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Synthesis and antibacterial evaluation of some hydrazones of flavanoid derivatives

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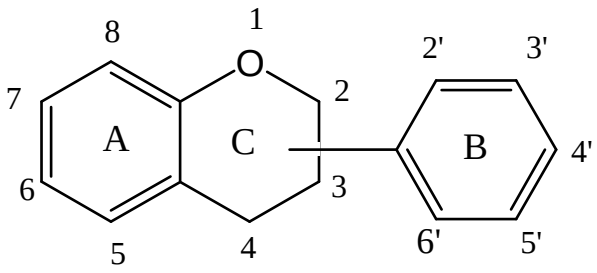
ABSTRACT

In an effort to synthesize potent anti-bacterial agents, few hydrazones of Flavanol derivatives have been synthesized and screened for in vitro anti-bacterial activity against 25 strains of Gram –ve and Gram +ve pathogenic bacteria. The chemical structures of compounds were established by IR, NMR spectra and elemental analysis. The synthesized compounds have shown inhibitory effect (MIC< 392 µg/ml) against few pathogenic bacterial strains and also posses activity against Methicillin-resistant Staphylococcus aureus strain because of presence of carbonyl region and hydroxyl group.

Key Words :, Flavanoid, Chalcones, Hydrazone derivative, Anti-bacterial agents.

INTRODUCTION

Flavanoids, polyphenolic plant secondary metabolites have shown to possess a large array of biological activity like anti-oxidant, anti-inflammatory, anti-viral, anxiolytic, anti-protozoal, anti-mitotic, anti-tumoral, anti-tubercular, anti-diabetic, cytotoxic activity against a multi-drug resistant cell line, tranquillizers, vasorelaxant, anti-acetylcholinesterase activity[1],[2]. All flavanoid aglycons consist of benzene ring ‘A’ condensed with a six member ring ‘C’, which in position 2 or 3 carries a phenyl ring ‘B’ as a substituent[3]. Flavanoids show anti-microbial activity because of presence of α-β unsaturated carbonyl group, that favours the π–electronic delocalisation of phenyl ring ‘B’[4] .

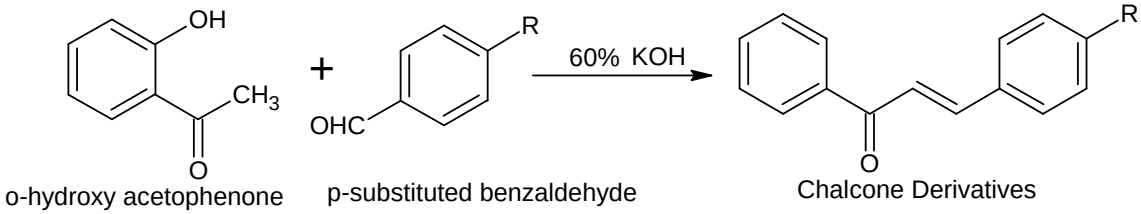


EXPERIMENTAL SECTION

Melting points were determined in open capillaries on Jindal melting point apparatus and were uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR RXI spectrophotometer. ^{1}H NMR spectra were recorded on DPX-300 (operating at 300 MHz for ^{1}H), spectrometer using $CDCl_3$ as solvent. Tetramethylsilane (0.00 ppm) serves as internal standard in ^{1}H NMR. Elemental analysis was done on Vario EL-III analyzer. Reactions were monitored on silica gel G TLC plates. Detecting agent used (for TLC) was iodine vapours.

CHEMISTRY

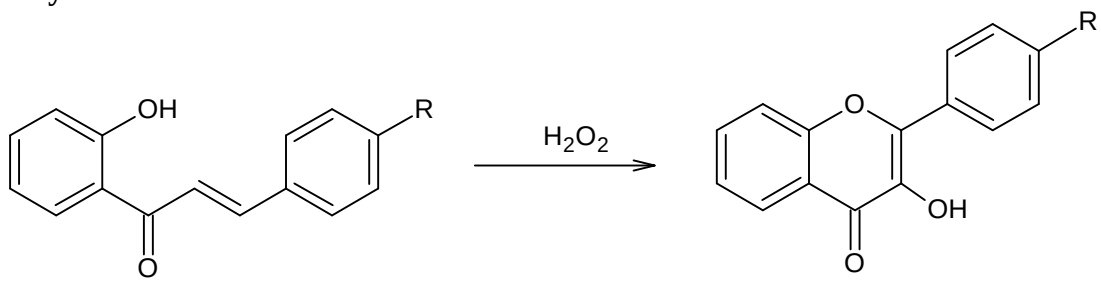
Step 1: synthesis of chalcone derivatives



R= -H, -Cl, -OCH_3, -NO_2, -CH_3

To a solution of o-hydroxy acetophenone (0.01 mol) in ethanol (15 ml), substituted benzaldehyde (0.01 mol) was added. Aquous potassium hydroxide (60%) was poured gradually with constant stirring till highly turbid solution is obtained and kept it for 24 hrs at 00C[4]. Completion of reaction was monitored by TLC. The precipitated chalcone was separated by ice-cold HCl (10%, 30 ml). The separated solid was filtered and washed off with ice –cold water (2 X 50 ml) till the washing was neutral to litmus. The compound was recrystallized with ethanol (99.5%) and dried at room temperature.

Step 2: cyclization of chalcone derivatives

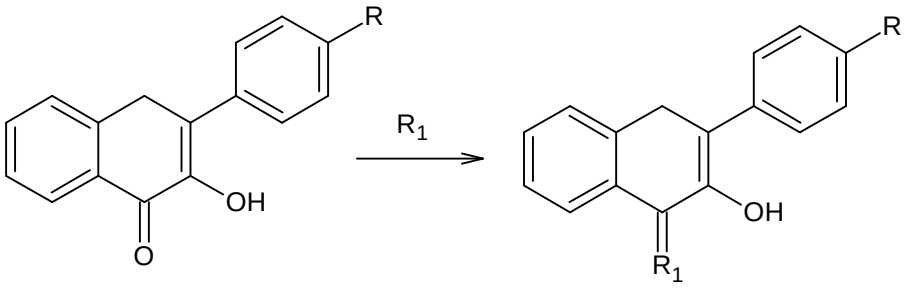


R= -H, -Cl, -OCH_3, -NO_2, -CH_3

Substituted chalcone (0.01 mol) was dissolved in a solution of 16% aq. Sodium hydroxide and 15% Hydrogen peroxide Solution (v/v 1:1). It was kept for few hours till the completion of

reaction which is monitored by TLC[5]. The compound was recrystallized with ethanol (99.5%) and dried at room temperature.

Step III: Synthesis of hydrazones of flavanol derivatives



R = -H, -Cl, $-OCH_3$, $-NO_2$, $-CH_3$

$\mathbf{R_1}$= $NHNH_2$, $-NHNHC_6H_5$, $-NHNHC_6H_5(NO_2)_2$

To the 0.1 mol of flavanol derivative dissolved in 200 ml methanol, 0.1 mol of reagent and few drops of glacial acetic acid was added. The mixture was refluxed for 10–12 h at 70–80°C in a water bath. The resulting solution was cooled to room temperature, and then poured onto crushed ice with constant stirring. The precipitate was filtered off and washed. The product was crystallized with hot methanol and dried.

SPECTRAL ANALYSIS

Compound J1:

IR (KBr, ν cm^{-1}): 3449.7 cm^{-1}(O-H str.), 3214.6 cm^{-1}(C-H str. Ar.), 2365.1 cm^{-1}(C-H str. Al.), 1607.6 cm^{-1}(C=O str. Am.), 1256.6 cm^{-1}(C-O-C str.), 1112.6 & 1179.4 cm^{-1}(C-O str.), 1611.1 cm^{-1} (N-H str. def.), 759.1cm^{-1}(Aromatic region, disubstituted); **^{1}H NMR (200 MHz, $CDCl_3$):** 2.10 (s, 3H, C<u>H</u>$_3$), 6.8 (s, 2H, N<u>H</u>), 7.1-7.9 (m, 8H, Ph-<u>H</u>), 15.6 (s, 1H, O<u>H</u>); **Elemental Analysis : Calculated (Found) :** C- 72.16 (72.87), H- 5.30 (5.55), N- 10.52 (10.74).

Compound J2:

IR (KBr, ν cm^{-1}) : 3475.9 cm^{-1}(O-H str.), 3286.3 cm^{-1}(C-H str. Ar.) 2366.0 cm^{-1}(C-H str. Al.), 1214.5 cm^{-1}(C-O-C str.), 1112.4 cm^{-1}(C-O str.), 1611.1 cm^{-1}(N-H str. def.), 760.7 cm^{-1} (Aromatic region, disubstituted); **^{1}H NMR (200 MHz, $CDCl_3$):** 2.16 (s, 3H, C<u>H</u>$_3$), 6.6 (s, 1H, N<u>H</u>), 6.32-7.38 (m, 13H, Ph-<u>H</u>), 15.01 (s,1H, O<u>H</u>); **Elemental Analysis : Calculated (Found):** C- 77.17 (77.89), H- 5.30 (5.68), N- 8.18 (8.69).

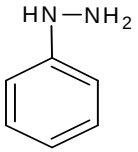
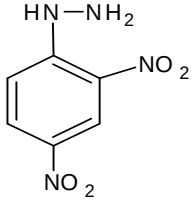
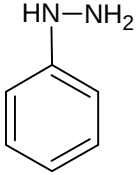
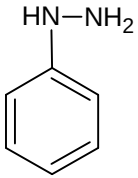
Compound J3:

IR (KBr, ν cm^{-1}) : 3395.3 cm^{-1} (O-H str.), 3021.8 cm^{-1} (C-H str. Ar.), 2365.9 cm^{-1} (C-H str. Al.), 1216.2 cm^{-1}(C-O-C str.), 1628.9 cm^{-1}(C=O str.), 1611.0 cm^{-1}(-O-N=O str.), 763.3 cm^{-1} (Aromatic region, disubstituted); **^{1}H NMR (200 MHz, $CDCl_3$):** 2.26 (s, 3H, C<u>H</u>$_3$), 7.12 (s, 1H, N<u>H</u>), 6.76-7.61 (m, 11H, Ph-<u>H</u>), 15.19 (s,1H, O<u>H</u>); **Elemental Analysis : Calculated (Found):** C- 61.11 (61.64), H- 3.73 (4.20), N- 12.96 (12.45).

Compound J4:

IR (KBr, ν cm^{-1}): 3434.5 cm^{-1}(O-H str.), 3021.6 cm^{-1}(C-H str. ar.), 2364.1 cm^{-1}(C-H str. al.), 1216.1 cm^{-1}(C-O-C str.)1628.9 cm^{-1}(C=O str.), 1601.7 cm^{-1}(-O-N=O str.), 761.9 cm^{-1}(Aromatic region, disubstituted), 1107.6 cm^{-1}(C-O str.); **^{1}H NMR (200 MHz, $CDCl_3$) :** 7.08 (s, 1H, N<u>H</u>), 6.31-8.21 (m, 13H, Ph-<u>H</u>), 15.14 (s,1H, O<u>H</u>); **Elemental Analysis : Calculated (Found):** C- 62.76 (62.23), H- 4.65 (4.19), N- 12.92 (12.37).

Table 1. Description of Synthesized Compounds

Compound Code	R	R_1	Mol. Weight Mol. formula	R_f Value	Melting Point (^{0} C)	Yield (%)	Refractive Index	Log P
J1	CH_3	NH_2-NH_2	$C_{16}H_{14}N_2O_2$ 266.29	0.512	200-202^{o}C	63 %	1.603	2.67
J2	CH_3		$C_{22}H_{18}N_2O_2$ 342.39	0.426	218-220^{o}C	55 %	1.595	3.28
J3	CH_3		$C_{22}H_{16}N_4O_6$ 432.38	0.596	212-214^{o}C	69 %	1.692	5.45
J4	NO_2		$C_{21}H_{15}N_3O_4$ 373.36	0.312	176-178^{o}C	80 %	1.673	5.08
J5	Cl	NH_2-NH_2	$C_{15}H_{11}ClN_2O_2$ 286.71	0.701	136-138^{0}C	87 %	1.698	2.20
J6	OCH_3		$C_{22}H_{18}N_2O_2$ 342.39	0.496	165-168^{0}C	63 %	1.613	4.58

Compound J5:

IR (KBr, ν cm^{-1})): 3391.1 cm^{-1}(O-H str.), 3018.6 cm^{-1}(C-H str. Ar.), 2332.2 cm^{-1}(C-H str. al.), 1212.1 cm^{-1}(C-O-C str.), 1621.4 cm^{-1}(C=O str.), 759.6 cm^{-1}(Aromatic region, disubstituted), 1179.4 cm^{-1}(C-O str.); **^{1}H NMR (200 MHz, $CDCl_3$) :**15.11 (s,1H, OH), 7.14 (s, 2H, NH_2), 6.24-7.41 (m, 8H, Ph-H); **Elemental Analysis : Calculated (Found):** C- 62.84 (62.16), H- 3.87 (2.99), N- 6.77 (6.25).

Compound J6:

IR (KBr, ν cm^{-1})): 3391.1 cm^{-1}(O-H str.), 3018.6 cm^{-1}(C-H str. Ar.), 2332.2 cm^{-1}(C-H str. al.), 1212.1 cm^{-1}(C-O-C str.), 1621.4 cm^{-1}(C=O str.), 759.6 cm^{-1}(Aromatic region, disubstituted), 1179.4 cm^{-1}(C-O str.); **^{1}H NMR (200 MHz, $CDCl_3$) :** 3.73 (s,1H, OCH_3), 7.0 (s, 1H, NH), 6.46-7.41 (m, 13H, Ph-H); **Elemental Analysis : Calculated (Found):** C- 77.84 (77.17), H- 5.96 (5.30), N- 7.66 (8.18), O-8.88 (9.35).

Antibacterial Screening

The synthesized compounds were evaluated for antibacterial sensitivity against 25 strains at 5000 μg/mL[6]. Further compounds were selected for MIC determination which was more sensitive in the initial test.

Table 2. *In vitro* Antibacterial activity of the compounds

MICs in μg/ml, Sulfamethoxazole(Standard Drug)
Note- All the sensitive compounds have MIC < 5000 μg/ml

S.N.	Compound / Strains	J1	J2	J3	J4	J5	J6	SUL*
1.	*Proteus mirabilis*	<5000	**392.0**	-	<5000	-	<5000	2500
2.	*E. coli ATCC-35218*	-	<5000	<5000	-	-	**392.0**	1250
3.	*Klebsiella oxytoca*	-	<5000	-	-	<5000-	-	2500
4.	*Proteus vulgaris*	<5000	<5000	-	-	-	-	2500
5.	*Shigella sonnei*	-	<5000	**392.0**	<5000	-	**392.0**	2500
6.	*Shigella boydii*	-	-	**392.0**	<5000	<5000	<5000	2500
7.	*Providentia rettgeri*	<5000	<5000	**392.0**	<5000	<5000	-	2500
8.	*H. pylori*	-	-	-	<5000	-	-	2500
9.	*K. pneumoniae*	<5000	-	-	-	-	-	2500
10.	*Ps ATCC-24853*	-	-	-	-	-	-	2500
11.	*S. typhi*	**392.0**	<5000	-	<5000-	**392.0**	**392.0**	2500
12.	*S. paratyphi*	**392.0**	<5000	-	<5000	**392.0**	**392.0**	2500
13.	*S. typhi MTCC-3216*	-	<5000-	-	<5000	-	-	2500
14.	*Morginella morgani*	-	-	-	<5000	-	-	2500
15.	*Shigella flexineri*	**392.0**	<5000	**392.0**	-	<5000-	-	2500
16.	*E. coli 25922*	**392.0**	<5000	-	-	-	<5000	1250
17.	*Salmonella enteritidis*	-	<5000	**392.0**	-	**392.0**	<5000	2500
18.	*S. aureus*	-	-	-	<5000-	-	<5000	5000
19.	*Ps. Aeruginosa*	-	<5000	-	-	-	<5000	2500
20.	*Ps. aeruginosa ATCC*	-	-	-	-	**392.0**	-	2500
21.	*Shigella dysentrica*	-	<5000	-	-	-	<5000	2500
22.	*M. smegmatis*	**39.2**	**392.0**	**392.0**	**392.0**	-	**392.0**	2500
23.	*V. parahaemolyticus*	-	-	-		**392.0**	-	2500
24.	*V. cholerae*	<5000	<5000	-	-	-	-	5000
25.	*E. faecalis*	**392.0**	**392.0**	-	**392.0**	**392.0**	**392.0**	5000

RESULTS AND DISCUSSION

Hydrazone, and Phenyl hydrazones of flavanol derivatives (J1-J6) have been synthesized with methoxy, methyl, chloro and nitro group in basic skeleton of flavanol. The antibacterial activity

performed on the synthesized flavanoid derivatives reveals that J1 has shown activity at MIC value<392 µg/ml against *S.typhi, S.paratyphi, Shigella flexineri, E.coli 25922, M.smegmatis* and *E.faecalis*. Phenylhydrazone derivative J2 inhibited growth at MIC value<392 µg/ml of *Proteus mirabilis, M.smegmatis* and *E.faecalis*. 2,4-dinitro phenyl hydrazine derivative with methyl group in basic skeleon has shown antibacterial activity at MIC value<392 µg/ml against *Shigella* species, *Salmonella* species, *Providentia retgeri* and *M.smegmatis*. Hydrazine derivative with nitro substitution in basic skeleton has shown activity against *M.smegmatis* and *E.faecalis* at MIC value <392 µg/ml. J5 with chloro substitution has shown activity against *Salmonella* species. J6 with methoxy substitution has shown inhibition against *E.coli ATCC-35218, Shigella sonnei, Salmonella* species, *M.smegmatis* and *E.faecalis* at MIC value<392 µg/ml.

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