**IJPSR (2017), Vol. 8, Issue 6** **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 November, 2016; received in revised form, 17 January, 2017; accepted, 02 February, 2017; published 01 June, 2017

# SYNTHESIS OF NEW FLAVANOID AND CHALCONE DERIVATIVES AS ANTIMICROBIAL AGENT BY GREEN CHEMISTRY APPROACH

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**Keywords:**

Green chemistry, Microwave, Flavonoids, Flavanone, Antibacterial agent, Antifungal agent

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**ABSTRACT:** Flavanoids are plant secondary metabolites, synthesized by microwave assisted synthesis and green chemistry approach since, the conventional method of synthesis uses various organic solvents, hazardous by product, tedious work that requires more reaction time. Flavonoids have general structure of 15-carbon skeleton which consists of two phenyl ring (A and B) and heterocyclic pyran ring(C). Flavones are one of the important class of flavanoids acquires a broad spectrum of activity. Chalcone (1, 3-diaryl-2-propen-1-ones), is a privileged structure, demonstrating promising anti-microbial, anti-inflammatory and anticancer activities. The basic moiety of flavanoids gives numerous biological activities henceforth; flavanoid and chalcone derivatives were synthesized and confirmed by physiochemical and spectral data. Biological screening was done for antibacterial especially for anti-methicillin resistant *Staphylococcus aureus* and antifungal screening with using standard drug Ofloxacin and Griseofulvin respectively. Compound NKP-3, NKP-4, NKP-8a, NKP- 9a and NKP-10a are more active and other compounds are less active against bacteria and fungi.

**INTRODUCTION: Green Chemistry:** Green chemistry has materialized in the United States as a common research program resulting from integrative cooperation of university teams, research groups, industries, scientific societies and governmental agencies, which have their own programs dedicated to decreasing pollution. [1-3] Green chemistry is the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances. Substance and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions and fires.

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DOI: 10.13040/IJPSR.0975-8232.8(6).2725-30

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (6). 2725-30

This principle can motivate chemistry at all levels: research, education and public perception. [4]

**Microwave Synthesis:** Microwave –enhanced chemistry is based on the efficient heating of materials by "microwave direct heating" effects. This phenomenon is dependent on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat. Microwaves are defined as electromagnetic waves with vacuum wavelength ranging between 10 - 100 cm equivalently with frequencies between 30 - 300 GHz. [5] Microwave heating is the best process due to the microwave couple directly with the molecule that are present in the reaction mixture, leading to fast rise in temperature, so called faster reaction and cleaner chemistry.

The microwave chemistry is also called as green chemistry because it does not produce any hazardous material like gas, fumes or heating using external source.

It uses electromagnetic radiation that passes through material and causes oscillation of molecule which produces heat. Microwave heating produces heat in the entire material in the same rate and at the same time at the high speed and at the high rate of reaction. [6] Microwave assisted synthesis has become an important tool to the chemist for rapid organic synthesis. [7] Microwave heating is instantaneous and very specific and there is no contact required between energy source and reaction vessel. Microwave dielectric heating is a non quantum mechanical effect and it leads to volumetric heating of the sample. [8] The basic principle behind heating in microwave oven is due to interaction of charged particle of the reaction material with electromagnetic wavelength of particular frequency.

The phenomena of producing heat by electromagnetic irradiation are ether by collision or by conduction and sometime by both. All the wave energy changes its polarity from positive to negative with each cycle of the wave. This cause rapid orientation and reorientation of molecule which cause heating by collision. If the charge particles of material are free to travel thorough the material (e.g. Electron in a sample of carbon) and current will induce which will travel in phase with the field. If charge particles are bound within regions of material, the electric field component will cause them to move until opposing force balancing the electric force. [9]

In microwave oven, material may be heated with use of high frequency electromagnetic waves. The heating arises from the interaction of electric field component of the wave with charge particle in the material.

Two basic principle mechanisms involve in the heating of material.

1. Dipolar Polarisation
2. Conduction Mechanism. [10-12]

**Flavonoids:** Flavonoids are extensive group of compounds occurring in plants. They are prominent plant secondary metabolites that have been found in dietary components including fruits, vegetables, olive oil, tea and red wine. It has been observed that even a high take of plant based dietary flavonoids is safe and not associated with any adverse health effect. [13] Over 5000 naturally occurring flavonoids have been characterized from various plants. Naturally and synthetic flavonoids have attracted considerable attention because of their broad spectrum of activity.

A word "Flavonoid" derived from **"**flavus**"** has meaning is yellow which is used to describe a wide collection of naturally occurring polyphenolic compounds. [14] Chemically flavonoids are based upon a fifteen-carbon skeleton consisting of two benzene rings that is ring A and ring B which is shown in figure and these two rings are linked via heterocyclic pyran ring which is ring C. The skeleton is represented as C6-C3-C6 system. [15]

In naturally occurring flavonoids, the A ring which is derived from the acetate malonate pathway and the B ring which is derived from the ring carbons of phenylalanine. The complete structure is numbered from the heterocyclic oxygen, which is designated as position 1, clockwise round the ring C to ring A position 8. The B ring is numbered separately with primed numbers, starting from ring C bound as 1' to 6'. [16-20]

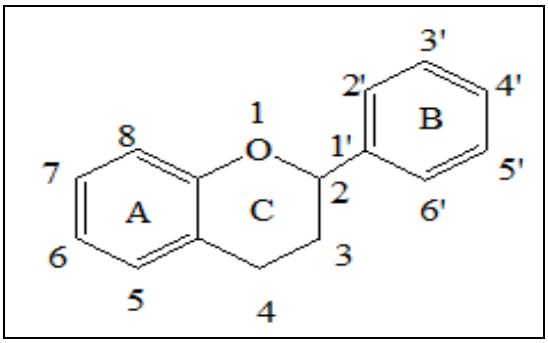



**FIG. 1: BASIC SKELTON OF FLAVANOID**

**MATERIALS AND METHODS:** Melting points of all the synthesized compounds were taken using "Veggo Microprocessor" based melting point apparatus having silicon oil bath. IR of synthesized compounds were taken using Bruker Alpha-T FT-IR spectrometer using potassium bromide discs. Mass spectrums of all synthesized compounds were done from Oxygen Healthcare Research Pvt. Ltd., Changodar, Ahmadabad. $^{1}$H-NMR of all synthesised compounds were performed by Bruker Advance Spectrometer (400 MHz) in DMSO and chemical shift were expressed in δ (ppm). Saurastra University, Rajkot. 2 cm X 5 cm pre- coated silica gel 60 $F_{254}$ (Merck) plates of thickness of 0.25mm.

The chromatograms were visualized under UV (254 nm) and/or exposure to iodine vapours. All chemicals and solvents used were of L.R grade, obtained from S.D fine chemicals, Spectrochem, Sigma Aldrich and purified by general laboratory techniques before use. All moisture free operation was performed in oven dried glassware.

**General procedure for synthesis of Flavanones and Aryl chalcones by microwave:** 2.5 mmole of Hetero Aldehyde/Aryl Aldehyde and 2.5 mmole of 2-hydroxy-4-substituted acetophenone were taken in 250ml RBF. 20 ml Ethanol and 0.1 mole of Potassium hydroxide were added in same RBF. The RBF was kept in Microwave at low voltage for 2-8 min. The reaction was moniterd by TLC. Ethanol was evaporated and solid washed with cold water. Recrystallized from Methanol.

**2, 3-dihydro-2-(thiophene-2-yl) chromen-4-one (NKP-1):** Molecular Weight: 230.04gm/mol, %Yield: 77.23%, M.P: 238-241˚C, $R_f$: 0.47 (Hexane: Ethyl acetate 7:3), IR(KBr, $cm^{-1}$): (3085.51) -CH Aromatic Stretch, (2946.32) C-H Aliphatic Stretch , (1690.34) C=O Stretch, (1377.81) C-O Stretch, MASS (m/z): 231.0 (M+1).

**2-(furan-2-yl) -2, 3 – dihydrochromen – 4 - one (NKP-2):** Molecular Weight: 214.22 gm/mol, %Yield: 92.45%, M.P: 145-150˚C, $R_f$: 0.52 (Hexane: Ethyl acetate 7:3), IR(KBr, $cm^{-1}$): (3127.28`) -CH Aromatic Stretch, (2860.92) C-H Aliphatic Stretch, (1641.17) C=O Stretch, (1389.25) C-O Stretch, MASS (m/z): 215.2 (M+1), NMR (δ,ppm): 7.90 (d,1H,Ar-H),7.65 (d,2H,Ar-H), 6.73 (d,2H,Ar-H), 7.54 (t,1H,Ar-H), 8.05 (d,1H,Ar-H), 7.17 (d,1H,Ar-H).

**2,3-dihydro-7- methoxy – 2 - (thiophene-2-yl) chromen-4-one (NKP-3):** Molecular Weight: 260.31gm/mol, %Yield: 82.81%, M.P: 122-126˚C, $R_f$ : 0.44 (Hexane: Ethyl acetate 7:3), IR(KBr, $cm^{-1}$): (3071.87) C-H Aromatic Stretch, (2891.97) C-H Aliphatic Stretch, (1635.23) C=O Stretch, (1563.67) C=C Stretch, (1371.10) C-O Stretch, MASS (m/z): 268 (M+1).

**2-(furan-2-yl)-2, 3-dihydro-7methoxychromen-4 one (NKP-4):** Molecular Weight: 244.24 gm/mol, %Yield: 56.34%, M.P: 152-155 ˚C, $R_f$: 0.49 (Hexane: Ethyl acetate 7:3), IR(KBr, $cm^{-1}$): (3045.75) C-H Aromatic Stretch, (2980.24) C-H Aliphatic Stretch, (1652.39) C=O Stretch, (1563.67), (1375.97) C-O Stretch, MASS (m/z): 243.4 (M+1), NMR (δ,ppm): 3.83 (s,3H,Ar-$OCH_3$),6.05 (s,2H,Ar-H), 7.20 (d,1H,Ar-H), 7.72 (d,1H,Ar-H), 7.83 (s,1H,Ar-H), 8.00 (d,1H,Ar-H), 8.14 (d,1H,Ar-H).

**3-(4-(dimethyl amino) phenyl)-1-(2-hydroxy phenyl) prop-2-en-1- one (NKP-5):** Molecular Weight: 267.32 gm/mol, %Yield: 55.94 %, M.P: 169-172˚C, $R_f$ : 0.60 (Hexane: Ethyl acetate 7:3), IR(KBr, $cm^{-1}$): (3064.53) -CH Aromatic Stretch, (2850.30) C-H Aliphatic Stretch, (1629.78) C=O Stretch, (1597.73) C=C Stretch, (1368.32) C-O Stretch, (3320.69) -OH Stretch MASS (m/z): 268 (M+1), NMR (δ,ppm): 3.82 (s,3H,Ar-$OCH_3$),3.84 (s,3H,Ar-$OCH_3$),5.60 (s,1H,-OH), 7.04 (d,1H,Ar-H), 8.04 (d,1H,Ar-H), 7.78 (d,1H,Ar-H).

**1-(2-hydroxyphenyl) - 3- (3, 4-dimethoxyphenyl) prop-2-en-1-one (NKP-6):** Molecular Weight: 284.31 gm/mol, %Yield: 82.66 %, M.P: 150-154 ˚C, $R_f$ : 0.58 (Hexane: Ethyl acetate 7:3), IR(KBr, $cm^{-1}$): (3001.56) C-H Aromatic Stretch, (2840.90) C-H Aliphatic Stretch, (1696.84) C=O Stretch, (1602.89) C=C Stretch, (1349.46) C-O Stretch, (3360.45) -OH Stretch, MASS (m/z): 285.4 (M+1).

**1-(2-hydroxyphenyl) – 3 -(2, 5-dimethoxyphenyl) prop-2-en-1-one (NKP-7):** Molecular Weight: 284.31 gm/mol, %Yield: 73.91 %, M.P: 155-160 ˚C, $R_f$ : 0.47 (Hexane: Ethyl acetate 7:3), IR(KBr, $cm^{-1}$): (3077.93) C-H Aromatic Stretch, (2923.92) C-H Aliphatic Stretch, (1648.80) C=O Stretch, (1600.75) C=C Stretch, (1323.32) C-O Stretch, MASS (m/z): 285.4 (M+1).

**3-(4-(dimethylamino) phenyl) – 1 -(2-hydroxy-4-methoxyphenyl) prop-2-en-1-one (NKP-8):** Molecular Weight: 297.35 gm/mol, %Yield: 75.34 %, M.P: 175-180˚C, $R_f$: 0.56 (Hexane: Ethyl acetate 7:3), IR (KBr, $cm^{-1}$): (3071.87) C-H Aromatic Stretch, (2891.97) C-H Aliphatic Stretch, (1635.23) C=O Stretch, (1563.67) C=C Stretch, (1371.10) C-O Stretch, MASS (m/z): 298.1 (M+1).

**1-(2-hydroxy-4- methoxyphenyl) – 3 - (3, 4-dimethoxy phenyl) prop-2-en-1-one (NKP-9):** Molecular Weight: 314.33 gm/mol, %Yield: 72.30

%, M.P: 160-163˚C, $R_f$: 0.59 (Hexane: Ethyl acetate 7:3), IR(KBr, $cm^{-1}$): (3076.77) C-H Aromatic Stretch, (2888.99) C-H Aliphatic Stretch, (1633.30) C=O Stretch, (1570.78) C=C Stretch, (1375.15) C-O Stretch, MASS (m/z): 315.1 (M+1).

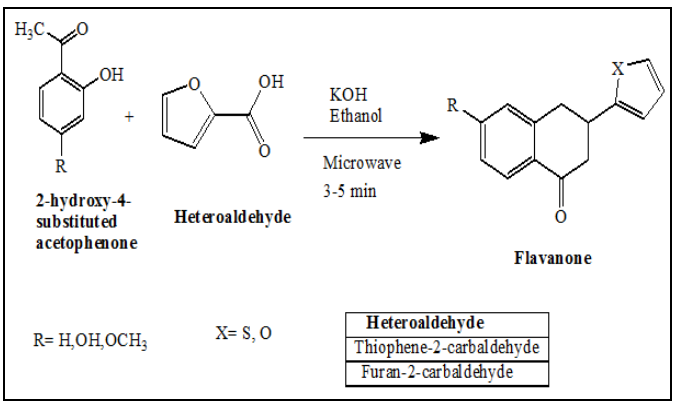
**1-(2-hydroxy-4-methoxyphenyl) - 3 - (2, 5-dimethoxyphenyl) prop-2-en-1-one (NKP-10):** Molecular Weight: 314.33 gm/mol, %Yield: 64.95 %, M.P: 159-164˚C, $R_f$: 0.59 (Hexane: Ethyl acetate 7:3), IR(KBr, $cm^{-1}$): (3006.96) C-H Aromatic Stretch, (2835.01) C-H Aliphatic Stretch, (1632.27) C=O Stretch, (1569.68) C=C Stretch, (1312.82) C-O Stretch , MASS (m/z): 315.1 (M+1), NMR (δ,ppm): 3.84 (s,6H,Ar-$OCH_3$), 3.82 (s, 3H, Ar-$OCH_3$),6.56 (d,1H,Ar-H), 6.59 (d,1H,Ar-H), 7.06 (d,1H,Ar-H), 7.97 (d,1H,Ar-H), 8.00 (d,1H,Ar-H), 8.29 (d,1H,Ar-H), 8.31 (d,1H,Ar-H).

**Antibacterial and Antifungal activity:** The preliminary antibacterial activity of synthesized compounds was studies against *S. aureus* (ATCC-25923) and antifungal activity of compound was studied against *C. albicans* (ATCC 10231). Ofloxacin and Griseofulvin were used to parent standard as standard for antibacterial and antifungal activity respectively. The result represented that the synthesized some derivatives shows good antibacterial activity against *S.aureus* (ATCC-25923) and also antifungal activity against *C. albicans* (ATCC 10231) compared drugs Ofloxacin and Griseofulvin. [21-22]

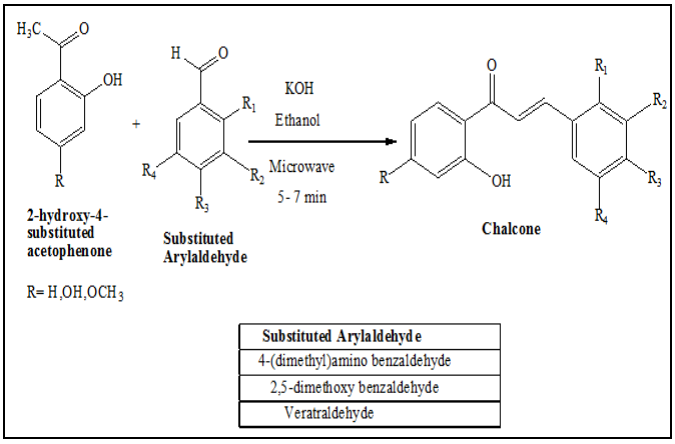
**Determination of minimum inhibitory concentration (MIC value):** [23-24] The agar dilution method was performed using Mueller-Hinton agar (Hi-Media) medium for antibacterial activity and Saburoud's dextrose agar (Hi-Media) medium for antifungal activity. The medium was sterilized by autoclaving at 15 lb pressure for 30 minutes. One loopful of the stock culture was inoculated at 37°C for 24 h to 7 days respectively for bacteria and fungi. About 3 ml of distilled water was added to the test tube and suspension of the culture was obtained by shaking for few minutes. The test compounds (5 mg) were dissolved in DMSO (5 ml) and volume was made upto 10 ml to produce a concentration of 500µg/ml. Further dilutions were made with DMSO to produce 10, 15, 20, 25 and 30µg/ml. Similarly, the dilutions were prepared for standard drug i.e., Ofloxacin and Griseofulvin in a concentration of 100µg/ml as reported. Sterile medium was melted on water bath and kept at 45 °C in constant temperature water bath in each sterile Petridis molten medium was added so that thickness was approximately 4-5mm and subculture organism under study was inoculated.

The inoculated dishes were allowed to set for 30 min at room temperature. Cups of 6 mm diameter were then made with the help of sterile stainless steel borer 100µl added to each cup. Petridish were kept in refrigerator for 30 min so as to allow diffusion of the solutions in the medium and then incubated at 37 °C for 24 hrs for antibacterial activity and 72hrs for antifungal activity. Zone of inhibition produced by test compounds were measured in mm in various axis and average reading was considered and the activity index was calculated against the standard. The MIC value was calculated as minimum concentration at which the zone of inhibition is higher.

**RESULT AND DISCUSSION:** The objective of the present work was to synthesis and biological evaluation of some new flavonoids associated with Flavanone and Chalcone derivatives. The yield of different synthesized compounds was founds to be in the range of 40-70% and the characterization was done by melting point and TLC. Characteristic IR bands show several functional vibrational modes which confirm the completion of reaction. New moieties structures were confirmed by $^1H$ NMR and Mass spectral studies. The antibacterial activity and antifungal of new derivatives showed activity against *S. aureus* and *C. albicans* strain. Compound was found most active as antibacterial and antifungal activities which suggest that a 7-Methoxy derivatives show more activity against bacteria and fungi.




**SCHEME: 1**




**SCHEME: 2**

## Antimicrobial activity:

**TABLE 1: ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS WAS EXPRESSED IN MINIMUM INHIBITORY CONCENTRATIONS (MIC) AGAINST THE BACTERIA AND FUNGI**

| Compounds | MIC value | |
|---|---|---|
| | ***S.aureus*** **(ATCC-25923)** | ***C. albicans*** **(ATCC 10231)** |
| NKP-1 | < 50 | < 50 |
| NKP-2 | < 50 | < 50 |
| NKP-3 | < 50 | < 50 |
| NKP-4 | < 50 | < 50 |
| NKP-5 | < 50 | < 50 |
| NKP-6 | < 50 | < 50 |
| NKP-7 | < 50 | < 50 |
| NKP-8 | < 50 | < 50 |
| NKP-9 | < 50 | < 50 |
| NKP-10 | < 50 | < 50 |

**CONCLUSION:** Present study describes the synthesis of flavanoids. The compounds were characterized by spectral techniques such as IR, MASS and $^{1}$H-NMR. All the compounds were screened for their antibacterial and antifungal activity against the *Staphylococcus aureus* (ATCC-25923) and *Candida albicans* ATCC 10231) respectively. In addition their MIC values were determined. The results shows that the substitution of electron withdrawing group (-$OCH_3$) and heteroaryl ring gives the good antibacterial and antifungal activity.

**ACKNOWLEDGEMENT:** Authors are grateful to Principal, Parul Institute of Pharmacy, Parul University for providing facilities to carry out research work.

**CONFLICT OF INTEREST:** The authors report no conflict of interest.

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**How to cite this article:**
Patel A, Panchal I, Parmar I, Mishtry B: Synthesis of new flavanoid and chalcone derivatives as antimicrobial agent by green chemistry approach. Int J Pharm Sci Res 2017; 8(6): 2725-30.doi: 10.13040/IJPSR.0975-8232.8(6). 2725-30.