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Synthesis, Characterization and Antimicrobial Analysis of Various Substituted 3-(3-(3-bromothiophen-2-yl)-1-(2,4-difluorophenyl)-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one

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ABSTRACT

Synthesis and biological activities of 3-(3-(3-bromothiophen-2-yl)-1-(2,4-difluorophenyl)-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one derivatives are described. The derivatives of novel chalcone were prepared by condensation of pyrazole aldehydes and various substituted aromatic ketones, in the presence of potassium hydroxide in ethanol. By using physical characteristics like melting point and TLC, followed by spectroscopic screenings to determine the molecular structure of the synthesized compound.

KEYWORDS: Pyrazole aldehyde, Chalcone, antimicrobial, Gram+ve and Gram–ve microorganisms.

I. INTRODUCTION

Chalcones are the aromatic ketones that belong to 1, 3-diaryl-2-propen-1-ones, chalcones form the central core for the synthesis of a variety of significant biologically active compounds. The compounds which are formed from chalcone have been reported to show a broad-spectrum variety of pharmacological activity such as antibacterial[i], anti-inflammatory[ii], antimalarial[iii], antifungal[iv], antituberculosis[v], antioxidant[vi], anticancer[vii], antileishmanial[viii]. Chalcone's novelty is that they serve as good precursors for the synthesis of numerous heterocyclic compounds like flavones, pyrazolines, aurones, flavanones, flavonols, pyrimidines, benzoylcoumarones as well as certain compounds like hydantions and deoxybenzoins which are few therapeutic importance[ix]. Due to the presence of an active α,β-unsatutated keto function in chalcones which is found to be responsible for its antimicrobial activity. Claisen–Schmidt condensation between benzaldehyde and acetophenone results in the formation of chalcone[x]. This reaction is both acids and bases catalyzed reaction under heterogeneous or homogeneous conditions. A lot of researchers have been yet reported the synthesis ofchalcone by using diverse catalysts like hydrotalcites and zeolites[xi], KF–Al2O3[xii], organolithium[xiii], zinc oxide[xiv], modified phosphates[xv] to get a chalcone with fewer by-products and higher yield. Due to numerous pharmacological activities and their synthetic utility, chalcones have attracted chemists to develop a lot of synthetic methodologies for their synthesis around the world.

II. MATERIALS AND METHODS

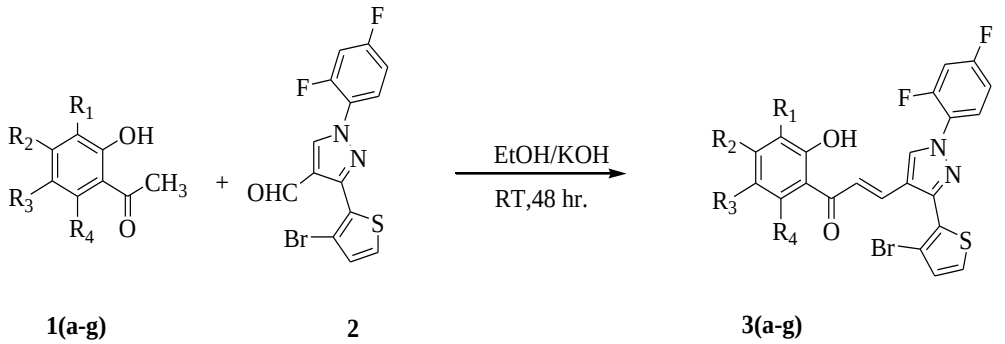
All starting materials and solvents which are used for each reaction are of the synthetic grade was obtained from S D Fine chemicals, and the obtained products checked for purity by melting point(physical constant) in open capillaries and which are uncorrected, and Thin Layer Chromatography (TLC).All the reactions were monitored by using thin layer chromatographyon pre-coated TLC plate which were obtained from Merck as stationary phase and a solvent mixture of hexane and ethyl acetate (80:20) as mobile phase. The ^{1}H NMR spectra were taken on Bruker Avance II 400 MHz NMR Spectrophotometer by using DMSO-d_6 and Tetra Methyl Silane as internal standards. The infra-red spectra were recorded by using FT-IR Spectrophotometer Model RZX (Perkin Elmer). Mass spectra of synthesized compounds were recorded on Macromass mass spectrophotometer (Waters) by using the electro-spray method (ES).

III.GENERAL PROCEDURE

A mixture of compound **1** (0.01 mole) and compound **2** (0.01 mole) was dissolved in 40 ml ethanol as solvent and contents were cooled in an ice bath up to 0^{o}C. In to this reacting mixture, 2g potassium hydroxide (KOH) pellets were added. The reacting mixture was stirred at RT (Room Temperature) for forty-eight hours. Then the reaction mixture was poured into the crushed ice and the contents were acidified by using 2M HCl which Resulted into yellow solid which was separated by filtration and washed using cold water. Using ethanol as a solvent product was crystallized. The same procedure was followed to prepare other analogs of this series. The physical data of the synthesized compounds **3(a-g)** were recorded in **Table 1**. The structures of synthesized compounds have been confirmed by ^{1}HNMR, IR and Mass spectra.

IR (3c) (cm^{-1}):1061(C-Cl), 1145(C-F), 1221(C-O),1535(C=C), 1579(C=N), 1643(C=O), 3179(O-H).
^{1}H NMR (3c) (DMSO-d_6)δ ppm: 6.9987-7.0105(d, 1H, Ar-H), 7.1344-7.1415(d, 1H,Ar-H), 7.2567-7.4571(m, 1H, Ar-H), 7.5123-7.6152(m, 2H, Ar-H), 7.6341-7.7006(d, 1H, CH=C-) 7.8570-7.8798(m, 2H, Ar-H), 7.9032-7.9061(d, 1H, Ar-H), 8.0457-8.0491(d, 1H,Ar-H),9.2468(s, 1H, pyrazole-H), 11.9687(s, 1H, Ar–OH).
ES-MS (3c) (m/z):521(M+1), 523(M+3).

IR (3f) (cm^{-1}):1064 (C-Cl),1107(C-F), 1202(C-O),1534(C=C), 1598(C=N), 1654(C=O), 3234(O-H).
^{1}H NMR (3f) (DMSO-d_6) δ ppm: 2.3159 (s, 3H, -CH3), 6.9781(s, 1H, Ar-H), 7.1984-7.2012(d, 1H, Ar-H), 7.3515-7.4541(m, 1H, Ar-H), 7.5136-7.5726(m, 1H, Ar-H), 7.7132-7.7164(d, 1H, CH=C-), 7.8024-7.8614(m, 1H, Ar-Hz), 7.9196-7.9664(m, 2H,Ar-H), 8.0127(s, 1H,Ar-H), 9.1941(s, 1H, pyrazole-H), 12.1468(s, 1H, Ar–OH).
ES-MS (3f) (m/z):535(M+1), 537(M+3).



1(a-g) **2** **3(a-g)**

- **Scheme 1: Synthesis of various 3-(3-(3-bromothiophen-2-yl)-1-(2,4-difluorophenyl)-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one**

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

Comp.	R_1	R_2	R_3	M.P. (°C)	Yield (%)
3a	H	H	H	132-134	74
3b	H	H	CH_3	176-178	79
3c	H	H	Cl	156-158	81
3d	Cl	H	Cl	202-204	69
3e	H	H	F	196-198	72
3f	H	CH_3	Cl	138-140	70
3g	H	H	Br	162-164	82

IV.RESULT AND DISCUSSION

The synthesized derivatives of chalcones were synthesized successfully in moderate to good yields. These newly synthesized derivatives were characterized by ^{1}H NMR spectral analysis, melting point range, IR, and Mass spectral analysis. All the newly synthesized compounds were screened for their antimicrobial activity using the disc diffusion method.

Antimicrobial activity: By using the paper disc diffusion method, the synthesized derivatives of chalcones **3(a-g)** were screened for their in vitro antimicrobial activity against *Pseudomonas aeruginosa (ATCC 27853),Staphylococcus aureus (ATCC 25923),Escherichia coli (ATCC 25922),* A reference standard drug is used as Gentamycin. Also, antifungal activity was screened against *Candida sp.*, Nystatin is used as a standard drug. At 100 µg/ml concentration, all the tests were evaluated. The culture media used was Muller Hinton agar. At about 37°C, the region of inhibition was measured in a milimeter after 24 hr of incubation. Microbial data for compounds 3(a-g) are summarized below in **Table 2.**

Table 2: Antimicrobial Analysis Data

Sr. No.	Comp. No.	*Escherichia coli (ATCC 25922)*	*Pseudomonas aeruginosa (ATCC 27853)*	*Staphylococcus aureus (ATCC 25923)*	*Candida sp.*
1	3a	7	4.1	3.9	4.1
2	3b	7.9	5.6	7.1	7.6
3	3c	-	3.1	-	6.4
4	3d	5.2	5.1	1.5	8.2
5	3e	6.1	-	1.8	3.3
6	3f	5.6	7.4	4.0	1.8
7	3g	7.4	8.1	3.4	7.6
8	*Gentamycin*	28 mm	23 mm	32 mm	--
9	*Nystatin*	--	--	--	23 mm

V. CONCLUSION

In conclusion, starting from the pyrazole aldehyde and o-hydroxy ketone, we have successfully synthesized chalcones and their derivatives, these newly synthesized compounds were screened for their in vitro antimicrobial activity as well as antifungal activity. Most of the compounds shows moderate antimicrobial activity as compared to standard drug and Most of the compounds shows good antifungal activities.

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