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Synthesis of some novel flavonol derivatives and its microbial activity

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ABSTRACT

A series of flavonol derivatives were synthesized according to Algar-Flym-Oyamada reactions and chalcone were was synthesis according to the Claisen-Schmidt reactions. Chalcones were prepared by condensing equimolar of o-hydroxy acetophenones with 6-methoxynapthadehyde in alcoholic alkaline medium at room temperature. The resultant chalcones were immediately reacted with H_2O_2 in the presence of a mixture of aqeous alcoholic alkali to obtained corresponding flavonol. All the syntesized flavonol were characterized by means of their, IR, ^{1}HNMR, Mass spectral data, elemental analysis and their physical properties. All flavonol were tested for their anfifungal and antibacterial activity. All the sysntesized flavonol exhibited moderate to good antimicrobial activity.

Key words: synthesis of chalcones, flavonol, Antifungal and Antibacterial activity.

INTRODUCTION

Flavonoids are phenolic secondary metabolites that are widely distributed throughout the plant kingdom. The average western diet includes upto 2g of flavonoids per day. The flavonoids are having very important pharmaceutical activity like antibacterial, antifungal, anti-inflammatory, antiviral, antioxidant, anti-allergic, antimalarial activity[1-7]. In plants, flavonoids function as UV-protectants, pollinator attractants and as signaling molecules between root and nitrogen fixing bacteria in the soil. An essential role in plant reproduction has been established for one class of flavonoid the flavonols.

Flavonols constitute a major class of plant natural products and have a wide range of biological activities. Flavonol have recently attracted lot of attention due to their proposed preventative role in coronary diseases as a result of dietary intake. Flavonols inhibit the development of intestinal carcinoma and are administrated to patients with uncreative colitis, who have an elevated risk of colorectal carcinogenesis[10]. Similarly pollen form maize and petunia mutant lacking flavonol is unable to germinate. However, the mutatn pollen is viable and the defect can be biochemically complemented by adding Kaempferol at the time pollination[11]. Kaempferal and it's glycosides show antiviral activity against human cytomegalovirus (HCMV) and some derivative of quercetin also used to inhibit the activity of cyclin dependent kinase[12]. Quercetagetin-3,7,3'-trimethylether in an antiviral agent[13] while quercetin exhibits strong radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH), super oxide anions and hydroxyl radical[14].

It was found that natural flavonol are commonly substituted at variable positions, mainly by hydroxyl, metoxy, isoprenyl and glycosyl groups, it was also found that biological activities of flavonol

is due to the presence of these substituents. One the other hand it has also been found that halogenated compounds also shows strong biological activities[15]. Literature serve reveals that no naphthalene substituted flavonol were synthesized and it was also found that halogenated and naphthalene substituted flavonols are not found in nature.

Due to high biological activities of flavonols, we wish to decide to synthesize some novel flavonol derivatives which are halogen substituted as well as naphthalene substituted and naphthalene is also substituted at 6 position by methoxy group. The synthesized compounds were characterized on the basis of IR, ^{1}HNMR, Mass spectral data and elemental analysis. These compounds were also evaluated for their antimicrobial activity.

EXPERIMENTAL

Meltings points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectra were recorded in KBr on Perkin-Elmer spectrophotometer. The ^{1}HNMR were recorded in $CDCl_3$ on Bruker spectrospin AV 400 MHz spectrometer using TMS as an internal standard. The mass spectra of the compounds were recorded on MDS spiex API 200 LC-MS Mass spectrophotometer. The purity of the compounds was checked by the TLC using silica gel-G (Merck).

General procedure for the preparation of chalcones from substituted o-hydroxy acetophenones and 6-methoxy napthyaldehyde (3a-i)

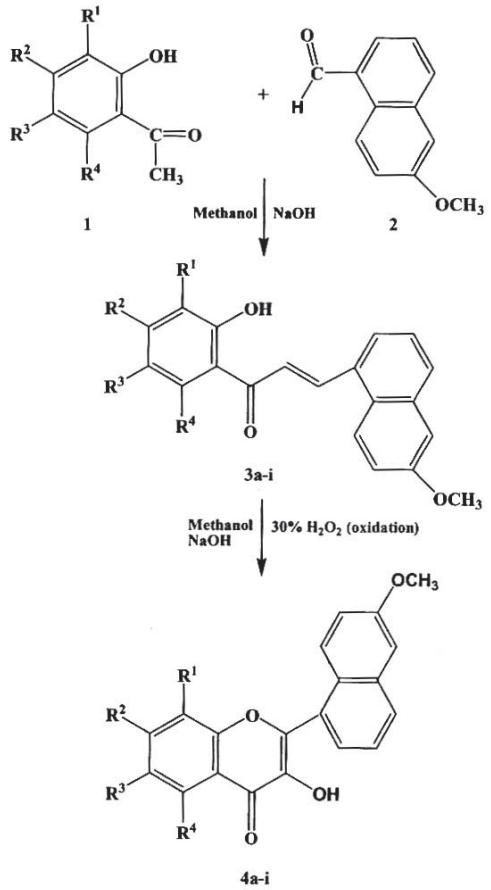
A mixture of substituted o-hydroxy acetophenones (0.01 moles) and 6-methoxy napthyaldehyde (0.01mole) was stirred in ethanol (30ml) and then sodium hydroxide solution (15ml, 0.02M) was added to it. The mixture was kept over night at room temperature and then it was poured on crushed ice and acidified with dilute hydrochloric acid. The solid obtained was filtered, washed with water, dried and crystallized from acetic acid scheme-1. Yield and melting point of the product(s) were determined and presented in table 1. It shows the following spectral data.

IR(KBr):- 3300-3320cm^{-1} (OH st.), 1625-1630 cm^{-1} (H=CH) 1645 cm^{-1} (>C=O st.)

^{1}HMNR:- 3.8δ to 3.9δ (S, 3H, OCH_3), 6.9-6.95δ (dd 1H, CH_A=C<), 7.1δ (dd, 1H, >C=CH_B-) 7.4δ-8.1δ (m, 9H, aromatic protons protons), 12.4δ (s, 1H, OH)

General procedure for the preparation of substituted flavonol (4a-i)

Compound (3a-i) (0.003 mole), ethyl alcohol (50ml) and sodium hydroxide solution (10ml, 1.25N) and 10ml solution of hydrogen peroxide (30%) was stirred continuously for 2 hr at room temperature. It was then diluted with ice cold water acidified with dil HCl. When solid separated, it was filtered, washed well with water, dried and crystallized from acetic acid scheme - 1. Yield and melting point of the products were determined and presented in table 2. The characterization data of the compounds are presented in table 3.



Scheme 1

Table 1: Physical data of compound 3a-i

Compound	R1	R2	R3	R4	m.p. (°C)	yield%
3a	H	H	H	H	156	94
3b	Cl	H	Cl	H	220	92
3c	H	H	Cl	H	194	95
3d	Cl	H	H	H	165	93
3e	H	H	Br	H	185	90
3f	CH_3	H	CH_3	H	149	90
3g	CH_3	H	H	H	156	94
3h	H	H	CH_3	H	133	92
3i	H	CH_3	Cl	H	191	94

Table 2: Physical data of compound 4a-i

Compound	R1	R2	R3	R4	m.p. (°C)	yield%
4a	H	H	H	H	232	92
4b	Cl	H	Cl	H	262	95
4c	H	H	Cl	H	186	94
4d	Cl	H	H	H	226	90
4e	H	H	Br	H	228	93
4f	CH_3	H	CH_3	H	242	92
4g	CH_3	H	H	H	192	95
4h	H	H	CH_3	H	232	94
4i	H	CH_3	Cl	H	218	95

Biological evaluation

Antimicrobial activity

The compounds (4a-i) were assayed for antibacterial activity against *E. coli, salmonella typhi, Staphylococcus aureus, Bacillus subtilis* and antifungal activity against Aspergillus niger, Aspergillus oragin and Fusarium moniliforme. The test for antibacterial activity was carried by agar cup method[16-17] (cup size 8mm) with nutrient agar as medium whereas antifungal activity was carried out by using potato-dextrose agar (PDA) medium by same cup plate method. All compounds were dissolved in DMSO and used as control. Concentration of each test compound was 10µg/ml. The experiments were performed in triplicate in order to minimize the errors. Zone of inhibtion were recorded after incubation for 24 hrs, zone of inhibtion produced by each compound was measured in mm. The results of antibacterial and antifungal studies are given in table 4 and 5 respectively.

RESULTS AND DISCUSSION

The target compounds (4a-i) were synthesize through the route depicted in the scheme 1. Literature survey reveals that all the synthesized flavonol derivatives are new. The structure of the synthesized compounds was confirmed on the basis of IR, ^{1}HNMR, Mass spectral data and elemental analysis.

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition zone record of the compounds indicate that compounds, 4b,d,e,f,g,h were highly active against *E. coli* and 4a,e,h are active against *Salmonella typhi*. Compounds 4b,c,e,h are highly active against *S. aureus.* All the compounds are active against *Bacillus subtilus*. Majority of the compounds are inactive against *S. typhi* and *S. aureus*.

Table 3: Characterization data of compounds 4a-i

Comp.	IR cm^{-1}	1H NMR δppm
4a	3270 (-OH), 1642(-C=O), 1494(C=C), 1266 (-C-O)	8.74 (s, 1H, benzene), 8.28 (m,2H, benzene), 7.88 (t, 2H, naphthalene), 7.44 (t, naphthalene), 7.68 (d, 1H, benzene), 7.44 (t, 1H, napthalene), 7.21 (m 2H, naphthalene), 3.96 (s, 3H, OCH_3)
4b	3177 (-OH), 1609(-C=O), 1476(C=C), 1272 (-C-O)	8.74(s, 1H, benzene), 8.26 (d, 1H, naphthalene), 7.99 (d, 1H, naphthalene), 7.96(d, 1H, naphthalene), 7.90 (t, 2H, naphthalene), 7.26 (s, 1H, benzene), 7.16 (dd, 1H, napthalene), 3.89 (s, 3H, OCH_3)
4c	3294 (-OH),1675(-C=O), 1499(C=C), 1380 (-C-O)	8.80(s, 1H, naphthalene), 8.25 (m, 1H, benzene), 7.95 (t, 2H, naphthalene), 7.89 (t, 2H, naphthalene), 7.82 (d, 1H, naphthalene), 7.26 (s, 1H, benzene), 7.16 (m 2H, naphthalene), 3.90 (s, 3H, OCH_3)
4d	3241 (-OH),1642 (-C=O), 1467(C=C), 1165 (-C-O)	8.85 (s, 1H, naphthalene), 8.40 (d, 1H, benzene), 8.19 (d, 1H, benzene), 7.89 (t, 1H, benzene), 7.80 (t, 2H, naphthalene), 7.80 (s, 1H, benzene), 7.36 (t, 1H, naphthalene), 7.20 (m, naphthalene) 3.97 (s, 3H, OCH_3)
4e	3290 (-OH),1645 (-C=O), 1477(C=C), 1170 (-C-O)	8.73(s, 1H, benzene), 8.27 (m, 1H, benzene), 8.18 (d, 1H, naphthalene), 7.94 (d, 2H, naphthalene), 7.81 (d, 1H, naphthalene), 7.39 (d, 1H, benzene), 7.22 (dd, 2H, naphthalene), 3.90 (s, 3H, OCH_3)
4f	3275 (-OH),1659 (-C=O), 1479(C=C), 1166 (-C-O)	8.76(s, 1H, benzene), 8.27 (m, 1H, maphthalene), 7.97 (d, 1H, naphthalene), 7.95 (d, 1H, naphthalene), 7.27 (s, 1H, benzene), 7.17 (dd, 1H, naphthalene), 2.68 (s, 6H, CH_3), 3.90 (s, 3H, OCH_3)
4g	3220 (-OH),1654(-C=O), 1475(C=C), 1163 (-C-O)	8.76(s, 1H, naphthalene), 8.30 (d, 1H, benzene), 8.17 (d, 1H, benzene), 7.86 (t, 2H, naphthalene), 7.55 (d, 1H, benzene), 7.35 (t, 1H, naphthalene), 7.20 (m 2H, naphthalene), 2.67 (s, 3H, CH_3) 3.95 (s, 3H, OCH_3)
4h	3287 (-OH),1728(-C=O), 1442(C=C), 1220 (-C-O)	8.75(s, 1H, naphthalene), 8.30 (d, 1H, benzene), 8.16 (d, 1H, benzene), 7.85 (t, 2H, naphthalene), 7.55 (d, 1H, benzene), 7.34 (t, 1H, naphthalene), 7.20 (m 2H, naphthalene), 2.65 (s, 3H, CH_3) 3.96 (s, 3H, OCH_3)
4i	3280 (-OH),1690(-C=O), 1485(C=C), 1180 (-C-O)	8.74(s, 1H, naphthalene), 8.28 (s, 1H, benzene), 8.18 (s, 1H, benzene), 7.84 (t, 2H, naphthalene), 7.36 (t, 1H, benzene), 7.22 (t, 1H, naphthalene), 7.22 (m, 2H, naphthalene), 2.64 (s, 3H, CH_3) 3.90 (s, 3H, OCH_3)

The investigation of antifungal activity data revealed that major of the compounds shows inhibitory effect against *Aspergillus niger, Aspergillus origin* but most of the compounds are inactive against Fusarium moneliforme. From all above studies it was concluded that in this paper flavonols were synthesized which are all new and which are substituted with naphthalene ring and naphthalene is also substituted by methoxy group. It was found that methoxy group substituted flavonol shows better activity thin those having other group, however it was also found that halogen substituted groups also shows better activity that those is sample scope for further study in developing these as commercial antimicrobial agent.

Table 4: Antibacterial screening results of the compound 4a-i

Compound	Antibcaterial activity (Inhibition zone in mm)			
	E. coli	***Salmonella typhi***	***Staphylocccus aures***	***Bacillius subtilis***
4a	6	18	-ve	15
4b	10	-ve	22	22
4c	7	-ve	27	20
4d	7.5	20	-ve	22
4e	11	24	35	24
4f	8	-ve	-ve	20
4g	7.5	-ve	-ve	18
4h	9	21	32	23
4i	-ve	-ve	-ve	-ve
Penicillin	12	26	40	27
DMSO	-ve	-ve	-ve	-ve

-ve no antibacterial activity

Table 5: Antibacterial screening results of the compounds 4a-i

Compound	Antibcaterial activity		
	Aspergillus niger	***Aspergilus flavus***	***Fusarium moneliforme***
4a	-ve	-ve	+ve
4b	-ve	+ve	-ve
4c	-ve	-ve	+ve
4d	+ve	+ve	+ve
4e	-ve	-ve	-ve
4f	-ve	-ve	+ve
4g	+ve	-ve	+ve
4h	-ve	-ve	-ve
4i	ve	+ve	+ve
Penicillin	-ve	-ve	-ve
DMSO	+ve	+ve	+ve

Legends: - +ve - Growth No Antifungal activity
- ve- No growth Antifungal activity observed

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