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SYNTHESIS OF SOME NEW HALOGEN SUBSTITUTED FLAVONE DERIVATIVES

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ABSTRACT

A new series of biologically active halogen substituted flavones (2a-j) were synthesized by the oxidative cyclization of corresponding halogen substituted 2'-hydroxychalcones (1a-j) using conventional method in dimethyl sulfoxide as solvent with excellent yields. The structures of these compounds have been characterized by IR, ^{1}H NMR and Mass spectral data. All the newly synthesized compounds were tested for their *in vitro* antibacterial activity against four different pathogenic bacteria such as *Escherichia coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis* and antifungal activity against four different fungi, namely *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme* and *Aspergillus flavus* which exhibited moderate to good activity against different strains of bacteria and fungi employed.

Keywords: Halohydroxychalcones, Flavones, Antimicrobial activity.

INTRODUCTION

Flavonoids are important group of natural products present in various plants. Many substituted flavonoids exhibit a broad range of biological activities[1-3], such as Analgesic [4], Anti-inflammatory [5], Chemopreventive [6], Anti-cancer [7, 8], Antitumor[9], Antioxidant [10], Antiglycation [11], Vasorelaxant [12], Cyclo-oxygenase-2 (COX2) [13], Antiplaque [14] and Anti-tuberculosis[15]. It is well known that halogen substituted flavonoid compounds are also strongly biologically active [16] but to our knowledge very few synthetic flavonoids have been reported with halogens as substituents. On the other hand, halogen and methyl group substituted in pyron ring also exhibit biological activity [17]. Considering these observations, we report herein, the synthesis of a number of new flavones (2a-j), having chloro, bromo, iodo and methyl moiety in pyron ring with the aim to find new more potential antibacterial and antifungal agents. We have synthesized a new series of halogen substituted-chromen-4-ones as antimicrobial agents by the oxidative cyclization of 2'-hydroxy-substituted chalcones in the presence of few crystals of iodine in dimethyl sulfoxide (DMSO). The structures of the newly synthesized compounds (2a-j) were confirmed on the basis of IR, ^{1}H NMR, and Mass spectral data. All the newly synthesized compounds were tested for their *in vitro* antibacterial activity against *Escherichia coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis* and antifungal activity against *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme* and *Aspergillus flavus,* using Peniciline and Greseofulvin as standard drugs.

MATERIALS AND METHODS

All the melting points were determined by open capillary method and are uncorrected (Table 1). IR spectra of compounds were scanned on FTIR Perkin Elmer model RXI Spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$, on Gemini 200 MHz instrument using TMS as an internal standard (Chemical shift are given in δ ppm). The mass spectra (MS) were recorded on VG 7070H mass spectrometer using ionisation energy of 70 eV. The purity of the compounds has been checked by TLC plates (Merck) using benzene and ethyl acetate as an eluent in the ratio of (7:3 v/v).

General procedure for the synthesis of flavones

Halogen substituted 2'-hydroxychalcones (0.001mol) were dissolved in Dimethyl sulfoxide (DMSO) (10 ml) and few crystals of iodine were added to it. The reaction mixture was refluxed for 30-50 min. The completion of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled at room temperature and diluted with water. The excess of iodine was washed with saturated sodium thiosulphate solution followed by washing with cold water and recrystallized from ethyl alcohol to get compounds

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(2a-j). The compounds didn't gave reddish pink coloration with concentrated H_2SO_4 and gave negative test for phenolic-OH group. The yields and melting points of the compounds are tabulated below in Table-1.

Experimental

Synthesis of 2-(2'-thienyl)-6-chloro-7-methyl-8-iodoflavone (2b):

A solution of 1-(2'-hydroxy-3'-iodo-4'-methyl-5'-chlorophenyl)-3-(2"-thienyl)-2-propen-1-one (0.01mole) in dimethyl sulphoxide (10.0ml) containing iodine (1-2 crystal) was refluxed for about 45min. The reaction mixture was cooled to room temperature and poured onto crushed ice with stirring. To the cold reaction mixture, an aqueous sodium thiosulphate solution (20%) was added until the solution was colourless, followed by ice-cold water (5ml). A solid get separated out and after filtration, drying and recrystallisation from dilute alcohol gave the flavone 2b.

Other flavones were also prepared by same method. Their melting points, yields, elemental analyses are tabulated as Table-1.

RESULTS AND DISCUSSION

This paper presents synthesis of novel halogen substituted flavones (2a-j) which were synthesized by oxidative cyclization of corresponding halohydroxychalcones (1a-j). All these flavones didn't gave violet coloration with ferric chloride solution and pink coloration with concentrated H_2SO_4. The structures of newly synthesized compounds have been confirmed by spectral data. The IR Spectra of synthesized flavones showed absorption at 1630-1660 cm^{-1} due to C=O stretching, 1565-1595cm^{-1} due to C=C. Lowering of carbonyl frequency is attributed to the conjugation. The ^1H NMR spectra of some representative flavones showed a singlet near at δ6.55-6.8 due to 1H of 3-H i.e. pyrone ring. It is the characteristic singlet for flavones. The multiplet at δ7.2 to 8.6 is due to aromatic protons. Such observed ^{1}HNMR data and complete absence of a peak near at δ12.0 due to orthohydroxy (aromatic) group proved their structures. The mass spectra of few flavones recorded confirm the oxidative cyclization of chalcones to flavones i.e. due to removal of two H atoms from chalcones. The mass spectra of corresponding flavones show their molecular formula weight less by two as compared to the MFW of chalcones.

All the newly synthesized compounds were screened for their antibacterial activity against four different selected pathogens, such as *Escherichia coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis*. The compounds 2a, 2b, 2c, and 2i showed maximum activity against *B. subtilis* while compounds 2d, 2g and 2j exhibited moderate activity.

All the compounds are not biologically active against *E. coli* pathogen as shown in the Table 2.The compounds 2c, 2d, and 2h showed maximum activity against *S. typhi*, while 2a, 2e, 2i and 2j showed moderate activity in comparison with standard drugs (Penicilin). The compounds 2f, 2g, and 2j exhibited most antibacterial activity against *S. typhi* as compared with peniciline. The compound 2c is most antibacterial active against *B. subtilis*. All the compounds of flavones showed moderate activity against *S. aureus*. The results revealed that most of the newly synthesized compounds exhibited moderats to good antifungal activity as comparison with (Greseofulvinas) standard drugs against four different pathogens such as *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme and Aspergillus flavus*. The presence of flavone moiety, the substituent's particularly bromo, chloro, iodo and methyl groups in phenyl ring may be responsible for antimicrobial activity of this class of compounds.

Spectroscopic data of compound 2b

IR : ν max: 1636, 1607, 1584, 1538, 1436, 1375, 1217, 1181, 1110, 764, 562 cm^{-1}

^{1}H NMR ($CDCl_3$): δ2.78(s, 3H, Ar-CH_3),6.68(s, 1H, 3-H pyrone),7.21-8.17(m, 4H, Ar-H).

MS : $^m/_z$ (% rel. intensity): 404,(M^++2, 32), 402(M^+, 100), 296(23),294(72), 167(18), 139(31), 135(06), 128(18), 111(80), 103(07), 89(14), 82(06), 75(32), 63(08), 45(30).

ANTIMICROBIAL ACTIVITY

All the newly synthesized flavones compounds were assessed for their antibacterial and antifungal activities against four different strains of bacteria such as *E. coli, S typhi, S. aureus* and *B. subtilis* and four fungi like *Aspergillus niger, Penicillium chrysogenum, Fusarium moneliforme and Aspergillus flavus* by using Cup Plate Method [18] at a concentration of 100 µg/ml. The Solvent DMSO was used as solvent control. Standard drugs like Peniciline and Greseofulvin were used for comparision purpose. The biological data of compounds as shown in table.2

The data of antimicrobial activity indicate that, compounds 2a, 2b, 2c, 2e, 2f and 2i exhibited most significant antibacterial activity against *B. subtilis* as compared with standard drug while 2d, 2g and 2j exhibited moderate activity. All the tested compounds do not show antibacterial activity against *E. coli*. The chlorinated, brominated and iodinated compounds of flavones exhibited moderate active against *S. typhi* as compared with peniciline. The compound 2c was most antibacterial active against *B. subtilis* as compared with peniciline. The results revealed that the newly synthesized compounds exhibited moderate to good antifungal activity as comparison with (Greseofulvinas) standard drugs.

Table 1. Physical data of synthesized halogen substituted Flavone derivatives (2a-j)

Compd.	Mol. Formula	Yield (%)	M.P. (^{0}C)	% Found (calcd.) X (Cl, Br, I)	N
2a	$C_{19}H_{16}O_5ICl$	78	194	33.35 (33.33)	--------
2b	$C_{14}H_8O_2IClS$	83	208	40.32 (40.29)	--------

2c	$C_{17}H_{13}O_3NBr_2$	62	212	36.47 (36.44)	3.19 (3.18)
2d	$C_{17}H_{12}O_5Br_2$	68	178	35.10 (35.08)	--------
2e	$C_{18}H_{14}O_6Br_2$	56	252	32.95 (32.92)	--------
2f	$C_{13}H_6O_3Br_2S$	52	186	39.84 (39.80)	--------
2g	$C_{17}H_{13}O_2NICl$	72	209	38.15 (38.11)	3.30 (3.29)
2h	$C_{17}H_{12}O_4ICl$	78	191	36.61 (36.65)	--------
2i	$C_{18}H_{14}O_5ICl$	75	160	34.37 (34.32)	--------
2j	$C_{13}H_6O_2IClS$	70	157	41.79 (41.75)	--------

All synthesised compounds were recrystallised from aqueous ethyl alcohol.

Table 2. Antimicrobial activity of synthesized Flavone derivatives (2a-j)

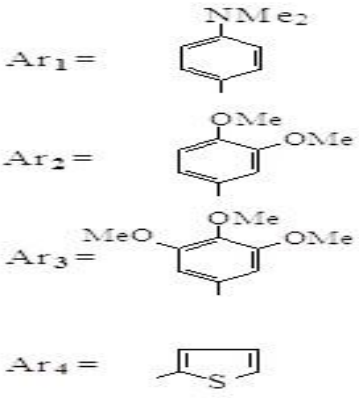
Sr. No.	Entry	Bacteria (Zone of Inhibition in mm)				Fungi (Zone of Inhibition in mm)			
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**
1	2a	--	--	18	27	-ve	-ve	-ve	-ve
2	2b	--	15	15	26	-ve	-ve	-ve	RG
3	2c	--	12	13	23	-ve	-ve	-ve	RG
4	2d	--	11	18	15	-ve	-ve	-ve	-ve
5	2e	--	--	17	22	-ve	-ve	-ve	RG
6	2f	--	15	12	26	-ve	-ve	-ve	RG
7	2g	--	17	13	22	-ve	-ve	-ve	-ve
8	2h	--	12	17	25	-ve	-ve	-ve	RG
9	2i	--	13	16	28	-ve	-ve	-ve	-ve
10	2j	--	17	15	18	-ve	-ve	-ve	-ve
+ve DMSO									
Control		-ve	-ve	-ve	-ve	+ve	+ve	+ve	+ve
Penicillin		12	20	34	22	X	X	X	X
-ve Control									
(Greseofulvin)		X	X	X	X	-ve	-ve	-ve	-ve

(Zone of Inhibition in mm)

A= *Escherichia coli*, **B**=*Salmonella typhi*, **C**= *Staphylococcus aureus*, **D**=*Bacillus subtilis* **E**= *Aspergillusniger*, **F**=*Penicillium chrysogenum*, **G**=*Fusarium moneliforme*, **H**= *Aspergillus flavus*- = No Antibacterial activity, -ve = Growth (Antifungal Activity Observed), RG= Reduced Growth (Moderate Activity), X = Not applicable.

Chalcones **Flavones (2a-j)**

	R_1	R_2	R_3	Ar
2a	I	CH_3	Cl	Ar_3
2b	I	CH_3	Cl	Ar_4
2c	Br	OH	Br	Ar_1
2d	Br	OH	Br	Ar_2
2e	Br	OH	Br	Ar_3
2f	Br	OH	Br	Ar_4
2g	I	H	Cl	Ar_1
2h	I	H	Cl	Ar_2
2i	I	H	Cl	Ar_3
2j	I	H	Cl	Ar_4



CONCLUSION

It is concluded from the results that, Cl, Br, I and methyl substituents on the flavones ring are responsible for the enhancement of the antibacterial activity. It can further be concluded that the percentage inhibition increases with increasing electronegativity of the halogen atoms on the flavones ring. The Cl is more electronegative, the chloro compounds show significant antibacterial activity. In the antifungal activity the halogen substituted compounds 2a, 2d, 2g, 2i and 2j displayed potent activity against four fungi. From the results it is evident that most of chloro, bromo, iodo and methyl group substituted compounds exhibited good antimicrobial activity. There is much scope to synthesise and screen further new halogenated flavones against a large number of gram positive and gram negative plant and human pathogens in order to find better antimicrobial agents.

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