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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL PYRAZOLINE AND FLAVONE DERIVATIVES DERIVED FROM FURAN CHALCONES

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ABSTRACT

A new series of 1-(3-(2-hydroxyphenyl substituted)-5-(furan-2-yl 4,5dihydropyrazol-1-yl) ethanone(**4a-g**) and 2-(furan-2-yl)-4H-chromen-4 -one derivatives(**5a-g**) were synthesized by reacting 3-(Furan-2yl)-1-(2- hydroxyl phenyl substituted) prop-2-en-1one (**3a-g**)with hydrazine hydrate in acetic acid and DMSO in catalytic quantity of iodine respectively. These compounds were characterized by means of their IR, ^{1}H NMR spectroscopic data. The synthesized products were evaluated for their antimicrobial activity .All the compounds exhibited significant antibacterial and antifungal activity.

KEYWORDS: Chalcones, pyrazolines, flavones, furan, antibacterial, antifungal activity.

INTRODUCTION

Heterocyclic compounds bearing nitrogen or oxygen as hetero atom in ring system like pyrazoline, flavones are gaining importance due to their wide range of pharmacological activites.

Pyrazolines are important nitrogen containing heterocycles possessing diverse biological activities such as antibacterial,[1] antifungal,[2] anti-inflammatory,[3] anticonvulsant[4] antitumor,[5] antidiabetic,[6] antiviral,[7] antiarthritic,[8] cerebroprotective effect,[9] cytotoxic[10] and antidepressant[11] activities. Few substituted pyrazolines also have bleaching property and also acts as luminescent and fluorescent agents.[12] They are also useful as biodegradable agrochemicals.[13] Pyrazolines also exhibits important role in immune system Synthesis of

novel flavones derivatives remains a main focus of chemist, due to their established pharmacological effects such as anti-oxidant,[14-17] Anxiolytic,[18] anticancer,[19] analgesic,[20-21] and antimicrobial,[22] anti-inflammatory activity.[23-24]

Taking in to consideration such broad spectrum of utilities of pyrazolines and flavones derivatives it was contemplated to synthesize a novel series of pyrazoline **4a-g** and flavone derivatives **5a-g** derived from3-(furan-2-yl)-1-(2-hydroxy phenyl substituted) prop-2en-1-one. These derivatives contain furan moiety, literature survey revealed that bioheterocycle derived from furan enhanced biological activity [25] at the same time aryl furan derivatives are useful in the treatment of diseases, by raising the level of cyclic adenosine 3', 5'-monophosphate (cAMP) through the inhibition of phosphodiesterase IV (PDE IV). Some furan derivatives are useful as chemotherapeutic agents. The semicarbazone of 5-nitrofuran-2-carbaldehyde is a bactericide; Ranitidine is an important chemotherapeutic agent for peptic ulcer. Hence it was thought worthwhile to synthesize the title compound with the hope that furan substituent in these nucleus may enhance biological activity. The results of these studies are presented in paper.

MATERIAL AND METHODS

Experimental

Melting points were determined in open capillaries and are uncorrected.IR spectra were recorded using Perkin –Elmer spectrometer.^{1}H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO by using TMS as internal standard. Thin layer chromatography was performed with E. Merk precoated TLC plates, silica gel 60F_{254} with thickness of 0.25mm and spots were visualised by irradiation with ultraviolet light (254 nm).

General procedure for the synthesis of 3-(Furan-2yl)-1-(2- hydroxyl phenyl substituted) prop-2-en-1one 3a-g

A mixture of substituted *o*-hydroxy acetophenone (0.01mol) and 2-furaldehyde (0.01mol) was dissolved in ethanol (20 ml) and then a solution of potassium hydroxide 10ml (15%) was added to it. The mixture was stirred and kept overnight. It was then poured on ice cold water and acidified with HCl. The Chalcone derivatives precipitates as solid, filtered, washed with water and crystallised from ethanol.

General procedure for the synthesis of1-(3-(2-hydroxyphenyl substituted)-5-(furan-2-yl 4, 5-dihydropyrazol-1-yl)ethanone 4a-g

A solution of Chalcone (0.01mol) and hydrazine hydrate (0.02mol) in 20 ml glacial acetic acid was refluxed for 8 hrs. The resulting solution was kept overnight, then poured on ice cold water, washed with water and crystallised from ethanol. Physical data of compounds are given in table 1.

General procedure for the synthesis of 2-(furan-2-yl)-4H-chromen-4–one derivatives 5a-g

A solution of Chalcone (0.01mol) was dissolved in 20 ml DMSO, to this catalytic quantity of iodine was added. Contents were refluxed for 1 hr. and then the reaction mixture was left overnight. It was then poured on ice cold water the separated solid was filtered washed with cold water followed by dilute sodium thiosulphate solution. The product was also washed with 1% NaOH. The product was crystallised from ethanol. Their characterization data are given in table 1.

Scheme 1

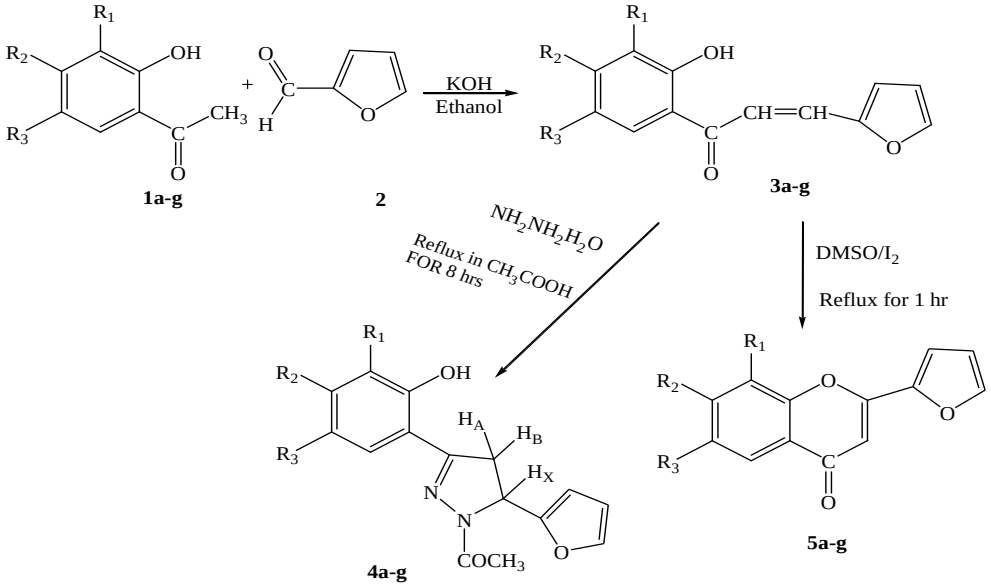

Table1-Physical constants and yields of 4a-g, 5a-g

Compd.	R1	R2	R3	M.P °C	Yield %
4a	H	H	Cl	186	90
4b	H	H	Br	196	80
4c	H	H	F	136	85
4d	Cl	H	Cl	202	92

4e	H	CH_3	Cl	190	90
4f	H	H	H	140	80
4g	Br	CH_3	Cl	174	92
5a	H	H	Cl	140	75
5b	H	H	Br	216	70
5c	H	H	F	184	65
5d	Cl	H	Cl	190	60
5e	H	CH_3	Cl	178	70
5f	H	H	H	110	62
5g	Br	CH_3	Cl	138	68

RESULT AND DISCUSSION

The synthetic route to the title compounds is outlined in scheme 1. The intermediate, chalcones **3a-g** were prepared as starting compound, by the action of substituted *o*-hydroxyl acetophenone**1a-g** with 2-furaldehyde **2** in the presence of ethanol with15% aqueous potassium hydroxide by Claisen-Schmidt condensation .The synthesized chalcones further refluxed with hydrazine hydrate in glacial acetic acid to give pyrazoline derivatives **4a-g** by Fischer and knovengeal method. Similarly these chalcones **3a-g** were oxidatively cyclised in the presence of dimethyl sulphoxide & iodine to furnish the flavone derivatives **5a-g** in good yields. All the compounds were characterized by using IR, and ^{1}H NMR data. The purity of these compounds was ascertained by TLC and spectral analysis.

The structure of synthesized compounds **4a-g** was confirmed on the basis of spectral data. The IR spectrum of **4a-g** exhibited a band at 1620-1617cm^{-1} due to C=N stretching of Pyrazoline ring and a band at 1665-1650cm^{-1} due to carbonyl group of -NCO-CH_3 , -OH stretching is observed in the range 3150-3140cm^{-1}. Further in their ^{1}H NMR (DMSO) spectrum the CH_2 protons of the Pyrazoline ring resonate as a pair of doublet of doublet near 3.51 ppm (H_A) and at 3.70 ppm (H_B).The CH (H_X) protons appeared as a doublet of doublet near 5.65 ppm due to vicinal coupling with the two magnetically non equivalent protons of methylene at position 4 of Pyrazoline ring. The methyl protons of –NCO-CH_3 appears at 3.35 δ as singlet. The protons belongining from aromatic ring and furan ring appears in 6 to 8δ with the expected chemical shift and integral value.

Similarly the structures of compounds **5a-g** were confirmed on the basis of IR and ^{1}H NMR .The IR absorption at 1595cm^{-1} showed the presence of >C=O(pyrone ring) and the absence of OH group confirmed the oxidation of Chalcone in to flavones. Further in their ^{1}H NMR spectrum the appearance of signal at 6.69-6.67 δ(s, 1H, pyrone ring), Supported the flavones derivatives showed in spectral data section.

Spectral data of compounds

1-(3-(5-chloro-2-hydroxyphenyl)-5-(furan-2-yl-4,5-dihydropyrazol-1-yl)ethanone (4a)

Elemental analysis Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; Cl, 11.63; N, 9.19; Found: C, 59.09; H, 4.28; Cl, 11.60; N, 9.15 %; IR(KBr pellets cm^{-1}) 3150(OH), 3110(N-Nstr), 1660(.C=O), 1620(C=N) 1215(C-O-N) ^{1}H NMR (DMSO, 400MHz)δ 3.30(s, 3H, CH_3), 3.55-3..56 (dd, 1H, CH_A), 3.72-3.79(dd, 1H, CH_B), 5.62-5.66(dd, 1H, CH_X), 6.35-6.39(dd, 2H, furanring), 6.95-6.97(d, 1H, Ar-H) 7.40-7.43(m, 2H, Ar-H), 10.22 (s, 1H, OH).

1-(3-(5-bromo-2-hydroxyphenyl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl) ethanone (4b)

Elemental analysis Calcd for $C_{15}H_{13}BrN_2O_3$: C, 51.60; H, 3.75; Br, 22.88; N, 8.02; Found: C, 51.55; H, 3.70; Br, 22.78; N, 7.98 %; IR (KBr pellets cm^{-1}) 3139 (OH), 3116(N-Nstr), 1658(C=O), 1617(C=N), 1225(C-O-N) ^{1}H NMR(DMSO, 400MHz) δ 3.35(s, 3H, CH_3), 3.51-3..52(dd, 1H, CH_A), 3.75-3.82(dd, 1H, CH_B), 5.60-5.64(dd, 1H, CH_X), 6.30-6.35(dd, 2H, furanring), 6.90-6.92(d, 1H, Ar-H) 7.37-7.40(m, 2H, Ar-H), 10.18(s, 1H, OH).

1-(3-(5-fluoro-2-hydroxyphenyl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)ethanone (4c)

Elemental analysis Calcd for $C_{15}H_{13}FN_2O_3$: C, 62.50; H, 4.55; F, 6.59; N, 9.72; Found: C, 62.49; H, 4.51; F, 6.55; N, 9.70 %; IR (KBr pellets cm^{-1}) 3160(OH) , 3105(N-Nstr), 1665(C=O), 1625 (C=N), 1230(C-O-N) ^{1}H NMR(DMSO, 400MHz)δ 3.35(s, 3H, CH_3), 3.51-3..54(dd, 1H, CH_A), 3.70-3.75 (dd, 1H, CH_B), 5.65-5.69 (dd, 1H, CH_X), 6.37-6.42 (dd, 2H, furanring), 6.95 6.97(d, 1H, Ar-H), 7.40 -7.43 (m, 2H, Ar-H), 10.25(s, 1H, OH).

1-(3-(5-chloro-6-methyl-2-hydroxyphenyl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)ethanone (4e)

Elemental analysis Calcd for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; Cl, 11.12; N, 8.79; Found: C, 60.26; H, 4.70; Cl, 11.09; N, 8.75 %; IR (KBr pellets cm^{-1}) 3160(OH), 3106(N-Nstr), 1650(C=O), 1620(C=N), 1220(C-O-N) ^{1}H NMR (DMSO, 400MHz)δ 3.05 (s, 3H, CH_3), 3.35(s, 3H, CH_3), 3.51-3..52(dd, 1H, CH_A), 3.70-3.77(dd, 1H, CH_B), 5.65-5.69(dd, 1H, CH_X), 6.30-6.35(dd, 2H, furanring), 6.90-6.92(d, 1H, Ar-H), 7.37-7.40(S, 1 H, Ar-H), 10.30 (s, 1H, OH).

6-chloro-2-(furan-2-yl)-4H-chromen-4 -one (5a)

Elemental analysis Calcd for $C_{13}H_7ClO_3$: C, 63.30; H, 2.86; Cl, 14.37; Found: C, 63.28; H, 2.80; Cl, 14.35 %; IR (KBr pellets cm^{-1}) 3110(Ar-H asym), 3065(Ar-H), 1658(C=C), 1595(C=O), 1230(C-O-C) ^{1}H NMR (DMSO, 400MHz) δ 6.60 (s, 1H, pyrone ring), 6.70-

6.72(d, 1H, furan ring) 7.30-7.32(d, 1H, J=8$H_{Z,}$ Ar-H), 7.62-7.64(d, 1H, J-=8$H_{Z,}$ Ar-H), 7.90 - 7.92(dd, 1H, furan ring), 8.14-8.15(d, 1H, furan ring), 8.25 (s, 1H, Ar-H).

6-bromo -2-(furan-2-yl)-4H-chromen-4 –one (5b)

Elemental analysis Calcd for $C_{13}H_7BrO_3$: C, 53.64; H, 2.42; Br, 27.45; Found: C, 53.60; H, 2.38; Br, 27.41 %; IR (KBr pellets cm^{-1}) 3110(Ar-H asym), 3065(Ar-H), 1658(C=C), 1595(.C=O), 1230(C-O-C); ^{1}H NMR(DMSO, 400MHz)δ 6.70(s, 1H, pyrone ring), 6.77-6.79(d, 1H, furan ring), 7.35-7.36 (d, 1H, J=8$H_{Z,}$ Ar-H), 7.64-7.66(d, 1H, J-=8H_Z), 7.92-7.94(dd, 1H, furan ring), 8.18-8.19 (d, 1H, furan ring), 8.25(s, 1H, Ar-H).

6-fluro-2-(furan-2-yl)-4H-chromen-4 -one (5c)

Elemental analysis Calcd for $C_{13}H_7FO_3$: C, 67.83; H, 3.07; F, 8.25; Found: C, 67.80; H, 3.00; F, 8.21 %; IR (KBr pellets cm^{-1}) 3110(Ar-H asym), 3065(Ar-H), 1658(C=C), 1595(C=O), 1230 (C-O-C); ^{1}H NMR(DMSO, 400MHz)δ 6.67(s, 1H, pyrone ring), 6.70-6.72(d, 1H, furan ring) 7.30-7.32 (d, 1H, J=8$H_{Z,}$ Ar-H), 7.62-7.64(d, 1H, J-=8H_Z), 7.90-7.93(dd, 1H, furan ring), 8.10-8.12 (d, 1H, furan ring), 8.24 (s, 1H, Ar-H)

6, 8- dichloro-2-(furan-2-yl)-4H-chromen-4 -one (5d)

Elemental analysis Calcd for $C_{13}H_6Cl_2O_3$: C, 55.55; H, 2.15; Cl, 25.23; Found: C, 55.51; H, 2.10; Cl, 25.20 %; IR (KBr pellets cm^{-1}) 3110(Ar-H asym), 3065(Ar-H), 1658(C=C), 1595(C=O), 1230 (C-O-C) ^{1}H NMR(DMSO, 400MHz)δ 6.67(s, 1H, pyrone ring), 6.75-6.77(d, 1H, furan ring), 7.62-7.64(d, 1H, Ar-H), 7.89-7.92(dd, 1H, furanring), 8.12-8.13(d, 1H, furan ring),8.18(s, 1H, Ar-H)

Table 2-Antibacterial screening results of the compounds 4a-g, 5a-g

Compd.	*E.coli*	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus subtilis*
4a	12	10	18	15
4b	14	15	15	17
4c	13	14	17	14
4d	12	13	20	16
4e	11	17	14	18
4f	12	12	15	16
4g	13	16	16	14
5a	10	12	12	10
5b	11	14	18	10
5c	10	12	20	12
5d	09	11	21	13
Penicillium	18	25	40	27
DMSO	-ve	-ve	-ve	-ve
-ve no antibacterial activity				

Table 3 Antifungal screening results of the compounds4a-g, 5a-g

Compd	*Aspergillus niger*	*Aspergillus flavus*	*Penicillum chrysogenum*	*Fusarium moneliforme*
4a	-ve	-ve	-ve	+ve
4b	-ve	-ve	-ve	RG
4C	-ve	-ve	-ve	+ve
4d	-ve	-ve	-ve	RG
4e	-ve	-ve	-ve	+ve
4f	RG	-ve	-ve	-ve
4g	-ve	-ve	+ve	-ve
5a	-ve	+ve	-ve	-ve
5b	-ve	-ve	+ve	-ve
5c	-ve	-ve	+ve	+ve
5d	-ve	-ve	-ve	RG
Griseofulvin	-ve	-ve	-ve	-ve
DMSO	+ve	+ve	+ve	+ve

-ve No growth Antifungal activity present

+ve Growth Antifungal activity absent

RG Reduced growth

Antimicrobial activity

The compounds **4a-g** and **5a-g** were screened for their antibacterial activity against *E.coli, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis* by agar cup method (26) using penicillin as standard and antifungal activity against *Aspergillus niger, Aspergillus flavus penicillium chrysogenum, Fusarium moneliforme,* by poison plate method[26] using Griseofulvin as reference standard and DMSO as control solvent. The investigation of antibacterial screening results indicate that compound **4a-g** showed promising activity against *E.coli, Salmonella typhi, Staphylococcus aureus* and *Bascillus subtilis,*whereas **5a-d** showed moderate activity compared with standard drug Penicillum.

The investigation of antifungal activity data revealed that compounds **4a-e** and **5d** have promising activity against *Aspergillus niger, Aspergillus flavus penicillium chrysogenum,* **4g** showed activity against *Aspergillus niger, Aspergillus flavus, Fusarium moneliforme*

compounds **5b** and **5c** showed activity against *Aspergillus niger*, *Aspergillus flavus* and *Fusarium moneliforme* and no activity for *penicillium chrysogenum.* Compounds **4a, 4c**, **4e, 5c** showed no antifungal activity against *Fusarium moneliforme.*

CONCLUSION

In this study we synthesised some novel 1-(3-(2-hydroxyphenyl substituted)-5-(furan-2-yl-4, 5-dihydropyrazol-1-yl)ethanone and of 2-(furan-2-yl)-4H-chromen-4 -one derivatives and characterized by spectral analysis. All the compounds were screened for antibacterial and antifungal activity, and found to have promising antibacterial and antifungal activity.

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