H, 1, 5-H), 7.26 (m, 2H, 2, 4-H); Ms M/z 342; Anal. Calcd for C₂₀H₁₉ClO₃ (342): C, 70.11; H, 5.59; O, 14.09. Found: C, 70.05; H, 5.54; O, 14.07.

Synthesis of 2-(4-dimethylamino-phenyl)-7-(3-methyl-but-2-enyloxy)-chroman-4-one 4d.

Red solid (0.50 g, 41.2%); mp. 181 °C; ir (KBr, cm⁻¹): 1635(v_{C=O}), 1540(v_{>C=C<}); 1070(v_{=CH-O-}); ¹H nmr (400 MHz, CDCl₃); 1.78 (s, 6H, =C (CH₃)₂), 4.58 (d, 2H, =CH-CH₂-), 5.46 (t, 1H, =CH-CH₂-), 2.78 (dd, 1H, J = 17.4 Hz and J = 3.3 Hz, H-3a), 3.20 (1H, dd, J = 17.4 and J = 12.9, H-3b), 5.62 (dd, 1H, J = 10.0 Hz and J = 4.0 Hz, H-2), 7.95 (d, 1H, 6-H), 6.34 (d, 1H, 5-H), 6.54 (s, 1H, 3-H), 7.13 (m, 2H, 1, 5-H), 7.26 (m, 2H, 2, 4-H); Ms M/z 323; Anal. Calcd for C₂₂H₂₅NO₃ (351): C, 75.19; H, 7.17; O, 13.66. Found: C, 75.05; H, 7.14; O, 13.47.

Antibacterial activities

The antibacterial activity of the compounds thus prepared has been evaluated following the filter paper disc technique of Vincent and Vincent. (Gram - negative) bacteria namely *Escherichia coli* (Gram - positive) bacteria, namely *S. aureus* have been used as test organisms. 30 mg of different prenylated chalcone derivatives Compounds **3a-f**, **4a-d** were dissolved in (15 mL) of acetone. They were apportioned into (6 mL) to (9 mL) into china dishes. The walkman filter paper disc (mm diameter) was added and shaken thoroughly. They were allowed to dry. The amount of substance per paper disc was calculated (600 and 900 µg / mL). Paper discs treated without chemical agent served as control. The filter paper discs with chemical substances were implanted onto a log phase bacterial seeded nutrient, agar plates, Petri plates thus prepared were incubated at 37 °C for 72 h and the zone of inhibition of bacterial growth was measured. Then, the antimicrobial activity of the test agents was determined by measuring the diameter of zone of inhibition expressed in mm. the experiment was carried out in triplicate.

RESULTS AND DISCUSSION

The synthesis of **3** was carried out by condensation of an ethanolic solution of a 4-prenyloxy, 2-hydroxy acetophenone **1** in the presence piperidine with P-methoxy benzaldehyde **2** as shown in the (scheme-1). The compounds **3** gave violet colouration with alcoholic FeCl₃ test indicating the presence of chelated hydroxyl group in it. IR spectra of compounds **3** showed a broad band centered at 3439 cm⁻¹ assignable to chelated hydroxyl (-OH) group. An intense absorption observed at 1622 cm⁻¹ is for hydrogen bonded carbonyl (C=O) function in the chalcone. Vinylic stretching of Tran's double bond (C=C) is observed at 1590 cm⁻¹ and 1415 cm⁻¹. The presence of Gem - dim ethyl function in the compound is indicated by the absorption at 1360 cm⁻¹ and (=CH-O-) group absorption at 1160 cm⁻¹. Other aromatic skeletal vibrations are also observed in the spectrum.

The ¹HNMR Spectra exhibited as a broad singlet due to Gem-dim ethyl function of 4'-O-prenyl group appeared at 1.75 δ integrating for six hydrogens. A doublet recorded at 4.62 δ is ascribed to one methylene group of isoprenyl substitution attached to hydroxyl group of aromatic ring. A triplet with intensity corresponding to two hydrogens is split due to coupling with Vinylic hydrogen in isopentenyl group which appear at 5.41 δ. This completes the set of peaks characteristic of 4'-prenyloxy group. Acetophenone ring of chalcone as A - ring has down field absorption observed at 7.95 δ. It is justifiable only if the hydrogen is present near carbonyl group since it can appear at a low field due to deshielding effect of carbonyl function and the remaining

two hydrogens appeared at 6.54 δ , 6.34 δ and 2'-hydroxy group (-OH) appeared as broad singlet at 13.54 δ .

The characteristic signals for C α , C β hydrogens of chalcone double bond appears as doublets which are observed at 7.92 δ (d, 1H, $J = 15.3$ Hz) and 8.12 δ (d, 1H, $J = 15.3$ Hz) respectively. 4'-Prenyloxy chalcone has p-methoxy phenyl as B-ring. The hydrogens of phenyl ring have appeared peaks in between 7.20 - 7.55 δ range, and three hydrogens of methoxy group appeared as broad singlet at 3.82 δ .

Confirmative proof for the structure proposed for 4'-prenyloxy chalcone **3** came from the fragmentation pattern observed in mass spectrum which is well supported by elemental composition offered by accurate mass 338 m/z measurement system. Some important fragmentation peaks 307 m/z, 254 m/z, 145 m/z, 69 (68 %) m/z, 41 (100 %) m/z. It is found to be in agreement with the literature.

The final step of the synthesis of flavanone **4** was to cyclise the corresponding chalcone **3**. Prior to this, chalcone **3** which was subjected to acid hydrolysis (HCl 10 %) and subsequent treatment with excessive NaOAc in ethanol has provided flavanone **4** as a yellow solid with mp. 129 - 131 $^{\circ}$ C, yield (39.3 %).

The IR spectrum of compound **4** absorption observed at 1622 cm^{-1} is for hydrogen bonded carbonyl (C=O) function group. Aromatic double bond (C=C) is observed at 1590 cm^{-1} and 1415 cm^{-1} . (=CH-O-) group is absorption observed at 1160 cm^{-1} and other aromatic skeletal vibrations are also observed in the spectrum.

The ^1H NMR Spectra data of flavanone **4** showed the signals of the prenyl group were still intact at δ 1.78 (s, 6H, 2x - CH $_3$), 4.58 (d, 2H, $J = 7.5$ Hz, =CH-CH $_2$ -), 5.46 (t, 1H, =CH-CH $_2$ -), 3.82 (s, 3H, -OCH $_3$), the formation of flavanone **4** was deduced from the characteristic signals at δ 2.78 (dd, 1H, $J = 17.4$ Hz and $J = 3.3$ Hz, H - 3a), 3.20 (1H, dd, $J = 17.4$ and $J = 12.9$, H - 3b), and 5.62 (dd, 1H, $J = 10.0$ Hz and $J = 4.0$ Hz, H-2) in addition the signal of phenolic protons were observed at 7.95 (d, 1H, 6 - H), 6.34 (d, 1H, 5 - H), 6.54 (s, 1H, 3 - H), 7.13 (m, 2H, 3, 5 - H), 7.26 (m, 2H, 2, 6 - H). Confirmative proof for the structure proposed for 4'-prenyloxy flavanones **4** came from the fragmentation pattern observed in mass spectrum which is well supported by elemental composition offered by accurate mass 336 m/z measurement system.

Antibacterial activities

All the prenyloxy chalcones were screened for their antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* using streptomycin as standard drug. Nutrient Agar was used as culture medium. Test solution and standard drug having 400 and 600 $\mu\text{g} / \text{mL}$ concentration were prepared in acetone and used for testing growth inhibition by filter paper disc technique of Vincent and Vincent [15].

The results revealed that majority of the synthesized compounds showed varying degrees of inhibition against the tested microorganisms. In general, the inhibitory activity against the Gram-negative bacteria was higher than that of the Gram-positive bacteria. The 3a, 3b showed excellent activity against Gram-negative bacteria, *E. coli* and 4a, 4b showing good activity against Gram-positive bacteria *S. aureus*. And 3e, 3f, 4c showed weak activities against *E. coli*

and *S. aureus* respectively. The preliminary result confirms the importance of prenyloxy nucleus and hetero nucleus with respect to antibacterial activity. The results of the compounds of preliminary antibacterial testing are shown in Table-1.

Table-1: Antibacterial activity of compounds 3a-f, 4a-d.

Compd	Antibacterial activity Inhibition(mm)		Compd	Antibacterial activity Inhibition(mm)	
	<i>E.Coli</i> (-)	<i>S.aures</i> (+)		<i>E.Coli</i> (-)	<i>S.aures</i> (+)
3a	7.8	8.5	4a	7.9	8.6
3b	6.9	7.8	4b	7.4	8.6
3c	5.4	6.5	4c	6.9	5.7
3d	4.8	4.3	4d	5.3	6.2
3e	3.6	5.0	<i>Streptomycin</i>	9.3	8.5
3f	3.8	4.0			

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