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Piperidine mediated synthesis of new series of prenyloxy chalcones, flavanones and comparative cytotoxic study

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ABSTRACT

The prenyloxy chalcones were synthesized by piperidine mediated condensation of an ethanolic solution of a 4-prenyloxy 2-hydroxy acetophenone with aromatic or hetero aldehydes and corresponding prenyloxy flavanones also were obtained from mixture of the prenyloxy chalcone and flavanone was subjected to column chromatography over silica-gel. In this article, mainly explained structural elucidations of newly synthesized compounds along with the brief description of the targets and reported piperidine mediated synthesis. The piperidine is planned to use a weaker base instead of strong base to enhance the better yields. The structures of the compounds have been established on the basis of elemental (C, H, and O) analysis and IR, 1H NMR, MS spectral data. Synthesized compounds were screened for comparative study of cytotoxic analysis.

Keywords: Prenyloxy chalcones, prenyloxy flavanones, cytotoxic analysis,

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INTRODUTION

Prenylated chalcones are well known naturally occurring pigments which serve as valuable intermediate in organic synthesis of flavonoid compounds [1]. It has found significant role in pharmaceutical effects [2], including anti oncogenic, anti-inflammatory, anti ulcerative, analgesic, antiviral, anti malarial and antibacterial activities. The prenylated chalcones and flavanones are a unique class of naturally occurring flavonoid characterized by the presence of a prenylated side chain in the flavonoid skeleton. It was reported that one phenolic group and certain degree of lipophilicity are required for the activity of the flavonoids[3] Substitution of the flavonoid ring system with prenyl groups would increase their lipophilicity and consequently enhance their interaction with cellular membranes[4]. A number of chalcones having hydroxy, methoxy groups in different position have been reported to possess anti-bacterial[5], antiulcer[6], antifungal[7], anticoagulating[8], vasodilatory[9], anti peptic ulcer[10], anti mitotic[11], narcosis potentiation[12], and antileshmanial[13], activities.

In the claisen-schemidt 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 reaction decreases 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. A series of new prnyloxy chalcones and flavanones were synthesized by piperidine mediated condensation and synthesized compounds were screened for comparative study of cytotoxic analysis.

MATERIALS AND METHODS

Melting points were determined in open capillary tubs and were not corrected. IR spectra (KBr, λ_{max} in cm^{-1}) were recorded on a Bruker IFS 66V spectrometer, 1H NMR spectra (chemical shifts in δ, Ppm) on a Gemini-400MHzz spectrometer in $CDCl_3$ using tetramethylsilane as the internal standard and MS spectra on a VG 7070H 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 major compound 1 was prepared from adopting the published procedure with the same melting point.

***Synthesis of* 1**.
A solution of β-resacetophenone (0.5g) in acetone (10ml) was refluxed with prenyl bromide (0.4ml) and anhydrous potassium carbonate (2gms) for 3hrs. The product crystallized from light petroleum ether at low temperature as colorless thick needles (0.5gms), m.p. 45-47^{o}c, red ferric reaction; R_F 0.30, solvent (benzene - light petroleum 1:1); Vmax 1640cm^{-1}.

Synthesis of 3.
To a mixture of 4'-prenyloxy, 2-hydroxyacetophenone (0.01mole) and aromatic aldehyde (0.01 moles) were dissolved in EtOH (50mL) and 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 (100mL). 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 3a-g.

Synthesis of 5.
To a mixture of 4-prenyloxy, 2-hydroxyacetophenone (0.01mole) and hetero aldehydes (0.01 mole) were dissolved in EtOH (50mL) and 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 (100mL). 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 **5a-b**.

Synthesis of 6.
To the prenyloxy chalcone 3a (800 mg) in ethanol (30 mL) Sodium acetate (6.0 g) was added. The mixture was maintained at 60-70˚C for 3-4 hr 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}

Compound 3a:
Yellow solid (0.68 g, 48.8%); mp.87 oC; IR (KBr, cm^{-1}): 3420(νOH), 1630(νC=O), 1130(ν=CH-O-); 1H NMR(400 MHz, CDCl3); 1.75 (s, 6H,=C (CH3)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, Cα H, J = 15.3Hz), 8.12 (d, 1H, Cβ H, J = 15.3Hz), 13.62 (s, 1H, 2'-OH), 7.33(m, 2H,1,5-H), 7.46(m,2H, 2,4-H); Mass M/z 338; Anal. Calcd for C21 H22 O4 (338.43); C, 74.71; H, 6.65; O, 18.98. Found: C, 74.52; H, 6.56; O, 18.90.

Compound 3b:
Yellow solid (0.61 g, 42.6%); mp.91 ^{o}C; IR (KBr, cm^{-1}): 3440(νOH), 1640(νC=O), 1160(ν=CH-O-); 1H NMR(400 MHz, CDCl3); 1.72 (s, 6H, =C (CH3)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, Cα H, J = 15.3Hz), 7.82 (d, 1H, Cβ H, J = 15.3Hz), 13.54 (s, 1H, 2'-OH), 7.13(m, 2H,1,5-H), 7.26(m,2H, 2,4-H); Mass M/z 322; Anal. Calcd for C 21H22 O3 (322.16); C, 78.48; H, 6.98; O, 14.98. Found: C, 78.23; H, 6.84; O, 14.88.

***Compound* 3c**.
Light yellow solid (0.53 g, 40.8%); mp.185 oC; IR (KBr, cm-1): 3500(νOH), 1650(νC=O), 1210(ν=CH-O-); 1H NMR(400 MHz, CDCl3); 1.75 (s, 6H, =C (CH3)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, Cα H, J = 15.3Hz), 7.64 (d, 1H, Cβ H, J = 15.3Hz), 13.70 (s, 1H, 2'-OH), 7.03(m, 2H,1,5-H), 7.29(m, 2H, 2,4-H); Mass M/z 342; Anal. Calcd for C20 H19Cl O3 (342.12); C, 70.11; H, 5.95; O, 14.18. Found: C, 70.07; H, 5.57; O, 14.04.

Compound 3d:
Dork red solid (0.38 g, 24.6%); mp.95 oC; IR (KBr, cm-1): 3420(νOH), 1630(νC=O), 1130(ν=CH-O-); 1H NMR(400 MHz, CDCl3); 1.78 (s, 6H, =C (CH3)2), 2.83 (s, 6H, -N(CH3)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, Cα H, J = 15.3Hz), 7.82 (d, 1H, Cβ H, J = 15.3Hz), 13.48 (s, 1H, 2'-OH), 7.13(m, 2H,1,5-H), 7.26(m,2H, 2,4-H); Mass M/z 351; Anal. Calcd for C22 H25 N O3 (351.18); 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

Compound 3e:
Yellow solid (0.54 g, 41.6%); mp.89 oC; IR (KBr, cm-1): 3420(νOH), 1630(νC=O), 1130(ν=CH-O-); 1H NMR(400 MHz, CDCl3); 1.78 (s, 6H, =C (CH3)2), 4.50 (d,2H,=CH-CH2-), 5.42 (t, 1H,=CH-CH2-), 7.83(d,1H,6'-H), 6.85(d,1H,5'-H), 6.95(s,1H,3'-H),7.02 (d, 1H, Cα H, J = 15.3Hz), 7.62 (d, 1H, Cβ H, J = 15.3Hz), 13.50 (s, 1H, 2'-OH), 7.03(m, 2H,3,6-H), 7.28(m,2H, 4,5-H); Mass M/z 323; Anal. Calcd for C20 H19Cl O3 (342.10); C, 70.11; H, 5.65; O, 14.28. Found: C, 70.09; H, 5.58; O, 14.01.

Compound 3f:
Light yellow solid (0.45 g, 36.6%); mp.103 oC; IR (KBr, cm-1): 3420(νOH), 1630(νC=O), 1130(ν=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-), 7.76(d,1H,6'-H), 6.40(d,1H,5'-H), 6.52(s,1H,3'-H),6.92 (d, 1H, Cα H, J = 15.3Hz), 7.82 (d, 1H, Cβ H, J = 15.3Hz), 13.45 (s, 1H, 2'-OH), 7.13(m, 2H,1,5-H), 7.26(m,2H, 2,4-H); Mass M/z 353; Anal. Calcd for C20 H19N O5 (353.13): 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.

Compound 3g:
Yellow solid (0.75 g, 26.6%); mp.161 oC; IR (KBr, cm-1): 3420(νOH), 1630((νC=O), 1130(ν=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-), 7.95(d,1H,6'-H), 6.34(d,1H,5'-H), 6.54(s,1H,3'-H),6.92 (d, 1H, Cα H, J = 15.3Hz), 7.82 (d, 1H, Cβ H, J = 15.3Hz), 13.62 (s, 1H, 2'-OH), 7.13(m, 2H,1,5-H), 7.26(m,2H, 2,4-H); Mass M/z 353; Anal. Calcd for C20 H19N O5 (353.14); C, 67.92; H, 5.54; O, 22.86 N, 3.98. Found: C, 67.52; H, 5.50; O, 22.46; N, 3.86.

Compound 5a:
Yellow solid (0.85 g, 52.2%); mp.78 oC; IR (KBr, cm-1): 3510(νOH), 1650(νC=O), 1160(ν=CH-O-); 1H NMR(400 MHz, CDCl3); 1.72 (s, 6H, =C (CH3)2), 4.51 (d, 2H, =CH-CH2-), 5.46 (t, 1H, =CH-CH2-), 7.05(d,1H,6'-H), 6.38(d,1H,5'-H), 6.48(s,1H,3'-H),7.60 (d, 1H, Cα H, J = 15.3Hz), 7.78 (d, 1H, Cβ H, J = 15.3Hz), 13.4 (s, 1H, 2'-OH), 6.73(d, 1H,furan), 6.60(t,1H, furan) 7.40(d,1H,furan); Mass M/z 298; Anal. Calcd for C18 H18 O4 (298.12); C, 72.51; H, 6.13; O, 21.52. Found: C, 72.47; H, 6.09; O, 21.47.

Compound 5b:
Dork yellow solid (0.89 g, 92.5%); mp.92 oC; IR (KBr, cm-1): 3480(νOH), 1640(νC=O), 1120(ν=CH-O-); 1H NMR(400 MHz, CDCl3); 1.73 (s, 6H, =C (CH3)2), 4.52 (d, 2H, =CH-CH2-), 5.45 (t, 1H, =CH-CH2-), 6.71(d,1H,6'-H), 6.35(d, 1H, 5'-H), 6.24(s, 1H, 3'-H), 7.60 (d, 1H, Cα H, J = 15.3Hz), 7.90 (d, 1H, Cβ H, J=15.3Hz), 13.4 (s, 1H, 2'-OH), 6.50 (t, 1H, thiophene), 6.52(d, 1H, thiophene), 6.58(d,1H,thiophene); Mass M/z 323; Anal. Calcd for C18 H18 S O3 (314.14); C, 68.83; H, 5.87; O, 15.28. Found: C, 68.76; H, 5.78; O, 15.26.

Compound 6a:
Yellow solid (0.520 g, 39.3%); mp. 129-131 oC; ir (KBr, cm-1); 1630 (νC=O), 1510 (ν >C=C<); 1130 (ν=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-), 3.82 (s, 3H, -OCH3), 2.78 (dd, 1H, J = 17.4 Hz and J = 3.3Hz, 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 C21H22O4 (338): C, 74.54; H, 6.55; O, 18.99. Found: C, 74.35; H, 6.41; O, 18.87.

Compound 6b:
Dork yellow solid (0.46 g, 38.9 %); mp. 167 oC; ir (KBr, cm-1): 1650((νC=O), 1540(ν >C=C<);1120(ν=CH-O-); 1H nmr (400 MHz, CDCl3); 1.73(s, 6H, =C (CH3)2), 4.61(d, 2H, =CH-CH2-), 5.43 (t, 1H, =CH-CH2-), 2.40 (s, 3H, -CH3), 2.82 (dd, 1H, J = 17.4 Hz and J = 3.3Hz,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 C21H22O3 (322): C, 78.71; H, 6.88; O, 14.99. Found: C, 78.25; H, 6.78; O, 14.87.

Compound 6c:
Light yellow solid (0.47g, 40.5%); mp. 183 ^oC; ir (KBr, cm^{-1}): 1645((νC=O), 1535(ν >C=C<); 1080(ν=CH-O-); 1H nmr (400 MHz, CDCl3); 1.76 (s, 6H, =C (CH3)2), 4.58 (d, 2H, =CH-CH2-), 5.46 (t, 1H, =CH-CH2-), 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.

Compound 6d:
Red solid (0.50 g, 41.2%); mp. 181 oC; ir (KBr, cm-1): 1635((νC=O), 1540(ν >C=C<); 1070(ν=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.

Cytotoxicity Analysis
Cellular viability in the presence of test compounds was determined by MTT-micro cultured tetrazolium assay. The cells seeded to flat bottom 96(10000cells/100ul) well plates & cultured in the medium containing 10% serum and allowed to attach and recover for 24 hours in a humid chamber containing 5% CO2. MTT (3-(4, 5-dimethylthiazol-2yl)-2,5diphenyl tetrazolium bromide; sigma catalog noM2128) was dissolved in PBS at 5mg/ml and filtered to sterilize and remove a small amount of insoluble residue present in MTT. Different concentrations of compounds were added to the cells. After 48 hours, stock MTT solution (10ul) was added to the culture plate. Cells were again kept in CO2 incubator for 2 hours. After incubation 100ulof DMSO was added and mixed.

The absorbance was read at 562nm in a plate reader. The results were represented as percentage of cytotoxity/viability. All the experiments were carried out in triplicates. From the percentage of cytotoxicity the I C -50 value calculated.

Media used was MEM Catalog No M0643
DPBS Catalog No D5652
1X antibiotic solution of 100X Catalog No A5955
1% Sodium pyruvate Catalog No.S8636
1% Non-essential amino acids Catalog No M7145
10% Fetal bovine serum Catalog No F2442
DMSO Catalog No D5879
Trypsin-EDTA solution (0.25%, 2.5 g porcine trypsin and 0.2 g EDTA), Catalog NoT4049.
Trypsin-EDTA solution used for detaching cells during sub culturing process.
Cis-Platin was taken as reference.

Table 2 : Cytotoxic Analysis

Compound	IC50 Values in A-549 cell Line
3a	>100mM
3b	> 100 mM
3c	> 100 mM
3d	> 100 mM
3e	15.05 uM
3f	14.54uM
3g,	19.55uM
5a	> 100mM
5b	11.21uM
6a	778.57uM 103.58Um
6b	20.22uM
6c	> 100 mM
6d	>100mM

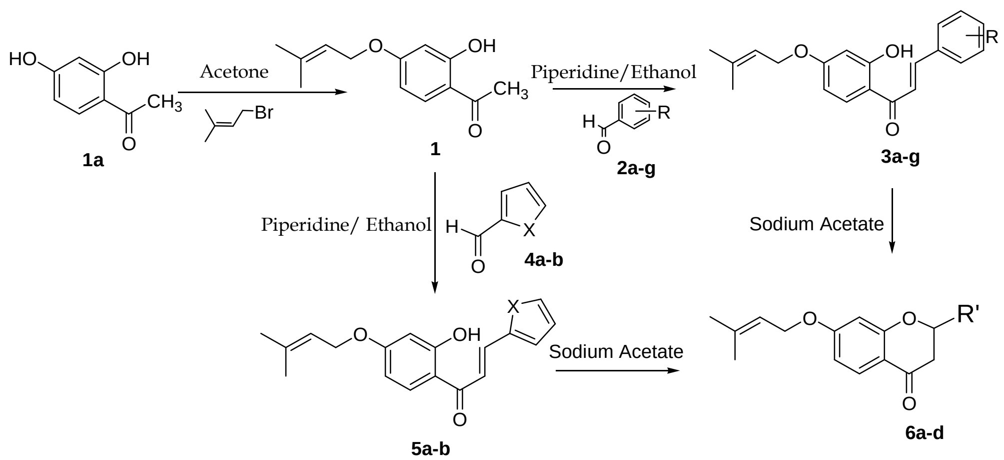
RESULTS AND DISCUSSION

The synthesis of 3a and 5a was carried out by condensation with an ethanolic solution of an 4-prenyloxy 2-hydroxy acetophenone 1 in the presence of piperidine with P–methoxy benzaldehyde 2a or furfuraldehyde 4a as shown in the scheme-1. The compounds 3a and 5a gave violet colouration with alcoholic $Fecl_3$ test indicating the presence of chelated hydroxyl group in it. IR spectra of compounds 3a showed a broad band centered at 3420 cm-1 assignable to chelated hydroxyl(-OH) group. An intense absorption observed at 1630 cm-1 is for hydrogen bonded carbonyl (>C=O) function in the chalcone. These two absorptions indicate the presence of a 2'- hydroxyl system in 4'-O-prenylated chalcone. Vinylic stretching of Tran's double bond (>C=C<) is observed at 1575 cm-1 and 1360 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 1130 cm^{-1}. Other aromatic skeletal vibrations were 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 (J=3Hz) is ascribed to one methylene group of prenyl 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 5.41δ. This completes the set of peaks characteristic of 4'-prenyloxy group. Acetophenone ring of chalcone as A-ring has down field absorption observed at 7.95δ. 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 6.54δ, 6.34δ. The characteristic signals for Cα, Cβ hydrogens of chalcone double bond appears as doublets which are observed at 7.92 δ (d, 1H, J=15.3Hz) and 8.12 δ (d, 1H, J=15.3Hz) respectively. 4'-Prenyloxy chalcone has p-methoxy phenyl as B-ring. The hydrogens of phenyl ring have appeared peaks in between 7.20δ - 7.55δ range, and three hydrogens of methoxy group appeared as broad singlet at 3.82δ and 2'-hydroxy group appeared as broad singlet at 13.54 δ

Confirmative proof for the structure proposed for 4'-prenyloxy chalcone 3a 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.

In present communication, we reported piperidine mediated synthesis of new prenyloxy chalcones and flavanones. The structural elucidations of the compounds have been established on the basis of elemental (C, H, and O) analysis, and IR, 1H NMR, MS spectral data. A series of New Prenyloxy chalcone and derivatives were synthesized and evaluated for their cytotoxicity against A549, human tumor cell lines. Compounds **3a, 3b, 3g.5a, 5b, 6a, 6b, 6c** and **6d** were identified as potent cytotoxic against **A549** cell lines, respectively. Further, cell cycle perturbations induced by the chalcones synthesized were also studied on the A549 cell lines. The present study revealed that these chalcones were potent anti proliferative agents against tumor cell lines without being more cytotoxic to normal cells. But when Naphthalene nucleus involved in the chalconic structure, activity was not observed.



Scheme - 1

Table-1: The synthesized derivatives of prenyloxy chalcones and favanones

Compd	R	Compd	X	Compd	R^1
3a	P-OCH_3	5a	O	6a	Ar-OCH_3
3b	P-CH_3	5b	S	6b	Ar-CH_3
3c	P-Cl			6c	Foran
3d	P-N $(CH_3)_2$			6d	Thiophen
3e	O-Cl				
3f	M-NO_2				
3g,	P-NO_2				

CONCLUSION

The conclusion was made that; different analogous of natural Prenyloxy Chalcones and Prenyloxy Flavanones can be synthesized from aromatic and hetero Aldehyde (s) and 4-prenyloxy 2-hydroxyacetophenone (s). For better yields, the weak base of Pipiridine is an efficient catalytic system; Possessed - lesser times for completion of reactions, recyclability and economic conditions. Compounds **3a, 3b, 3g.5a, 5b, 6a, 6b, 6c** and **6d** were identified as potent cytotoxic against A549 cell lines. The results of this study may find a lead toward the development of new therapeutic agents to fight cancer.

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