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Synthesis and Biological Evaluation of Some Heterocycles from 1-Phenyl-3-(pyridine-3-yl)-1*H*-pyrazole-4-carbaldehyde

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Various substituted 2-hydroxy acetophenones (**1**) on condensation with 1-phenyl-3-(pyridin-3-yl)-1*H*-pyrazole-4-carbaldehyde (**2**) yields 1-(2-hydroxyphenyl)-3-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl) prop-2-en-ones (**3**), which on treatment with DMSO/I_2 give chromones (**4**) and treatment with hydrazine hydrates to give pyrazoline derivatives (**6**). Compound (**4**) react with hydrazine in ethanol to afford the pyrazole derivatives (**5**). The compounds were evaluated for their antimicrobial activities against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida* sp. The antibacterial screening suggests that the analogs with electron releasing substituents emerged as promising antibacterial agents. The compounds synthesized were characterized by melting point, EI-MS, NMR and FT-IR.

Key Words: Synthesis, Biological evaluation, Heterocycles, 1-Phenyl-3-(pyridine-3-yl)-1*H*-pyrazole-4-carbaldehyde

INTRODUCTION

Chalcones are natural or synthetic compounds belonging to the flavonoid family. Literature survey reveals that chalcones have attracted considerable attention as they are endowed with wide spectrum of activities like antiviral[1], insecticidal[2] and antimicrobial[3].

Pyrazolines are well known and important nitrogen-containing 6 and 5 membered heterocyclic compounds. Several pyrazoline derivatives have been found to possess considerable biological activities including antiviral[4], antiinflamatory[5], antimicrobial[6] and antiHIV[7].

Chromones have broad spectrum of application in the field of synthetic chemistry[8], pharmacological[9] and physiological processes[10]. 2-Phenyl chromone and 5-styryl-chromones are a group of flavonoid type compounds widely occurring in plants, where they play several biological functions[11]. Last decade 5-hydroxy-2-styryl-chromones were obtained from the blue green algae[12] chrysophaeum taylari. These compounds show potent *in vitro* cytotoxic activity against leukemia cells[12].

Pyrazole an important class of compounds in medicinal chemistry, constitute the basic framework of drugs such as celecoxib and are well recognized for their

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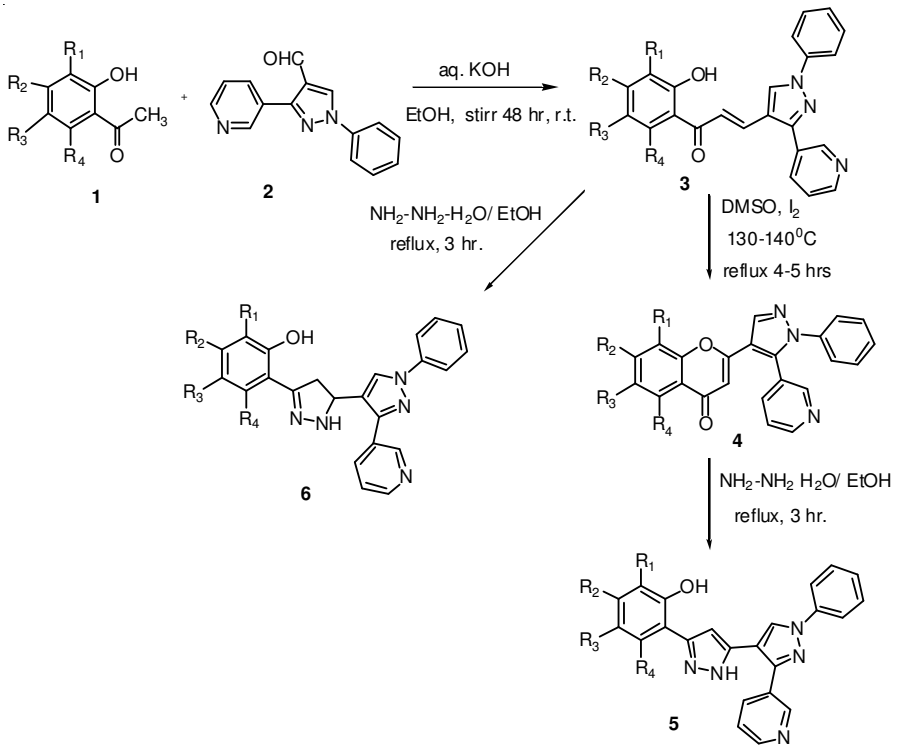
multifaceted pharmacological[13] and medicinal applications[14]. Pyrazole derivatives have been associated with various biological activities such as antiinflammatory[15], fungicidal[16] and antibacterial activity[17].

Keeping in view of these observations and in continuation of our work on chalcone[18], pyrazole[19], chromone[20] and pyrazoline[21] derivatives herein we report synthesis of these heterocycles (**Scheme-I**) containing pyridine moiety.



Scheme-I

EXPERIMENTAL

Melting points were recorded in open capillaries and are uncorrected. The completion of reactions was monitored by TLC. IR spectra were recorded in KBr disc on Jasco spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument in DMSO-d_6, $CDCl_3$ and TMS as an internal standard.

(E)-1-(5-chloro-2-hydroxyphenyl)-3-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl)prop-2-en-1-ones (3a-h): 1-Phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-carbaldehyde (0.005 mol) **2** and 2-hydroxy acetophenone **1** (0.005) were taken in 100 mL round bottom flask with 20 mL ethanol. To this reaction 2 g of KOH was added and resulting reaction was stirred at room temperature for 48 h. The contents were poured over crushed ice and acidified with conc. HCl, solid thus obtained

were separated by filtration and crystallized from ethanol. IR: (KBr, ν_{max}, cm^{-1}) **3c**: 3141 (-OH), 1681 (-C=O), 1490 (C=N). ^{1}H NMR: δ **3g**: 6.9 (d, 1H ethylene proton), 7.26-8.78 (m, 13H, Ar-H), 8.77 (s, 1H, pyrazole proton), 12.70 (s, 1H, -OH). Mass (M + 1): **3c**: 382.

2-(1-Phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl)-4*H*-chromen-4-ones (4a-h): (E)-1-(2-Hydroxyphenyl-3-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl) prop-2-en-1-ones (0.005 mol) **3** were taken in 100 mL round bottom flask with 5 mL DMSO and catalytic amount of I_2 was added. Resulting reaction mixture was refluxed for 3 h. The contents were poured over crushed ice containing 2-3 g of sodium thiosulphate, solid thus obtained were separated by filtration and crystallized from ethanol. IR (KBr, ν_{max}, cm^{-1}): **4a**: 1652 (C=O), 1595 (C=C), 1466 (C=N). ^{1}H NMR: δ **4a**: 6.49 (s, 1H, chromone), 8.85 (s, 1H, pyrazole), 7.16-8.65 (m, 13H, aromatic). Mass (m/z): **4a**: 366.

2-(5-(1-Phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazol-3-yl)phenol (**5a-h**): Compounds **4** (0.003 mol) were taken in 100 L round bottom flask with 15 mL ethanol. To this reaction mixture 1 mL hydrazine hydrate was added and the contents were heated under refluxed for 1 h. Then to the reaction mixture 1 mL glacial acetic acid was added and heating was continued for further 2 h. After completion of reaction contents were cooled to room temperature and poured over crushed ice. The solid thus obtained was separated by filtration and crystallized with ethanol. IR (KBr, ν_{max}, cm^{-1}): **5a**: 3200 (-OH), 3057 (-NH), 1464 (-C=N). ^{1}H NMR: δ **5a**: 13.12 (s, 1H, -OH), 10.95 (s, 1H, -NH), 8.9 (s, 1H, pyrazole), 6.52-8.86 (m, 15H, aromatic). Mass (m/z): **5c**: 394.

2-(4,5-Dihydro-5-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazol-3-yl)-4-methylphenol (6a-h): Compounds **3** (0.003 mol) were taken in 100 mL round bottom flask with 15 mL ethanol. To this reaction mixture 1 mL hydrazine hydrate was added and the contents were refluxed for 1 h. Then 1 mL glacial acetic acid was added and heating was continued for further 2 h. After completion of reaction contents were cooled to room temperature and poured over crushed ice. The solid thus obtained was separated by filtration and crystallized with ethanol. IR: (KBr, ν_{max}, cm^{-1}): **6a**: 3150 (-OH), 3062 (-NH), 1500 (C=N). ^{1}H NMR: δ **6c**: 2.3 (s, 1H, $-CH_3$), 3.20 (d, 1H, one of the methine proton), 3.49 (d, one of the 1H methylene proton), 5.60 (d, one of the 1H methylene proton), 8.64 (s 1H, N-H) 6.91-8.11 (m, 14 Ar-H), 9.10 (s 1H, -OH). Mass (m/z): **6a**: 382.

Antibacterial activity: Compounds **3**, **4**, **5** and **6** were evaluated for their antibacterial activity *in vitro* against *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923) and *Candida* sp. using disc diffusion method and muller hinton agar as culture medium. Compounds were found to be active, on comparing with control. Test solution was prepared by dissolving 1 mg in 1 mL of DMSO and 0.1 mL of this solution was used for testing. The zone of inhibition was measured in mm. **4b** was found to be active against gram positive bacteria.

RESULTS AND DISCUSSION

In the present investigation a series of novel 2-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl)-4*H*-chromen-4-one (**4**) derivatives were synthesized by oxidative cyclization of (E)-1-(2-hydroxyphenyl-3-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl) prop-2-en-1-ones (**3**) in DMSO/I_2 and 2-(5-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazol-3-yl)phenols (**5**) derivatives were synthesized by reaction of 2-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl)-4*H*-chromen-4-ones (**4**) with hydrazine hydrate in ethanol and 2-(4,5-dihydro-5-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl)-1*H*-pyrazol-3-yl)-4-methylphenol (**6**) derivatives were synthesized by reaction of (E)-1-(2-hydroxyphenyl-3-(1-phenyl-3-(pyridine-3-yl)-1*H*-pyrazol-4-yl) prop-2-en-1-ones (**3**) with hydrazine hydrate in ethanol. The physical characteristics of the synthesized compounds are given in Table-1. The compounds were evaluated

TABLE-1
CHARACTERIZATION DATA OF SYNTHESIZED COMPOUNDS **3**, **4**, **5** AND **6** (**a-h**)

Compound	R_1	R_2	R_3	R_4	m.p. (ºC)	Yield (%)
3a	H	H	H	H	186	80
3b	H	CH_3	Cl	H	102	74
3c	H	H	CH_3	H	213	67
3d	H	H	Br	H	178	62
3e	CH_3	H	CH_3	H	133	64
3f	Cl	H	Cl	H	> 300	68
3g	H	H	Cl	H	172	67
3h	H	H	OCH_3	H	238	65
4a	H	H	H	H	238	64
4b	H	CH_3	Cl	H	211	65
4c	H	H	CH_3	H	216	63
4d	H	H	Br	H	272	72
4e	CH_3	H	CH_3	H	133	45
4f	Cl	H	Cl	H	223	70
4g	H	H	Cl	H	108	50
4h	H	H	OCH_3	H	206	50
5a	H	H	H	H	221	78
5b	H	CH_3	Cl	H	202	67
5c	H	H	CH_3	H	93	64
5d	H	H	Br	H	> 300	52
5e	CH_3	H	CH_3	H	168	58
5f	Cl	H	Cl	H	197	66
5g	H	H	Cl	H	122	68
5h	H	H	OCH_3	H	278	50
6a	H	H	H	H	121	86
6b	H	CH_3	Cl	H	140	70
6c	H	H	CH_3	H	93	72
6d	H	H	Br	H	150	68
6e	CH_3	H	CH_3	H	140	69
6f	Cl	H	Cl	H	138	70
6g	H	H	Cl	H	122	74
6h	H	H	OCH_3	H	> 300	64

for their antimicrobial activities against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida* sp. The antibacterial screening suggests that the analogs with electron releasing substituents emerged as promising antibacterial agents (Table-2).

TABLE-2
SCREENING OF ANTIBACTERIAL ACTIVITIES
OF SOME REPRESENTIVE COMPOUNDS

Compounds	*E. coli* ATCC 25922	*Pseudomones arruginosa* ATCC27853	*Staphylococcus aureus* ATCC 25923	*Candida* sp.
3a	–	–	–	–
3c	–	–	–	–
3b	–	–	–	–
3f	–	–	–	–
4a	–	–	–	–
4c	–	–	–	–
4b	–	–	13 mm	–
4g	–	–	–	–
5a	–	–	–	–
5c	–	–	–	–
5b	–	–	–	–
5f	–	–	–	–
6a	–	–	–	–
6c	–	–	–	–
6b	–	–	–	–
6f	–	–	–	–
Gentamycin	23 mm	24 mm	23 mm	–
Cefixime	28 mm	–	15 mm	–
Ketoconazole	–	–	–	23 mm

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