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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ANALYSIS OF VARIOUS SUBSTITUTED 3-(3-(5-bromothiophen-2-yl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one

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ABSTRACT
We have developed a protocol for the synthesis of some novel chalcones, also used a green, efficient and rapid procedure for the synthesis, this synthesis done by the condensation of pyrazole aldehyde and O-hydroxyketone, in the presence of KOH in EtOH. All the synthesized products were characterized by NMR, IR and Mass spectral data also. These synthesized compounds have been screened for their antimicrobial activity against Gram –ve and gram +ve microorganisms. A few of them shows moderate antimicrobial activity.

Keywords: Aldehyde, O-hydroxyketone, Pyrazole, Chalcone, Condensation, KOH, EtOH.

INTRODUCTION
Chalcones are natural products which are found in a variety of plant species with the general formula Ar-CH=CH-CO-Ar in which the two aromatic rings are joined by α, β-unsaturated carbonyl system. These are rich in edible plants and are considered as precursors of flavonoids and isoflavonoids. Chalcones have been generally prepared by Claisen-Schmidt (Aldol) condensation reaction of aromatic aldehydes with aryl ketones in presence of suitable agents. They show diverse chemical reactions and act as precursor for the synthesis of various heterocyclic compounds[1] like benzodiazepine, thiadiazines, isoxazoles, quinolinones, benzofuranones, tetrahydro-2-chromens flavones[2] etc. Chalcones and their derivatives have attracted greater attention towards it due to several pharmacological applications. They shows a broad spectrum of pharmacological activities, like antibacterial[3,4], antimicrobial[5], anti-inflammatory[6,7], antifungal[8,9], antimalarial[10-13], anticancer [14,15], antioxidant[16], antiprotozoal (antileishmanial and antitrypanosomal)[17], antifilarial[18], larvicidal [19], anticonvulsant[20] activities have been reported yet. Also they have shown inhibition of the enzymes, especially mammalian alpha-amylase[21], monoamine oxidase (MAO)[22] and cyclo-oxygenase (COX) [23]. Having a lot of pharmacological activity and their synthetic utility, chemists are attracted towards chalcones to develop a lot of synthetic methodologies for their synthesis around the world.

MATERIALS AND METHODS
For the synthesis of the compounds, all used chemicals were obtained specially from Sigma Aldrich and SD Fine chemicals. By using simple open capillaries Melting points were recorded and are uncorrected. By using 400 MHz NMR Spectrophotometer, ^{1}H NMR spectra were recorded in this analysis DMSO-d_6 used as solvent and TMS as an internal standard. By using FT-IR Spectrophotometer Model RZX (Perkin Elmer) the infra-red spectra were recorded. On Macromass mass spectrophotometer (Waters) mass spectra were recorded using electro-spray method (ES). On TLC purity of the all synthesized compounds were checked. TLC silica gel coated plates were obtained from Merck in which stationary phase and mobile phase were mixture of hexane / ethyl acetate (80:20).

GENERAL PROCEDURE
Mixture of **1** (0.01 mole) and **2** (0.01 mole) was dissolved in 50 ml of ethanol, and contents were placed in ice bath at 0^{o}C. To maintaining temperature below 5^{o}C, 2g KOH pellets were added in this reaction mixture. This reacting mixture was stirred for 48 hr at room temperature. After 48 hours this reaction mixture was poured in ice cold water and acidified with 2M HCl then yellow solid was obtained and filtered for separation, also washed with cold water. Product was recrystallized in ethanol. By using this typical experimental procedure, other analogs were prepared of this series. The physical data of the compounds **3(a-h)** were recorded in **Table 1**. Their structures have been confirmed by analyzing method like ^{1}HNMR, Mass and IR spectra.

IR (3c) (cm^{-1}):832(C-Cl), 1021(C-F), 1247(C-O), 1530(C=C), 1563(C=N), 1637(C=O), 3134(O-H).

^{1}H NMR (3c) (DMSO-d_6)δ ppm: 6.8054-6.8954(s, 2H, Ar-H), 6.9874-7.0034(s, 1H, Ar-H,), 7.0657-7.0857(m, 2H, Ar-H), 7.0974-7.2145(m, 1H, CH=C-), 7.4125-7.5921(m, 2H, Ar-H) 7.6851-7.7521(m, 2H, Ar-H), 7.8745-7.9241(d, 1H, Ar-H, *J*= 19.8 Hz), 8.6984(s, 1H, pyrazole-H), 12.3974(s, 1H, Ar–OH).

ES-MS (3c) (m/z):503(M+1), 505(M+3).

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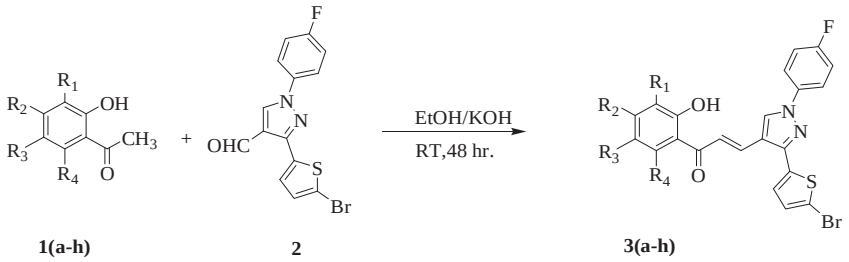
IR (3f) (cm^{-1}):832(C-Cl), 1011(C-F), 1223(C-O), 1511(C=C), 1561(C=N), 1640 (C=O), 2970(O-H).

^{1}H NMR (3f) (DMSO-d_6)δ ppm: 2.4121-2.4524(s, 3H, -CH_3), 6.8324(s, 1H, Ar-H), 7.3956-7.4001 (d, 1H, Ar-H. J=1.8 Hz), 7.4256-7.5069(m, 1H, Ar-H), 7.5498-7.5949(m, 2H, Ar-H), 7.7089-7.7224(d, 1H, CH=C-, *J*=5.4 Hz), 7.9678-7.9956(m, 2H, Ar-Hz), 7.9172-7.9367(m, 1H,Ar-H), 8.0063(s, 1H,Ar-H), 8.9964(s, 1H, pyrazole-H), 12.5987(s, 1H, Ar–OH).

ES-MS (3f) (m/z):519(M+1), 521(M+3).



➢ **Scheme 1: Synthesis of series of various (E)-3-(3-(5-bromothiophen-2-yl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-one**

Table-1: Physical data of compounds 3(a-h)

Comp.	R_1	R_2	R_3	M.P. (^{o}C)	Yield (%)
3a	**H**	**H**	**H**	148-150	78
3b	**H**	**H**	**CH_3**	168-170	77
3c	**H**	**H**	**Cl**	158-160	79
3d	**Cl**	**H**	**Cl**	208-210	70
3e	**H**	**H**	**F**	192-194	66
3f	**H**	**CH_3**	**Cl**	152-154	82
3g	**H**	**H**	**Br**	200-202	69
3h	**CH_3**	**H**	**CH_3**	154-156	76

RESULT AND DISCUSSION

Eight chalcone derivatives were synthesized successfully with good yields. All newly synthesized compounds were analyzed from melting point range, IR, ^{1}H NMR, Mass spectral analysis. All newly synthesized compounds were screened for antimicrobial activity using disc diffusion method.

Antimicrobial activity: Compounds **3(a-h)** were screened for their antimicrobial activity against Gram positive (*Salmonella typh, Enterobacter aerogenes, Escherichia coli, Pseudomonas aerogenosa, Salmonella abony, Shigella boydii)* and Gram negative pathogens(*Bacillus subtilis, Megaterium Bacillus, Staphylococcus aureus, Bacillus cereus*) by paper disc diffusion method using tetracyclin as a reference standard drug. Using Nystatin as standard drug, antifungal activity was screened against *Candida albicans, Saccharomyces cerevisiae, Aspergillus niger* at 100 µg/ml concentration. Muller Hinton agar was the culture media. The zone of inhibition was measured in mm, after the 24 hr of incubation at 37^{o}C. Microbial data for 3(a-h) are summarized in **Table 2.**

Table-2: Antimicrobial Analysis Data of 3(a-h)

	Bacterial pathogens										**Fungal pathogen**		
	Gram negative pathogen						**Gram positive pathogen**						
Compounds	***Salmonella typhi***	***Enterobacter aerogenes***	***Escherichia coli***	***Pseudomonas aerogenosa***	***Salmonella abony***	***Shigella boydii***	***Bacillus subtilis***	***Bacillus Megaterium***	***Staphylococcus aureus***	***Bacillus cereus***	***Candida albicans***	***Saccharomyces cerevisiae***	***Aspergillus niger***
3a	07	-	10	09	13	-	07	10	**07**	08	-	13	08
3b	08	06	08	-	11	05	06	-	08	11	09	-	10
3c	06	09	-	08	18	-	10	-	07	10	-	-	10

ISSN 2394 - 7780

3d	09	07	15	09	30	12	09	11	10	12	16	19	25
3e	-	13	12	10	16	-	-	07	-	07	15	-	11
3f	05	-	09	-	-	05	-	-	06	-	-	-	09
3g	-	19	-	11	-	16	07	-	-	06	-	27	10
3h	06	10	08	07	13	-	09	10	11	11	13	08	12
DMSO	-	-	-	-	-	-	-	-	-	-	-	-	-
STND.	22	20	20	33	21	26	25	20	30	25	24	20	25

*Standard for bacterial pathogens-tetracyclin, for fungal pathogens-nystatin

CONCLUSION

All eight compounds were synthesized successfully; these newly synthesized compounds were screened for their antimicrobial activity against Gram positive as well as Gram negative bacterial strains and against fungal pathogens. The synthesized compounds show moderate activity as compared to standard drugs. The obtained data through the present work shows a good agreement between the experimental and computed spectral data.

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