AN EFFICIENT ULTRASOUND SONICATION SYNTHESIS OF SOME NOVEL BIOACTIVE FLAVONES

Balasaheb B. Musle[1], Nana V. Shitole[2], Suraj B. Ade[2] and Subhash M. Lonkar*

[1]Shri Guru Buddhiswami Mahavidhyalaya, Purna (Jn.), Dist. Parbhani (M.S.)
[2,*]P. G. Research Center, Department of Chemistry, Shri Shivaji College, Parbhani (M.S.)

Abstract : A highly efficient and an environmentally friendly synthesis of a series 3-hydroxy substituted flavones **(2a-2i)** under green chemistry condition was reported from different substituted chalcones and hydrogen peroxide in presence of aqueous ethanol by using Ultrasound Sonication technique. The remarkable advantages of this method are environmentally friendly, short reaction time, simple work-up procedure and excellent yields of the products. All the synthesized 3-hydroxy substituted flavones were elucidated on the basis of spectral analysis such as IR, ^{1}HNMR, and Mass spectroscopy. These 3-hydroxy substituted flavones were evaluated for their in vitro antibacterial and antifungal activity. Majority of the synthesized flavones were shown moderate to good antibacterial and antifungal activity against all used strains with higher values.

Keywords: Different substituted chalcones, Hydrogen peroxide, Aqueous ethanol, Sonicator, Antimicrobial.

I. INTRODUCTION

The flavones (2-phenylchromones) are naturally occurring heterocyclic compounds belonging to the flavonoid group and these are widely distributed in vascular plants[1]. On the other hand Chalcones (1,3-diaryl-2-peopen-1-ones) are natural/synthetic compounds belonging to the flavonoid family, chalcones of plant origin are known[2]. Chalcones present great interest as compounds exhibiting antimalerial[3], anticancer[4] antitrichomonal[5], antileishmanial[6], and cytotoxic activities. Chalcones and its derivatives show various biological activities. Chalcones are medicinally important class of compounds. It is also used as main intermediate for synthesis of heterocyclic compounds like pyrozolines[7]. Flavones are a class of flavonoids based on the backbone of 2- phenylchromen-4-one[8].

Substituted 4-hydroxyl chalcones are widely distributed in the plant kingdom[9-13]. Similarly, "Flavones" the subgroup of flavanoids are also a major constituent which are distributed from ferns to higher plants possessing various biological activities such as antioxidant, antifungal , antibacterial, anti inflammatory, antitumor, antiasthamatic, antiviral, antihypertensive, estrogenic antixiolytic diuretic activity and inhibition of hormone dependent proliferation of cancer cells[14-15]. The usage of sonicator energy to accelerate organic reactions is of increasing interest and offers several advantages over conventional techniques. The remarkable advantages of this method are environmentally friendly, short reaction time, simple work-up procedure and excellent yields of the products. In one half of the century Ultrasound sonicator energy had been used for the heating of food material [16-17]. But now the application of this energy has been utilized in organic synthesis.

In 1855, Robert Bunsen invented the burner which acts as energy source for heating a reaction vessel and synthesis of organic compound by heating on burner was become a traditional method[18-20]. In continuation of our research work to extend green chemistry protocol we thought worthwhile to synthesize some novel 3-hydroxy substituted flavones which may be shows higher antimicrobial activity.

II. Experimental:

Melting points of all the synthesized 3-hydroxy substituted flavones were determined in open capillaries and uncorrected. IR spectra were recorded using Perkin-Elmer FTIR-RX1 spectrophotometer. ^{1}HNMR spectrum was recorded using $CDCl_3$ on Bruker Advance (400 MHz) and their chemical shifts were recorded in δ (parts per million) units with respect to tetramethyl silane (TMS) as internal standard. Mass spectra were recorded on a Waters Q-T of micro MS. All the reagents and solvents used were of AR grade. Progress of the reactions was monitored using TLC, performed on silica gel, using ethyl acetate: benzene as the solvent system.

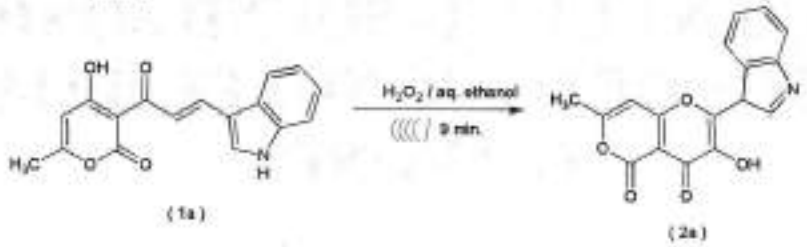
General Procedure:

Take 0.01 mole of 4-hydroxy substituted chalcone **(1a)** dissolved in aqueous ethanol (15ml) in a conical flask having 150 ml capacity. To this add (10 ml, 20%) Sodium hydroxide and (15 ml, 20%) H_2O_2. The reaction mixture was kept in Ultrasound sonicator in water bath at 38-40 ^{0}C for 9-10 min. The completion of reaction was monitored on TLC using benzene/ethyl acetate combination (1:1,V/V) as mobile Phase. After completion of reaction the reaction mixture was cooled at room temperature and poured into crushed ice, acidified with little amount of very dilute HCl solution. The separated solid product, 3-hydroxy substituted flavones **(2a)** was filtered with Buchner funnel, washed with cold water, dried and recrystallized from chloroform:methanol (9:1). Similarly, all the other 3-hydroxy substituted flavones **(2b to 2i)** were prepared by the same procedure and evaluated for their antimicrobial activity.

Co-ordinator
IQAC
Shri Guru Buddhiswami Mahavidyalaya

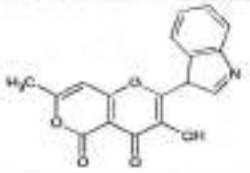
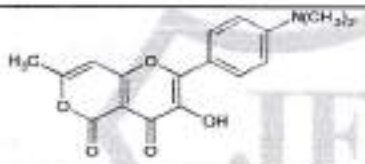
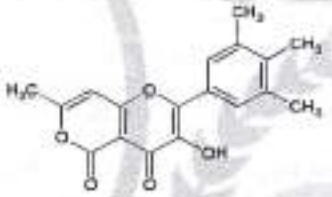
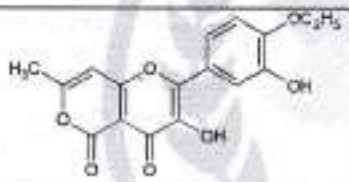
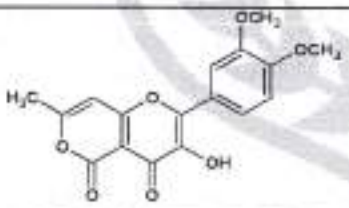
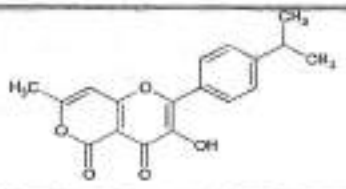
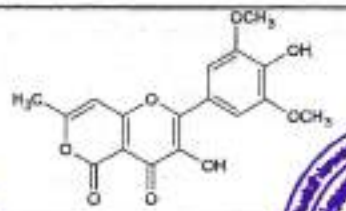
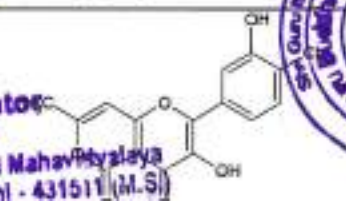
PRINCIPAL
Shri Guru Buddhiswami Mahavidyalaya
Purna (Jn.) Dist.Parbhani

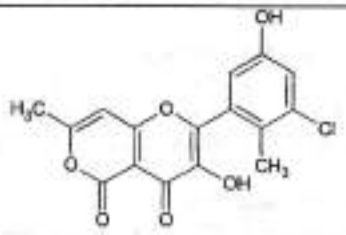
Scheme



(1a) (2a)

Table-1: Physical data of synthesized 3-hydroxy substituted flavones:

Sr. No.	Structure of Synthesized Compounds	Reaction Time (in min.)	Yield (%)	M.P (°C)
2a		9.00	80	164
2b		9.50	83	172
2c		9.22	79	188
2d		9.35	88	119
2e		9.48	85	144
2f		9.45	90	180
2g		9.10	82	178
2h		9.20	78	160

2i		9.36	84	189

Antimicrobial Activity:

All the synthesized 3-hydroxy substituted flavones were tested for their antibacterial and antifungal activity by measuring zone of inhibition on agar plates using disc diffusion method[21] with *Escherichia coli* and *Aspergillus niger*. These compounds possess moderate to good activity against all stains in comparison with Tetracycline and Griseofulvin was listed in **Table-2.**

Table 2: Zone of Inhibition (mm) of 3-hydroxy substituted flavones

Compound	Antimicrobial *Escherichia coli*	Antifungal *Aspergillus niger*
2a	11	09
2b	12	13
2c	09	12
2d	15	14
2e	12	16
2f	13	11
2g	16	10
2h	11	15
2i	15	13
Tetracycline	20	00
Control	00	00
Griseofulvin	00	20

III. RESULT AND DISCUSSION:

In the present investigation and in continuation of earlier research work devoted towards development green chemistry and new synthetic methodologies in organic chemistry herein, we report a simple, efficient and environmentally benign procedure for synthesis of some novel 3-hydroxy substituted flavones from 4-hydroxy substituted chalcone and Hydrogen peroxide in presence of Sodium hydroxide by ultrasonication irradiation in aqueous ethanolic medium. The notable advantages of present protocol are one step neat reaction conditions with high yield, simple procedure, no need of purification, save time as well as heat energy.

All the synthesized 3-hydroxy substituted flavones were fully characterized and evaluated for their antibacterial and antifungal activity. The flavones compounds are a group of natural products found in flowers, fruits, vegetables, nuts and seeds as well as in teas and are important constituent of human diet. They have been demonstrated to possess antioxidant, antihypertensive and anti-allergic. Therefore it can be concluded that the 3-hydroxy substituted flavones will have great importance in medicinal chemistry as antibacterial and antifungal agents.

Spectral Analysis:

3-hydroxy-2-(3*H*-indol-3-yl)-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-dione;(2a)
IR (KBr): ν (cm^{-1}): 3282 (-OH str.), 1720 (C=O str.), 1638 (C=N str.), 1085(C-N), 1615 [C=C str. (aromatic)], 1345(C-O-C str.), 1230(-OH bend.), 2900 [C-H str. (aliphatic)], 3015 [C-H str. (aromatic)]; **^{1}H-NMR (CDCl$_3$)δ:** 7.82(d, 1H, Ar-H), 7.76(d, 1H, Ar-H), 7.61-64 (m, 2H, Ar-H), 5.58 (d, 2H), 1.72 (s,3H,-CH$_3$), 2.22 (s,1H), 15.20(s, 1H,-OH), **Mass (m/z):** 309 [M+H]$^+$

2-[4-(dimethylamino)phenyl]-3-hydroxy-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-dione;(2b)
IR (KBr): ν (cm^{-1}): 3412 (-OH str.), 1727 (C=O str.), 1090(C-N), 1620 [C=C str. (aromatic)], 1315(C-O-C str.), 1220(-OH bend.), 2909 [C-H str. (aliphatic)], 3025 [C-H str. (aromatic)],**^{1}H-NMR (CDCl$_3$)δ:** 7.70-7.98(m, 4H, Ar-H), 4.63 (s,1H), 15.51(s, 1H,-OH), 2.09 (s,3H,-CH$_3$), 1.80 (s,3H,-CH$_3$), 1.58 (s,3H,-CH$_3$); **Mass (m/z):** 313 [M+H]$^+$

3-hydroxy-7-methyl-2-(3,4,5-trimethylphenyl)-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-dione;(2c)
IR (KBr): ν (cm^{-1}): 3380 (-OH str.), 1725 (C=O str.), 1575 [C=C str. (aromatic)], 1316(C-O-C str.), 1238(-OH bend.), 2860 [C-H str. (aliphatic)], 3025 [C-H str. (aromatic)]; **^{1}H-NMR (CDCl$_3$)δ:** 7.85 (s, 1H, Ar-H), 7.69 (s, 1H, Ar-H), 5.12 (s,1H), 15.41(s, 1H,-OH), 2.35(s,3H,-CH$_3$), 2.20 (s,3H,-CH$_3$), 1.78 (s,3H,-CH$_3$), 1.62 (s,3H,-CH$_3$); **Mass (m/z):** 312 [M+H]$^+$

2-(4-ethoxy-3-hydroxyphenyl)-3-hydroxy-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-dione; (2d)
IR (KBr): ν (cm^{-1}): 3378 (-OH str.), 1690 (C=O str.), 1600 [C=C str. (aromatic)], 1320(C-O-C str.), 1233(-OH bend.), 2885 [C-H str. (aliphatic)], 3045 [C-H str. (aromatic)]; **^{1}H-NMR (CDCl$_3$)δ:** 7.77 (s, 1H, Ar-H), 6.89-6.95 (d, 2H, Ar-H), 5.53

2-(3,4-dimethoxyphenyl)-3-hydroxy-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-dione;(2e)
IR (KBr): ν (cm^{-1}): 3392 (-OH str.), 1700 (C=O str.), 1515 [C=C str. (aromatic)], 1328(C-O-C str.), 1198(-OH bend.), 2898 [C-H str. (aliphatic)], 3045 [C-H str. (aromatic)]; **^{1}H-NMR (CDCl$_3$)δ:** 7.57 (s, 1H, Ar-H), 6.80 (d, 1H, Ar-H), 6.76 (d, 1H, Ar-H), 6.63 (s,1H), 15.27 (s, 1H,-OH), 3.8 (s, 3H,-OCH$_3$), 3.3 (s, 3H,-OCH$_3$), 1.75 (s,3H,-CH$_3$); **Mass (m/z):** 330 [M+H]$^+$

3-hydroxy-2-(4-isopropylphenyl)-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-dione;(2f)
IR (KBr): ν (cm^{-1}): 3280 (-OH str.), 1710 (C=O str.), 1622 [C=C str. (aromatic)], 1335(C-O-C str.), 1235(-OH bend.), 2910 [C-H str. (aliphatic)], 3035 [C-H str. (aromatic)]; **^{1}H-NMR (CDCl$_3$)δ:** 7.80-8.00 (dd, 2H, Ar-H), 7.49-7.52 (dd, 2H, Ar-H), 6.46 (s,1H), 15.77 (s, 1H,-OH), 2.5 (m, 1H), 1.71 (s,3H,-CH$_3$), 1.10 (d,3H,-CH$_3$), 0.09 (d,3H,-CH$_3$); **Mass (m/z):** 312 [M+H]$^+$

3-hydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-dione; (2g)
IR (KBr): ν (cm^{-1}): 3442 (-OH str.), 1690 (C=O str.), 1565 [C=C str. (aromatic)], 1333(C-O-C str.), 1238(-OH bend.), 2900 [C-H str. (aliphatic)], 3050 [C-H str. (aromatic)]; **^{1}H-NMR (CDCl$_3$)δ:** 7.50 (s, 1H, Ar-H), 6.85 (s, 1H, Ar-H), 5.84 (s,1H), 15.05 (s, 1H,-OH), 11.25 (s, 1H,Ar-OH), 3.86 (s, 3H,-OCH$_3$), 3.35 (s, 3H,-OCH$_3$), 1.67 (s,3H,-CH$_3$); **Mass (m/z):** 346 [M+H]$^+$

2-(4-chloro-3-hydroxyphenyl)-3-hydroxy-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-dione;(2h)
IR (KBr): ν (cm^{-1}): 3362 (-OH str.), 1718 (C=O str.), 1580 [C=C str. (aromatic)], 1295 (C-O-C str.), 1210(-OH bend.), 2888 [C-H str. (aliphatic)], 3075 [C-H str. (aromatic)], 760 (C-Cl str.); **^{1}H-NMR (CDCl$_3$)δ:** 7.68 (d, 1H, Ar-H), 6.83 (d, 1H, Ar-H), 6.69 (s, 1H, Ar-H), 5.80 (s,1H), 15.77 (s, 1H,-OH), 10.85 (s, 1H,Ar-OH), 1.74 (s,3H,-CH$_3$); **Mass (m/z):** 320 [M+H]$^+$

2-(3-chloro-5-hydroxy-2-methylphenyl)-3-hydroxy-7-methyl-4*H*,5*H*-pyrano[4,3-*b*]pyran-4,5-dione;(2i)
IR (KBr): ν (cm^{-1}): 3380 (-OH str.), 1734 (C=O str.), 1615 [C=C str. (aromatic)], 1340 (C-O-C str.), 1220(-OH bend.), 2910 [C-H str. (aliphatic)], 3036 [C-H str. (aromatic)], 775 (C-Cl str.); **^{1}H-NMR (CDCl$_3$)δ:** 7.88 (s, 1H, Ar-H), 7.13 (s, 1H, Ar-H), 5.55 (s,1H), 15.00 (s, 1H,-OH), 10.63 (s, 1H,Ar-OH), 2.78 (s,3H,-CH$_3$), 1.76 (s,3H,-CH$_3$); **Mass (m/z):** 334 [M+H]$^+$

IV. **ACKNOWLEDGEMENT:**
The authors are thankful to Dr. B.U. Jadhav, Principal, M. S. P. Mandal's Shri Shivaji College, and Parbhani, for providing laboratory facilities. Authors are also thankful to Dr. K. Rajkumar Principal, Shri Guru Buddhiswami Mahavidhyalaya, Purna for his constant support, helpful discussion and encouragement and IDA, Jeedemetla, Hyderabad for providing spectral analysis.

REFRENCES:

1. M. J. Menezes, S. Manjrekar, V. Pai, R. E. Patre and S.G. Tilve, Indian J. Chem., **(2009)**, 48B, 1311-1314.
2. Belsare D. P., Kazi Asim, *IOSR J.Pharm.*, **(2013)**, 3(4), 23-27.
3. Chen G. F, DOI Jia H. M., Zhang L.Y, Chen and Li J. T, *Ultrason sonochem* , 20(2) , 607-632 , **(2013).**
4. Prasad Y. R, Rao A. L. and Rambabu R., *Eur. Journal of Chemistry*,**(2008)**, 5(3):461-466.
5. Ballesterons J. F., Sanz M. J. Ubeda M., A Lborra S., Paya M., Alcarazm. , *J. Med chem.*, **(1995)**,382794.
6. Srivasava S. and Das B., *Der pharma chemica.*, **(2011)**,l3(6),103-111
7. Kaniwa, K Arai, M. A ; Li ,X ;Ishibashi, M., *Bioorg & med chem. Lett*, **(2014)**,17,4254.
8. Ji –Tai Li ,Xiao –Hui Zang and Zhi- Ping Lin Beilstein., *J. Org. Chem.*, **(2007)**;3-13.
9. A.It.Chen, W.B.kuo,C.W.Chen. *J. Chinese chemical society*, **(2003)**,50:123-127.
10. Lajis N. H., Khan M. N., Kiew R. B., J. B. Pertanika, *J. Sci & Technol.* **(1993)**, 1(2):195-198.
11. Ngameni B, Ngadjui BT, Folefoc BN, Jean Watchueng J,Abegaz BM. *Phytochemistry Lett.*, **(2004)**, 65(4):427-432.
12. Reddy RVN, Reddy NP, Khalivulla SI, Reddy MVB, Gunasekar D, Blond A, Bodo B. *Phytochemistry Lett.* **(2008)**; 1(1):23-26.
13. Tanaka T, Asai F, Iinuma M., *Phytochemistry Lett.*, **(1998)**, 49(1):229-232.
14. Abegaz BM, Ngadjui BT, Dongo E, Ngameni B, Nindi MN, Bezabih M. *Phytochemistry*, **(2002)**, 59(8):877-883.
15. Shibata K, Tatsukawa A, Umeoka K, Hua Seng Lee HS, Ochi M. Crinatusins, *Tetrahedron*,**(2000)**, 56(45):8821.
16. (a) Cimanga K., Ying L., Debruyne T., Apers S., Hermans N. Bakana P., Tona L., KambuK Kalenda D.T. Pieters L, Vandden B D & Vlientinck A., *J. Franaco* ,64, **2001**,96 (b) Khan M.Sy. & Hasan S.M., *Indian J. Chem.*,(**2003**),42B,1970.
17. (a)Wang Y, Tan w,LiW &Li Y, *J. Nat. Prod.*, **(2001)**,64, 196; (b) Nijveldt R.J. NOOD E HOORN d Baselens P.G. Nooren K & Leeuwen P, *Am. J. Clin. Nutrition*,**(2001)**,74,418.
18. Rajendra,S., *Encyclopedia of Organic Synthesis*,**(1999)**,16 538-593.
19. Varma R.S., *Indian J Chem.*, **(1999)**,1,132-147.
20. Aken K.V, Strekowski .L and Patiny L, *Beistein Journal of organic chemistry*, **(2006)**, 2, 3.
21. Beena R. Nawghare, Sunil V. Gaikwad, Abdul R. [illegible] Lokhande, **(2014)**, 51(1), 2284-2286.

Co-ordinator
IQAC
Shri Guru Buddhiswami Mahavidyalaya

Estd.1983

PRINCIPAL
Shri Guru Buddhiswami Mahavidyalaya
Purna (Jn.) Dist.Parbhani