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Synthesis, Characterization and Antimicrobial Activity of Novel Chalcones from Fluorinated Formyl Pyrazole

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ABSTRACT

Various substituted 2-hydroxy acetophenones (1) on condensation with 3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde (2) yields the title compounds Chalcones (E)-3-(3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazol-4-yl)-1-(2-hydroxyphenyl)prop-2-en-1-ones (3). Spectral techniques like IR, ^{1}H NMR and Mass spectral data confirms the structures of novel synthesized compounds. Antimicrobial screening of newly prepared compounds was carried out.

Keywords: Chalcones, antimicrobial activity, 3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1H-pyrazole-4-carbaldehyde

INTRODUCTION

Pyrazole and derivatives are key substructures in a large variety of compounds with important biological activities and pharmacological properties [1-3]. Synthesis of chalcones is carried out by Claisen-Schmidt condensation of aldehyde and ketone in presence of base or acid which on subsequent dehydration yield chalcones. A variety of important biological compounds possess central core of chalcones. Three carbon α,β-unsaturated highly electrophilic carbonyl system in chalcone has assumed more importance because of its versatile nature in the preparation of many heterocyclic compounds. Chalcone have been reported to possess various biological activities like anti-inflammatory, antiulcerative, analgesic, antiviral, antifungal, antimalarial, antibacterial and anticancer activities [4-11]. Chalcone considered being a very good synthon for the preparation of various heterocycles like isoxazole, pyrimidine, pyrazole, thiazine, diazepine, oxazine, pyridine [12,13]. Hence, preparation of chalcones has attracted much interest particularly in organic chemistry.

Synthesis of chalcones can be carried out by several methods as reported in literature. The most widely adopted method is Claisen-Schmidt base catalyzed reaction of an aldehyde and a methyl ketone using Potassium Hydroxide (KOH) [14], Lithium Hydroxide ($LiOH{\cdot}H_2O$) [15] and Sodium Hydroxide (NaOH) [16] and Barium Hydroxide ($Ba(OH)_2$) [17]. In the present communication we report the reaction of 3-(2,4-difluorophenyl)-1-(4-fluorophenyl)-*1H*-pyrazole-4-carbaldehyde with differently substituted 2-hydroxy acetophenones to afford novel chalcones [18-24].

MATERIALS AND METHODS

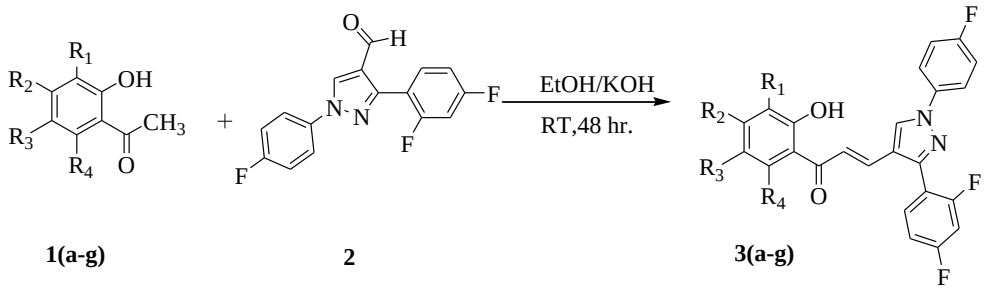
All the chemicals were obtained from Sigma Aldrich and SD Fine chemicals. Melting points were determined in open capillaries and are uncorrected. Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded on Bruker Avance II 400 MHz NMR Spectrophotometer in Deuterated Dimethyl Sulfoxide (DMSO-d_6) using Tetramethylsilane (TMS) as an internal standard. The Infra-Red (IR) spectra were recorded as potassium bromide disk using Fourier Transform Infrared (FTIR) Spectrophotometer Model RZX (Perkin Elmer). Mass spectra were recorded on Macromass spectrophotometer (Waters) by Electro-Spray method (ES). The purity of the compounds was checked by Thin Layer Chromatography (TLC) silica gel coated plates obtained from Merck as stationary phase and solvent mixture ethyl acetate/hexane (20:80) as mobile phase.

Procedure for the synthesis of (*E*)-1-(5-chloro-2-hydroxy-4-methylphenyl)-3-(3-(2, 4-difluorophenyl)-1-(4-fluorophenyl)-1*H*-pyrazol-4-yl) prop-2-en-1-one (3f)

A mixture of 1 (0.01 mol) and 2 (0.01 mol) was dissolved in 40 ml ethanol and contents were cooled to 0°C in ice bath. To this reaction mixture, 2 g KOH pellets were added maintaining temperature below 5°C. The stirring of reaction mixture was continued for 48 h at room temperature. Then reaction mixture was poured on to crushed ice and contents were acidified with 2 M HCl. Resulting yellow solid obtained was separated by filtration and washed with cold water several times. Product was recrystallized from ethanol. This typical experimental procedure was followed to prepare other analogs of this series. The melting point and percentage yield of the compounds 3(a-g) were recorded in Table 1 (Scheme 1).

IR (3c) (cm^{-1}): 1067(C-Cl), 1230 (C-O), 1537 (C=C), 1585 (C=N), 1649 (C=O), 3139 (O-H). ^{1}H-NMR (3c) (DMSO-d_6) δ ppm: 6.9824-7.0045 (d, 1H, Ar-H, *J*=8.84 Hz), 7.1954-7.2624 (dd, 1H, Ar-H), 7.2938 7.3798 (m, 3H, Ar-H), 7.5034-7.5249 (d, 1H, Ar-H, *J*=8.6 Hz), 7.6216-7.6495 (d, 1H, CH=C-, *J*=11.16Hz), 7.6671-7.6874 (d, 1H, Ar- H, *J*=8.12 Hz), 7.8158-7.8538 (d, 1H, CH=C-, *J*=15.2 Hz), 7.9515-8.0784 (m, 3H, Ar-H), 9.4032 (s, 1H, pyrazole-H), 12.5869 (s, 1H, Ar–OH). ES-MS (3c) (m/z): 455.38 (M+1), 457.40 (M+3).

IR (3f) (cm^{-1}): 1059 (C-Cl), 1228 (C-O), 1536 (C=C), 1587 (C=N), 1651(C=O), 3143(O-H). ^{1}H-NMR (3f) (DMSO-d_6) δ ppm: 2.3618 (s, 3H, -CH_3), 7.0169 (s, 1H, Ar-H), 7.2683-7.3160 (m, 1H, Ar-H), 7.3784-7.4838 (m, 3H, Ar-H), 7.5039-7.5749 (m, 1H, Ar-H), 7.6628-7.7218 (dd, 1H, Ar-H, *J*=6.64 Hz & J=8.48 Hz), 7.8205-7.8589 (d, 1H, CH=C-, *J*=15.36 Hz), 7.9454-7.9570 (d, 1H, Ar-H, *J*=4.64 Hz), 7.9680-7.9797 (d, 1H, Ar-H, *J*=4.68 Hz), 8.0834 (s, 1H, Ar-H), 9.4339 (s, 1H, pyrazole-H), 12.5092 (s, 1H, Ar–OH). ES-MS (3f) (m/z): 469.25 (M+1), 471.25 (M+3).



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

Scheme 1: Melting point and percentage yield

Table 1: Melting point and percentage yield of the compounds 3(a-g)

Compound	R_1	R_2	R_3	R_4	Melting point (°C)	Yield (%)
3a	H	H	H	H	160-162	65
3b	H	H	CH_3	H	224-226	67
3c	H	H	Cl	H	170-172	72
3d	Cl	H	Cl	H	234-236	80
3e	H	H	Br	H	212-214	78
3f	H	CH_3	Cl	H	230-232	74
3g	H	H	F	H	208-210	69

RESULTS AND DISCUSSION

The chalcones were synthesized successfully in good yields. The novel compounds were identified by physical techniques on the basis IR, ^{1}H-NMR, Mass spectral data. All compounds were screened for antimicrobial activity using disc diffusion method.

Antimicrobial activity

Compounds 3(a-g) and 2 were screened for their *in vitro* antimicrobial activity against *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923) using gentamycin as a reference standard drug by paper disc diffusion method. Antifungal activity was evaluated against *Candida sp.* using nystatin as standard drug. All the tests were evaluated at 100 µg/ml dose levels. The culture media was Muller Hinton agar. The zone of inhibition was measured in mm after 24 h of incubation at 37^{o}C. Microbial data for corresponding compounds is summarized in Table 2.

Table 2: Antimicrobial analysis data

S. No.	Compound number	*Escherichia coli* (ATCC 25922)	*Pseudomonas aeruginosa* (ATCC 27853)	*Staphylococcus aureus* (ATCC 25923)	*Candida sp.*
1	2	No zone	No zone	08 mm	No zone
2	3a	No zone	No zone	No zone	No zone
3	3b	No zone	No zone	No zone	No zone
4	3c	No zone	No zone	No zone	No zone
5	3d	No zone	No zone	No zone	No zone
6	3e	No zone	No zone	No zone	No zone
7	3f	No zone	No zone	No zone	No zone
8	3g	No zone	No zone	No zone	No zone
9	Gentamycin	28 mm	23 mm	32 mm	-
10	Nystatin	-	-	-	23 mm

CONCLUSION

The synthesized compounds were tested against *Candida sp.* and Gram-positive as well as Gram-negative bacterial strains. Among them, the compound 2 exhibited good activity only against *S. aureus* (ATCC 25923) bacteria. The other chalcone compounds 3(a-g) containing fluorine have shown no activity compared to standard drug.

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