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Der Pharma Chemica, 2013, 5(2):8-13
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis and antimicrobial activity of novel falvonols

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ABSTRACT

*A novel series of falvonols (16a-s) were synthesized by the reaction of respective chalcones (2a-s) and hydrogen peroxide. The structures of all the compounds were confirmed by spectral data and tested for their antimicrobial activities against both gram positive B.subtilis, gram negative E.coli bacteria and antifungal activity against P.notatum C. tropicalis, A. niger and C. albicans by using cup plate method. Among the synthesized compounds, Flavanol derivatives bearing electron releasing functional group (16b, 16n and 16s) showed good activity against E.Coli . Derivative bearing dimethoxy group (16n) showed good activity againe**st** B. Subtilis. Flavonol derivatives showed moderate to weak activity against A. niger, C. albicans and Penicillium notatum fungi.*

Keywords: Chalcones, Antimicrobial Activity, Flavonoides.

INTRODUCTION

Flavonoids constitute an important component of a variety of traditional Chinese medicines and phytomedicines bearing C6–C3–C6 carbon skeleton with diverse pharmacological properties, such as anticancer, antioxidant, anti-aging and antibacterial effect. [1–3]

Generally, they occur as plant pigments in a broad range of fruits and vegetables as well as in tea, red wine, coffee, and beer. Till today about 3000 varieties of flovonoids are known [4]. Some of them are widely used in medicine for maintenance of capillary integrity [5] and as anti-inflammatory, antihepatotoxic and anti-ulcer agents [6, 7]. Many have antiallergic, antiviral actions and some of them provide protection against cardiovascular mortality [8, 9].They also inhibits tumor development in experimental animals [10].

On the other hand, Benzofuran and their analogues constitute a major group of naturally occurring compounds that are of particular interest due to their pharmacological properties. However, the association of Benzofuran nucleus in natural product with oxygen heterocycles is less common. The biological significance of these Heterocycles has received considerable attention in recent years [11]. Benzofuran derivatives, which are known to be present in many natural products [12] have sedative, hypnotic [13] antibacterial [14] and antifungal activities [15].In the search of newer potential drugs, coupling of falvonol with other bioactive heterocycles has been a most common approach in

many laboratories. Because of great synthetic potentiality, the heterocyclic analogous of Chalcones are most useful synthons. Hence, it was thought of modifying Benzofuran analogous of Chalcones into falvonols ring system so as to produce biheterocyclic Benzofuryl falvonols.

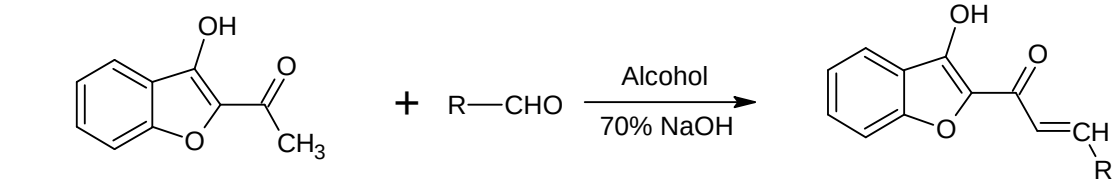
In the present paper, we described the synthesis of flavonol derivatives and the evaluation of these compounds as antimicrobial agents. The required starting material, 2-acetyl -3 hydroxy benzofuran was prepared by a single step method[16].The treatment of ethanolic solution of 2-acetyl – 3 hydroxy benzofuran and aromatic aldehyde with 50% aqueous sodium hydroxide at 5-10 ^{o}C led to the formation of 1-(3 ^{1}- hydroxy benzofuran-2 ^{1}–yl)–3- aryl – 2- propene –1- one (2a –s) in yields ranging from 40-89%. The structures of Benzofuran analogous of Chalcones were confirmed chemically by their conversion into 2-4- dinitrophenyl hydrazones and also on the basis of spectroscopic data. The I.R spectrum of compounds 2a-g exhibited a broad hump in the region of 3400- 3450 cm $^{-1}$ (OH), sharp band in the region of 1650-1660 cm $^{-1}$ (C= O) due to the α, β, unsaturated carbonyl group and a series of bands in the region of 1640-1560 cm -1(C=C) due to the aromatic side chain groups. In the ^{1}H NMR spectrum ($CDCl_3$) doublets at δ 8.40 (1H, C=CH – Ar), δ 6.76-7.74(10H, Ar-H) and δ 6.60(1H, COCH =C) δ 8.3-8.9(OH) were observed.

The synthesis of biheterocyclic flavonols using hydroxy benzofuran chalcones was accomplished by reacting with hydrogen peroxide in presence of sodium hydroxide in ethanolic solution at reflux temperature.Various 2-[phenyl)-4(H)-pyrano (3.2-b) (1) benzofuran-4-ones (16a-16s) were obtained in a yield ranging from 25-65%. The IR spectra of synthesized flavonols revealed the presence of broad hump in the region of 3400-3450 cm $^{-1}$ (enolic OH). The ^{1}H NMR spectrum of 16f was recorded displayed broad peak due to enolic OH proton of flavonol moiety at δ 7.19. Mass spectral data also confirms the formation of final compounds. Further spectroscopic details of remaining compounds are presented in the experimental part

MATERIALS AND METHODS

Melting points were determined with open capillary and are uncorrected. I.R spectra were recorded on a Shimadza FTIR model 8010 spectrophotometer, ^{1}H NMR spectra were recorded in (MeOD / DMSO) on aBruker supercon FT-NMR instrument using TMS as internal standard.

General procedure for the synthesis of Chalcones by Claisen-Schmidt condensation (2a-s):



2-acetyl-3-hydroxy benzofuran

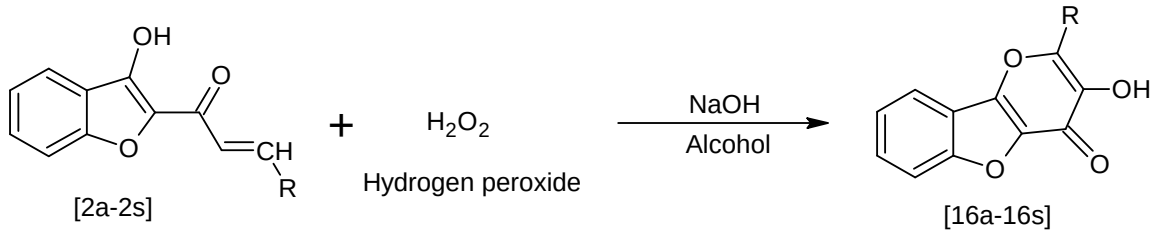
Aromatic aldehyde

Chalcone derivative

[2a-2s]

A solution of 2- acetyl-3(2H) benzofuran(,0.005 mol) and aromatic aldehydes (0.005 mol)in ethanol (25ml) was cooled with drop wise addition of aqueous sodium hydroxide (2.5 ml, 70%).Reaction mixture was magnetically stirred for 30 minutes and then left over night. The resulting dark solution was diluted with ice water and carefully acidified using dilute hydrochloric acid. The benzofuran analogues of chalcones which were separated as solids were collected by filtration and purified by column chromatography on silica gel (100-200 mesh, Merck) with a mixture of ethyl acetate and pet ether as the mobile phase.The products were obtained in yield ranging from 35 to 75%.

General method for the synthesis of 2-[phenyl)-4(H)-pyrano (3.2-b)(1)benzofuran-4-one



Hydrogen peroxide 30 %(2.5ml) was added slowly with shaking to a well cooled solutionof 1-(3-hydroxy benzofuran-2-yl)-3-aryl-2-propene-1-ones (0.03 mol) in alcohol containing aqueous sodium hydroxide (3 ml.5%) and continue the stirring for half an hour. The reaction mixture kept overnight. Dilute with water and acidified with con sulphoric acid. Colored Solid product obtained, filtered, washed with water and dried. Further purification was done by recrystallization and column chromatography by using solvents petroleum ether and ethyl acetate (1:0.5 ratios).

Sample code	Ar
16a	3''-hydroxy-4'methoxyphenyl
16b	4''-(dimethylamino)phenyl
16c	4''-chlorophenyl
16d	3'-indolyl
16f	4''-nitrophenyl
16g	2''-hydroxyphenyl
16h	2''-furanyl
16i	4''-methoxyphenyl
16k	3'',4'',5''-trimethoxyphenyl
16l	4''-methylphenyl
16n	3'',4''-dimethoxyphenyl
16r	9'' dihydroanthracenyl
16s	4''-hydroxyphenyl

3-hydroxy-2-(3-hydroxy-4-methoxyphenyl)-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16a)
Yield: 60 %; m.p: 123-129; IR (cm^{-1}): 3407 (OH stretching), 3018 (C=C stretching), 2919 (OCH_3 stretching) and 1710 (C=O stretching) ^{1}H NMR δ (ppm): 7.1- 7.8 (m, Ar-H, 8H), 7.09 (b, due to enolic OH), 3.9 (s, OCH_3, 3H),; MS *m/z* 324 (M^+).

2-[4-(dimethylamino) phenyl]-3-hydroxy-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16b)
Yield: 65 %; m.p: 123-129ºC; IR (cm^{-1}): 3392 (OH stretching), 3092 (C=C stretching), 2934 (CH_3 stretching) and 1690 (C=O stretching) ^{1}H NMR δ (ppm): 7.12- 7.9 (m, Ar-H, 8H), 7.12 (b, due to enolic OH), 2.8 (s,$(CH_3)_3$, 3H),; MS *m/z* 321 (M^+).

2-(4-chlorophenyl)-3-hydroxy-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16c)
Yield: 45 %; m.p: 142-144ºC; IR (cm^{-1}): 3409 (OH stretching), 3108 (C=C stretching), and 1691 (C=O stretching), 711(Cl stretching), ^{1}H NMR δ (ppm): 7.36- 7.87 (m, Ar-H, 8H), 7.19 (b, due to enolic OH), ; MS *m/z* 315 (M^{+2}).

3-hydroxy-2-(1*H*-indol-2-yl)-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16d)
Yield: 43 %; m.p: 122-123ºC; IR (cm^{-1}): 3422 (OH stretching), 3401 (NH stretching), 3098 (C=C stretching), and 1694 (C=O stretching), ^{1}H NMR δ (ppm): 7.24- 7.77 (m, Ar-H, 9H), 7.2 (b, due to enolic OH), 6.19 (s, 1H, NH), ; MS *m/z* 317 (M^+).

3-hydroxy-2-(4-nitrophenyl)-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16f)
Yield: 60%; m.p: 143-145ºC; IR (cm^{-1}): 3403 (OH stretching), 3022 (C=C stretching), and 1682 (C=O stretching), 1598 (NO stretching), ^{1}H NMR δ (ppm): 7.36- 7.87 (m, Ar-H, 8H), 7.19 (b, due to enolic OH); MS *m/z* 324 (M^{+1})

3-hydroxy-2-(2-hydroxyphenyl)-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16g)
Yield: 34 %; m.p: 153-156ºC; IR (cm^{-1}): 3415 (OH stretching), 3072 (C=C stretching), and 1679 (C=O stretching), ^{1}H NMR δ (ppm): 6.96- 7.81 (m, Ar-H, 9H), 7.13 (b, due to enolic OH); MS *m/z* 294 (M^{+1})

2-(furan-2-yl)-3-hydroxy-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16h)
Yield: 56 %; m.p: 161-164ºC; IR (cm^{-1}): 3402 (OH stretching), 3043 (C=C stretching), and 1692 (C=O stretching), ^{1}H NMR δ (ppm): 7.26- 7.79 (m, Ar-H, 7H), 7.18 (b, due to enolic OH); MS *m/z* 268 (M^{+1}).

3-hydroxy-2-(4-methoxyphenyl)-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16i)
Yield: 57 %; m.p: 147-150ºC; IR (cm^{-1}): 3412 (OH stretching), 3021 (C=C stretching), 2923 (OCH_3 stretching) and 1689 (C=O stretching), ^{1}H NMR δ (ppm): 6.82- 7.91 (m, Ar-H, 8H), 7.26 (b, due to enolic OH) 3.8 (s, OCH_3, 3H); MS *m/z* 308 (M^+).

3-hydroxy-2-(3, 4, 5-trimethoxyphenyl)-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16k)
Yield: 61 %; m.p: 156-160ºC; IR (cm^{-1}): 3419 (OH stretching), 3008 (C=C stretching), 2934 (OCH_3 stretching) and 1709 (C=O stretching), ^{1}H NMR δ (ppm): 6.91- 7.91 (m, Ar-H, 6H), 7.23 (b, due to enolic OH) 3.75 (s, $(OCH_3)_3$, 9H); MS *m/z* 368 (M^+)

3-hydroxy-2-(4-methylphenyl)-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16l)
Yield: 44 %; m.p: 119-122ºC; IR (cm^{-1}): 3461 (OH stretching), 3046 (C=C stretching), 2943 (CH_3 stretching) and 1704 (C=O stretching), ^{1}H NMR δ (ppm): 6.92- 7.98 (m, Ar-H, 8H), 7.12 (b, due to enolic OH) 2.55 (s, CH_3, 3H); MS *m/z* 298 (M^+).

2-(3,4-dimethoxyphenyl)-3-hydroxy-4*H*-pyrano[3,2-*b*][1]benzofuran-4-one(16n).
Yield: 43 %; m.p: 166-168ºC; IR (cm^{-1}): 3528 (OH stretching), 3064 (C=C stretching), 2939 (CH_3 stretching) and 1661 (C=O stretching), ^{1}H NMR δ (ppm): 6.94- 7.99 (m, Ar-H, 7H), 7.1 (b, due to enolic OH) 3.75 (s, $(OCH_3)_2$, 6H); MS *m/z* 338 (M^+).

2-(anthracen-9-yl)-3-hydroxy-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16r)
Yield: 61%; m.p: 130-132ºC; IR (cm^{-1}): 3442 (OH stretching), 3051 (C=C stretching), and 1666 (C=O stretching), ^{1}H NMR (MeOD) δ (ppm): 6.6- 10.00 (m, Ar-H, 12H); MS *m/z* 379 (M^{+1}).

3-hydroxy-2-(4-hydroxyphenyl)-4*H*-pyrano [3, 2-*b*][1]benzofuran-4-one(16s)
Yield: 25 %; m.p: 122-124ºC; IR (cm^{-1}): 3419 (OH stretching), 3102 (C=C stretching), and 1692 (C=O stretching), ^{1}H NMR δ (ppm): 6.92- 7.89 (m, Ar-H, 9H), 7.22 (b, due to enolic OH); MS *m/z* 294 (M^{+1})

Antimicrobial activity:
All the newly synthesized compounds were screened for antimicrobial activity against both gram positive B.subtilis and gram negative E.coli bacteria and antifungal activity against P.notatum C. tropicalis, A. niger and C. albicans according to cup plate method [17] at a concentration of 50, 75 and 100 µg/ml. Ampicillin and Fluconazole were used as standard for comparison of antibacterial and antifungal activity. Solvent DMF was used as control. The results of screening are given in table 2, 3 and 4.

RESULTS AND DISCUSSION

Electron donating substituent's like –OH, -OCH_3 group exerted positive influence on antifungal activity against C.tropicalis when they are attached to phenyl ring.Compounds having such groups on phenyl moiety can be prepared and tested for potential antifungal activity. On the other hand, the presence of other substituent's which may be electron withdrawing like – Cl, -NO_2 or relatively bulky electron donating groups like dimethylamino, trimethoxy make the derivatives inactive against C. albicans and C.tropicalis.

Table 2. Zone of inhibition for antibacterial activity of synthesized compounds

Sample code	*Escherichia Coli*			*Bacillus Subtilis*		
	50µg/mL (Mean# ± SEMa)	75µg/mL (Mean# ± SEMa)	100 µg/mL (Mean# ± SEMa)	50 µg/mL (Mean# ± SEMa)	75µg/mL (Mean# ± SEMa)	100 µg/mL (Mean# ± SEMa)
16a	23.1± 0.083**	25.3±0.658**	26.4± 0.384**	23.2±0.687**	25.6± 0.587**	26.8± 0.597**
16b	23.5± 0.088**	25.2±0.008**	27.1± 0.088**	23.6± 0.087**	25.7± 0.597**	26.2± 0.578**
16c	22.4± 0.251**	25.4±0.083**	26.1± 0.284**	22.7± 0.997**	25.6± 0.057**	26.5± 0.057**
16d	23.06±0.578**	24.3±0.058**	25.8± 2.916**	23.5± 0.889**	24.7± 0.057**	25.6± 0.577**
16f	22.1± 0.554**	25.6±0.548**	26± 0.202**	23.3± 0.607**	25.2± 0.567**	26.6± 0.786**
16g	22± 0.208**	24.6±0.584**	26.5± 0.731**	22.9± 0.087**	24.2± 0.057**	25.6± 0.798**
16h	22.5± 0.088**	23.8±0.518**	25.3± 0.581**	22.5± 0.987**	24.6± 0.157**	26.4± 0.587**
16i	23.1± 0.384**	24.6±0.876**	27.1± 2.325**	22.5± 0.690**	24.6± 0.587**	27.1± 0.597**
16k	23.2± 0.152**	24.3±0.658**	25.5± 0.650**	25.5± 0.097**	26.6± 0.597**	28.2± 0.578**
16l	20.8± 0.577**	24.6±0.958**	25.7± 0.617**	21.8± 0.867**	24.4± 0.057**	25.6± 0.057**
16n	22.6± 0.793**	24.6±0.598**	27.9± 0.348**	22.6± 0.087**	24.7± 0.057**	26.6± 0.577**
16r	22.9±0.290**	24.6±0.897**	25.9± 0.458**	23.2± 0.087**	24.6± 0.567**	26.3± 0.786**
16s	22.5± 0.272**	17.6±0.658**	28.2± 1.333**	22.9± 0.087**	25.7± 0.057**	26.9± 0.798**
Standard	29±0.577**	32.3±1.202**	34.3± 0.333**	27.8± 0.897**	28.9± 1.367**	29.2± 0.786**
Control	0	7	7	0	7	7

Table3. Zone of inhibition for antifungal activity of synthesized compounds

Sample code	*Aspergillus Niger*			*Candida albicans*		
	50 µg/mL (Mean# ± SEMa)	75µg/mL (Mean# ± SEMa)	100 µg/mL (Mean# ± SEMa)	50 µg/mL (Mean# ± SEMa)	75µg/mL (Mean# ± SEMa)	100 µg/mL (Mean# ± SEMa)
16a	14.1± 0.707**	16.4± 0.157**	18.8± 0.577**	15.6± 0.237**	17.2± 0.137**	19.8± 0.837**
16b	15.8± 0.087**	17.6± 0.587**	20.8± 0.597**	14.9± 0.227**	17.8± 0.057**	18.7± 0.733**
16c	14.5± 0.087**	17.5± 0.597**	21.5± 0.578**	15.6± 0.367**	16.7± 0.573**	19.5± 0.837**
16d	14.3± 0.509**	19.6± 0.557**	22.4± 0.057**	16.6± 0.673**	17.5± 0.457**	19.2± 0.827**
16f	13.8± 0.367**	17.7± 0.057**	22.5± 0.457**	17.5± 0.227**	18.7± 0.357**	19.2± 0.837**
16g	13.6± 0.087**	18.2 ± 0.567**	20.6± 0.786**	16.5± 0.167**	17.6± 0.057**	19.7± 0.237**
16h	13.6±0.687**	18.5± 0.037**	21.6± 0.788**	15.3± 0.867**	16.3± 0.857**	17.5± 0.087**
16i	13.9± 0.087**	18.6±0.437**	22.7±0.687**	14±0.067**	15.4±0.857**	19.5±0.237**
16k	13.6+ 0.087**	18.5 + 0.557**	23.6+ 0.786**	16.7± 0.734**	17.4± 0.957**	17.8± 0.677**
16l	13.1+0.687**	18.5+0.037**	24.6+0.788**	13.7±0.677**	14.8±0.573**	18.7±0.354**
16n	13.9+ 0.087**	16.6+ 0.437**	25.7+ 0.687**	16.4± 0.637**	18.3+ 0.754**	19+ 0.587**
16r	14.6+ 0.587**	16.9 + 0.557**	23.6+ 0.786**	15.3± 0.367**	16.6± 0.537**	19.7± 0.837**
16s	14.1+ 0.087**	18.5+ 0.037**	24.6+ 0.788**	15.9± 0.367**	16.3± 0.157**	19.8± 0.837**
Standard	18.75+ 0.587*	23.8+ 0.874*	28.7+ 0.037*	23.2+ 0.087***	26.2+ 0.087***	30.2+ 0.087***
Control	0	7	7	0	7	7

Table 4.Data of antifungal activity of the synthesized derivatives

Sample code	*Candida Tropicalis*			*Penicillium notatum*		
	50 µg/mL (Mean# ± SEMa)	75µg/mL (Mean# ± SEMa)	100 µg/mL (Mean# ± SEMa)	50 µg/mL (Mean# ± SEMa)	75µg/mL (Mean# ± SEMa)	100 µg/mL (Mean# ± SEMa)
16a	21.1± 0.183**	23.25± 0.183**	26.4± 0.384**	15.6± 0.237**	17.2± 0.137**	19.8± 0.837**
16b	20.5± 0.588**	24.2± 0.483**	27.1± 0.088**	14.9± 0.227**	17.8± 0.057**	18.7± 0.733**
16c	19.4± 0.651**	24.6± 0.483**	26.1± 0.587**	15.6± 0.367**	16.7± 0.573**	19.5± 0.837**
16d	22.6±0.778**	23.7± 0.456**	25.8± 0.167**	16.6± 0.673**	17.5± 0.457**	19.2± 0.827**
16f	22.1± 0.654**	22.9± 0.083**	26± 0.525**	17.5± 0.227**	18.7± 0.357**	19.2± 0.837**
16g	22± 0.608**	24.7± 0.983**	26.5± 0.631**	16.5± 0.167**	17.6± 0.057**	19.7± 0.237**
16h	22.5± 0.688**	23.8± 0.583**	25.3± 0.781**	15.3± 0.867**	16.3± 0.857**	17.5± 0.087**
16i	23.1± 0.884**	26.9±0.5***	27.1± 0.825***	14±0.0**	15.4±0.857**	19.5±0.237**
16k	23.2± 0.152**	24.7± 0.483**	25.5± 0.570**	16.7± 0.734**	17.4± 0.957**	17.8± 0.677**
16l	20.8± 0.577**	24.1± 0.463**	25.7± 0.987**	13.7± 0.677**	14.8± 0.573**	18.7± 0.354**
16n	22.6± 0.793**	24.3± 0.583**	28.1± 0.736***	16.4± 0.637**	18.3± 0.754**	19± 0.587**
16r	22.9±0.290**	24.2± 0.063**	25.9± 0.798**	15.3± 0.367**	16.6± 0.537**	19.7± 0.837**
16s	22.5± 0.272**	23.9± 0.893**	27.2± 0.673***	15.9± 0.367**	16.3± 0.157**	19.8± 0.837**
Standard	24.8± 0.765***	26.7±0.654***	29.2±0.753***	23.2± 0.087***	26.2± 0.087***	30.2± 0.087***
Control	0	7	7	0	7	7

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