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New Flavonols Synthesized from 2-hydroxynaphthyl Chalcones using 2-ethoxy ethanol solvent as as Antibacterial Agents

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Abstract: In this study new series of flavonols (**3a-3j**) were synthesized from 2-hydroxynaphthyl chalcones and hydrogen peroxide by using solvent 2-ethoxy ethanol. The Synthesized flavonols were evaluated for antibacterial activity against four pathogenic bacteria, two gram positive and two gram negative. The antibacterial data showed that electron rich and halogen disubstituted (**3g, 3h, 3i** and **3j)** flavonols exhibit higher antibacterial activity against all bacterial strain tested. It also revealed that all compounds showed good to moderate activity compared to standard drug.

Keywords: Chalcone, Hydrogen peroxide, 2-ethoxy ethanol, Flavonol, Antibacterial activity.

1. Introduction:

Flavonoids are a family of bioactive polyphenolic compounds; they are present in many commonly consumed vegetables, fruits, and other plant-based foods[1]. Over 4000 different flavonoids have been described, and they are categorized into flavones, flavonols, flavanones, catechins, isoflavonoids and anthocyanidins. They are widely distributed throughout the plant kingdom and are of importance and interest to a wide variety of physical and biological scientists[2].

Flavonol is the major representative of the flavonoid subclass; they are the most abundant and broadly distributed in nature and are considered as the most active compound within the flavonoid group. Flavonol have the 3-hydroxyflavone backbone. They differ due to different positions of the phenolic -OH groups. Flavonols such as quercetin, myricetin and kaempferol attract considerable interest due to their diverse biological activities[3-9].

Naturally occuring flavonols and their derivatives show various biological and pharmacological activities such as anticancer[10], antioxidant[11], antimicrobial[12], antifungal[13], anxiolytic[14], Antiulcerogenic[15], cytotoxic[16], and

antibacterial activity[17-19]. In recent time, due to these activities, the chemistry as well as the pharmacology of these groups of flavonoids has been attracted much attention to the scientific community.

In present research work, this effective biological and medicinal importance of flavonol derivatives promoted us to work on flavonol containing halogen, benzyloxy, methoxy, hydroxy groups. Herein, we describe an operationally simple, highly efficient method for the synthesis of flavonol derivatives from hydroxy chalcones and hydrogen peroxide using potassium hydroxide as a base and 2-ethoxy ethanol as a solvent by stirring method and screened for their antibacterial activity against four pathogenic bacteria.

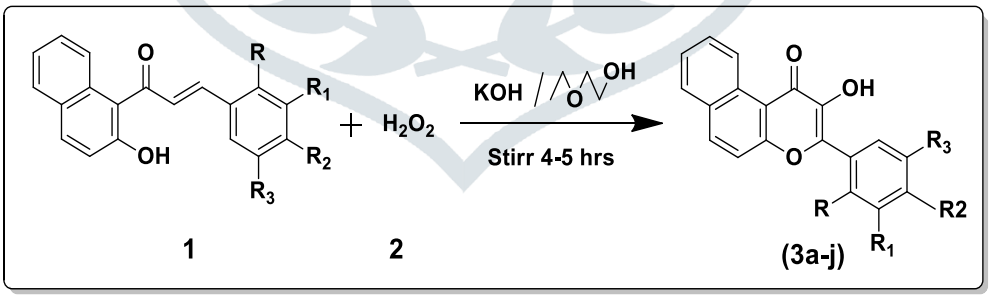
2. Experimental Section:

2.1. Materials and Methods

All the Chemicals used in the synthesis are used were of laboratory grade. Melting points were determined in an open capillary tube and are uncorrected. Purity of compounds and completion of the reaction was monitored by thin layer chromatography using hexane/ethyl acetate (7:3) as the mobile phase on precoated sheets of silica gel-G (Merck, Germeny) using UV chamber for detection. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer. H^1NMR spectra were recorded on Avance spectrometer (Bruker, Germany) 300 MHz in CDCl3 using TMS as an internal standard and chemical shifts are reported in δ units. Elemental analysis was performed on Perkin-Elmer 240 CHN elemental analyzer.

2.2. General Procedure for Synthesis of Flavonols (3a-3j)

To a well-stirred solution of substituted hydroxyl chalcones (0.007 mol) in 2-ethoxy ethanol (20 ml) and aq. KOH (10 ml, 20%), cooled at 5-10°C, then 30% H_2O_2 (10 ml) were added drop wise over 1 hr. The reaction mixture was further stirred for 4-5 hrs and the resulting reaction mixture was poured on crushed ice and neutralized with dilute hydrochloric acid[20]. The obtained solid was filtered, washed with water and dried in bulb oven. The crude product was recrystallized with ethanol to afford pure flavonol derivatives.



Scheme-1: Synthesis of Flavonols

3a. R= H, R_1= H, R_2 = F, R_3 = H

3b. R= H, R_1= H, R_2 = CN, R_3 = H

3c. R= H, R_1= OCH_2CH_3, R_2 = OH, R_3 = H

3d. R= H, R_1= OCH_2CH_3, R_2 = OH, R_3 = Br

3f. R= H, R_1= OCH_3, R_2 = $OCH_2C_6H_5$, R_3 = H

3g. R= OH, R_1= Br, R_2 = H, R_3 = Br

3h. R= OH, R_1= I, R_2 = H, R_3 = I

3i. R= H, R_1= H, R_2 = OCH_3, R_3 = H

3e. R= H, R_1= $OCH_2C_6H_5$, R_2 = OCH_3, R_3 = H **3j.** R= H, R_1= OCH_3, R_2 = OCH_3, R_3 = H

3. Results and Discussion:

Here we describes the synthesis of flavonols from substituted 2-hydroxynaphthyl chalcones and hydrogen peroxide in 2-ethoxy ethanol solvent. All the synthesized compounds (**3a-3j**) have been characterized by their melting point, Elemental analysis, IR, H^1NMR and mass spectra (scheme-**1**).

The structure of flavonol derivatives were characterized by recording their IR, H^1NMR and Mass spectra. All the flavonols showed IR absorption band in the region 3350-3480 cm^{-1} due to hydroxyl (OH) stretching and 1630-1710 cm^{-1} is due to >C=O (carbonyl) stretching vibration. In H^1NMR spectra δ value for aromatic proton observed in between 7.10-8.58 ppm with coupling constant (J) value 1.8, 8.1 and 8.7 Hertz where as OH proton of flavonol ring appear at δ 9.40-10.20 ppm as a singlet.

3.1. Spectral Characterization

3.1.1. 3-(4-fluorophenyl)-2-hydroxy-1*H*-benzo[*f*]chromen-1-one. (3a)

Yield: 79%; M.p.:156ºC; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.30-8.35 (m, Ar-H, 10H), 9.95 (s, OH, 1H); IR (KBr, cm^{-1}): 3431 (OH), 1636 (C=O); Anal. Calc. for $C_{19}H_{11}FO_3$ (306): C 74.51, H 3.62, F 6.20 ; Found: C 74.48, H 3.60, F 6.20.

3.1.2. 4-(2-hydroxy-1-oxo-1*H*-benzo [*f*]chromen-3-yl)benzonitrile. (3b)

Yield: 67%; M.p.:148ºC; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.20-8.30 (m, Ar-H, 10H), 9.90 (s, OH, 1H); IR (KBr, cm^{-1}): 3431 (OH), 2210 (CN), 1630 (C=O); Anal. Calc. for $C_{20}H_{11}NO_3$ (313): C 76.67, H 3.54, N 4.47; Found: C 76.65, H 3.55, N 4.48.

3.1.3. 3-(3-ethoxy-4-hydroxyphenyl)-2-hydroxy-1*H*-benzo[*f*]chromen-1-one. (3c)

Yield: 70%; M.p.:175ºC; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 3.83 (t, CH_3, 3H), 4.45 (q, OCH_2, 2H), 7.10-8.32 (m, Ar-H, 9H), 9.45 (s, OH, 1H), 9.95 (s, OH, 1H); IR (KBr, cm^{-1}): 3446 (OH), 3364 (OH), 1653 (C=O); Anal. Calc. for $C_{21}H_{16}O_5$ (348): C 72.41, H 4.63; Found: C 72.40, H 4.60.

3.1.4. 3-(3-bromo-5-ethoxy-4-hydroxyphenyl)-2-hydroxy-1*H*-benzo[*f*]chromen-1-one. (3d)

Yield: 80%; M.p.:197ºC; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 3.85 (t, CH_3, 3H), 4.48 (q, OCH_2, 2H), 7.20-8.30 (m, Ar-H, 8H), 9.50 (s, OH, 1H), 9.95 (s, OH, 1H); IR (KBr, cm^{-1}): 3450 (OH), 3380 (OH), 1650 (C=O); Anal. Calc. for $C_{21}H_{15}BrO_5$ (427): C 59.04, H 3.54, Br 18.70; Found: C 59.02, H 3.52, Br 18.72.

3.1.5. 3-(3-(benzyloxy)-4-methoxyphenyl)-2-hydroxy-1*H*-benzo[*f*]chromen-1-one. (3e)

Yield: 74%; M.p.:188ºC; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 3.60 (s, OCH_3, 3H), 5.10 (s, OCH_2, 2H), 7.00-8.35 (m, Ar-H, 14H), 10.10 (s, OH, 1H); IR (KBr, cm^{-1}): 3430 (OH), 1650 (C=O); Anal. Calc. for $C_{27}H_{20}O_5$ (424): C 76.40, H 4.75; Found: C 76.38, H 4.73.

3.1.6. 3-(4-(benzyloxy)-3-methoxyphenyl)-2-hydroxy-1*H*-benzo[*f*]chromen-1-one. (3f)

Yield: 78%; M.p.:185ºC; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 3.50 (s, OCH_3, 3H), 5.20 (s, OCH_2, 2H), 7.10-8.30 (m, Ar-H, 14H), 10.10 (s, OH, 1H); IR (KBr, cm^{-1}): 3430 (OH), 1650 (C=O); Anal. Calc. for $C_{27}H_{20}O_5$ (424): C 76.40, H 4.75; Found: C 76.41, H 4.76.

3.1.7. 3-(3,5-dibromo-2-hydroxyphenyl)-2-hydroxy-1*H*-benzo[*f*]chromen-1-one. (3g)

Yield: 83%; M.p.:194^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.25-8.30 (m, Ar-H, 8H), 9.50 (s, OH, 1H), 10.10 (s, OH, 1H); IR (KBr, cm^{-1}): 3450 (OH), 3360 (OH), 1645 (C=O); Anal. Calc. for $C_{19}H_{10}Br_2O_4$ (556): C 49.39, H 2.18, Br 34.58; Found: C 49.35, H 2.20, Br 34.60.

3.1.8. 2-hydroxy-3-(2-hydroxy-3,5-diiodophenyl)-1*H*-benzo[*f*]chromen-1-one. (3h)

Yield: 84%; M.p.:203^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 7.35-8.38 (m, Ar-H, 8H), 9.55 (s, OH, 1H), 10.20 (s, OH, 1H); IR (KBr, cm^{-1}): 3440 (OH), 3350 (OH), 1653 (C=O); Anal. Calc. for $C_{19}H_{10}I_2O_4$ (556): C 41.04, H 1.81, I 45.64; Found: C 41.00, H 1.82, I 45.62.

3.1.9. 2-hydroxy-3-(4-methoxyphenyl)-1*H*-benzo[*f*]chromen-1-one. (3i)

Yield: 62%; M.p.:189^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 3.75 (s, OCH_3, 3H), 7.05-8.10 (m, Ar-H, 10H), 9.80 (s, OH, 1H); IR (KBr, cm^{-1}): 3380 (OH), 1645 (C=O); Anal. Calc. for $C_{20}H_{14}O_4$ (318): C 75.46, H 4.43; Found: C 75.45, H 4.41.

3.1.10. 3-(3,4-dimethoxyphenyl)-2-hydroxy-1*H*-benzo[*f*]chromen-1-one (3j)

Yield: 77%; M.p.:191^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 3.62 (s, OCH_3, 3H), 3.85 (s, OCH_3, 3H), 7.13-8.28 (m, Ar-H, 9H), 9.65 (s, OH, 1H); IR (KBr, cm^{-1}): 3360 (OH), 1651 (C=O); Anal. Calc. for $C_{21}H_{16}O_5$ (348): C 72.41, H 4.63; Found: C 72.42, H 4.61.

3.2. Antibacterial Activity of Flavonols

All the newly synthesized flavonols were screened for *in vitro* antibacterial activity evaluated against 24 hrs culture of different bacteria such as *Staphylococcus aureus*, *Streptococcus pyogenes* (Gram +ve) and, *Escherichia coli*, *Pseudomonas aeruginosa* (Gram –ve) at a concentration of 50 µg ml^{-1}. The cultures were diluted with 5% of autoclaved saline and the final volume was adjusted to a concentration of approximately 105-106 CFU ml^{-1}. The synthesized compounds were diluted with acetone for the antibacterial sensitivity assay for agar disc diffusion method. The liquid form of test compound was soaked on to a disc (5mm) and then allowed to air dry, such that the disc became completely saturated with the test compound. The saturated chemical discs were introduced onto the upper layer of medium evenly loaded with the bacteria and incubated at 37^{0}C for 24 to 48 hrs for better inhibition of bacteria. The zone of inhibition was measured after 24 to 48 hrs. All the experiments were performed in triplicates and the results are expressed as zone of inhibition in mm. The zone of inhibition of the synthesized compounds was compared with zone of inhibition of standard antibiotic ofloxacin (50 µg mL^{-1}). The DMSO is used as negative control. The results were recorded in table **1**.

From the screening studies (**table 1**), we found that the compounds **3g, 3h, 3i** and **3j** shows excellent antibacterial activity against all tested bacteria this could be due to electron rich and halogen disubstituted group present on phenyl ring whereas compounds **3e** and **3f** having benzyloxy group shows good antibacterial activity. The compounds **3b, 3c, 3d** shows moderate antibacterial activity this might be due to the free hydroxyl group present on para position of phenyl ring. The antibacterial data showed that electron rich and halogen disubstituted flavonols showed higher activity against all bacterial strain tested.

Table 1. Antibacterial Activity of Flavonols (3a-j)

Sr. No	Compounds	Diameter of zone of inhibition (in mm)			
		Gram +ve bacteria		Gram –ve bacteria	
		S.aureus	*S.pygenes*	*E.coli*	*P.aeruginosa*
01	**3a**	19	20	22	21
02	**3b**	12	16	16	15
03	**3c**	18	20	22	20
04	**3d**	16	20	20	20
05	**3e**	20	22	25	22
06	**3f**	18	21	20	23
07	**3g**	22	23	24	21
08	**3h**	23	24	25	23
09	**3i**	24	25	26	24
10	**3j**	20	24	24	22
11	**Ofloxacin**	26	28	30	27

4. Conclusion:

In this work, we have synthesized some new flavonol derivatives from different substituted 2-hydroxynaphthyl chalcones and hydrogen peroxide in solvent 2-ethoxy ethanol. The newly synthesized flavonols were obtained in good yield and its formation is confirmed by spectral analysis. The antibacterial data showed that electron rich and halogen disubstituted flavonols showed higher antibacterial activity against all bacterial strain tested. It also observed that all compounds showed good to moderate activity as that of standard drug used. Hence, finaly we conclude that flavonols having electron rich group and halogen disubstitution better over the other substitution pattern and exhibit higher activity against all bacterial strain.

5. Conflict of Interest:

There is no conflict of interest in the present study.

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