SYNTHESIS, CHARACTERIZATION OF SOME 1-(2-HYDROXY-PHENYL)-3-(1-PHENYL-3-THIOPHEN-2-YL-1H-PYRAZOL-4-YL)-PROPENONE, 3-CHLORO-2-(1-PHENYL-3-THIOPHEN-2-YL-1H-PYRAZOL-4-YL)-CHROMON-4-ONE AND 2-(1'-PHENYL-3'-THIOPHEN-2-YL-3,4-DIHYDRO-2H,1H'-[3,4]BIPYRAZOL-5-YL)-PHENOL

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Abstract: Base catalyzed condensation of **1** with **2** gives compound **3** [1-(2-hydroxy-phenyl)-3-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-propenone]. **3** on oxidative cyclization with DMSO-$CuCl_2$ gives 3-chloro-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-chromon-4-one **4**. **3** on condensation with hydrazine hydrate gives 2-(1'-phenyl-3'-thiophen-2-yl-3,4-dihydro-2H,1H'-[3,4]bipyrazol-5-yl)-phenol **5**. The products **3**, **4** and **5** were characterized by IR, ^{1}H NMR and mass spectroscopy.

Introduction

Chalcones, or 1, 3-diaryl-2-propen-1-ones, are natural or synthetic compounds belonging to the flavonoid family. Chalcones possess a broad spectrum of biological activities, including antibacterial, anthelmintic, amoebicidal, antiulcer, antiviral, insecticidal, antiprotozoal, anticancer, cytotoxic, and immunosuppressive activities[1,2]. Many biological activities are associated with chalcones having heterocyclic substituents[3].

Some chalcones were found to possess germicidal, fungicidal and carcinogenic properties[4-8]. 3-(2-furyl) and 3-(2 and 3-pyridyl) acrylophenones are having coronary dilating properties[9]. Acrylophenones having heterocyclic substituents at 3-position is having anticancer activity against friend virus Leukemia[10].

Like other nitrogen heterocycles, pyrazoles also exhibit a range of biological activities, viz. antioxidant, antiinvasive, antiviral, antipyratic, anti-inflammatory, antidepressant, blood pressure lowering[11-18].

Chromones constitute an important class of oxygen heterocycles[19]. Various natural and synthetic Chromones, especially those having heterocyclic substituents at C-2 and C-3 positions have good pharmaceuticals activities, such as coronary spasmolytic and bronchodilatory activities and are useful in the treatment of asthma[20-24]. 3-Chlorochromones are prepared by reacting dimethyl sulfoxide and copper chloride with chalcones and flavonones[25].

Thiophene derivatives have been studied for decades using the concept of bioisosterism wherein the aromatic moiety of known drug agents is replaced by the heteroaromatic thiophene ring[26,27].

Various pyrazoline derivatives were found to possess important biological and pharmaceutical activities, which stimulated research activity in the field of these nitrogen-containing heterocyclic compounds. Some examples of their most important effects include antimicrobial[28], central nervous system[29] and immunosuppressive[30] activities. Although 2-pyrazolines appear to be useful compounds in drug research, their syntheses have been reviewed in only a few accounts[31-33].

Activities associated with chalcones, pyrazolines, chromones, chlorochromones and in continuation of our work[34] on thiophene and pyrazole containing biologically important heterocyclic compounds, it was thought worthwhile to synthesize some thiophene and pyrazole containing chalcones, pyrazolines , 3-chlorochromones.

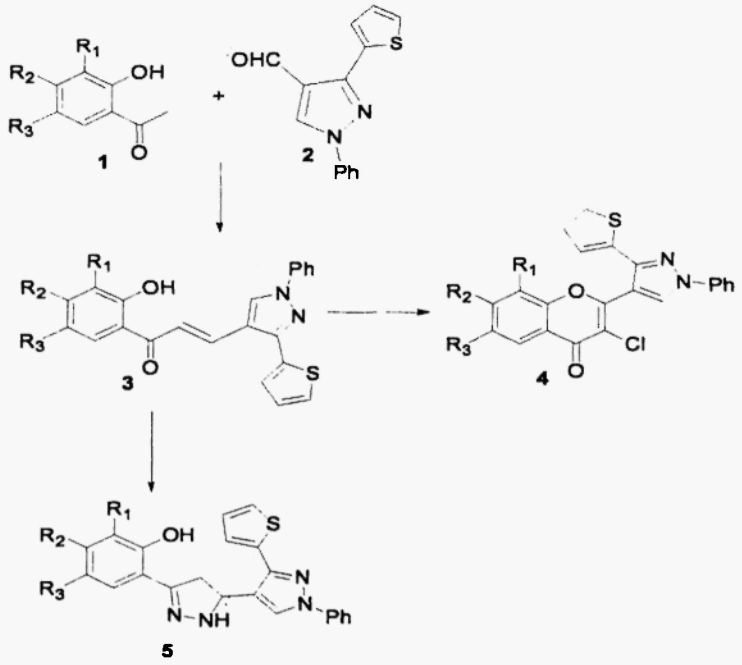
Result and Discussion

In the present investigation 1-(2-hydroxy-phenyl)-3-(1-phenyl-3-thiophen-2-yl-1h-pyrazol-4-yl)-propenone 3 have been obtained by the Claisen-Schmidt condensation of 2-hydroxy acetophenone 1 and 2 by known literature method. The desired 3-chloro-2-(1-phenyl-3-thiophen-2-yl-1h-pyrazol-4-yl)-chromon-4-one 4 were prepared by oxidative cyclization of 3 in DMSO-$CuCl_2$.

The desired 2-(1'-phenyl-3'-thiophen-2-yl-3,4-dihydro-2H,1H'-[3,4]bipyrazol-5-yl)-phenol **5** were prepared by condensing **3** with hydrazine hydrate. Their structures were established by elemental and spectral studies.

A α,β-unsaturated group which is characteristic of compounds **3** has been observed between 1670 to 1688 cm^{-1}. Compounds **3** synthesized by us also show characteristic peaks at around 3450 cm^{-1} to 3400 cm^{-1} due to –OH group. For chalcones ^1H NMR shows common peak at around 12δ due to –OH group, 9.4 δ due to pyrazole protons, olefinic signals are observed in the range of 7.5 to 7.8 δ. The structures of these compounds are also confirmed by their mass spectra. For 3-chlorochromones **4** IR absorption bands at around 1660 cm^{-1} due to C=O functionality, band at around 750 cm^{-1} due to C-Cl is observed. For compounds **4** ^1H NMR shows all peaks in aromatic region. The structures of these compounds are also confirmed by their mass spectra. For pyrazolines **5** IR absorption bands at around 3300 & 3250 cm^{-1} due to O-H and N-H functionality. For compounds **5** ^1H NMR shows doublet of doublet at around 3 δ and 3.8 δ due to methylene protons. It also shows doublet of doublet at around 5δ due to proton adjacent to methylene protons. The structures of these compounds are also confirmed by their mass spectra.

SCHEME:-



Experimental:- Melting points were recorded in open capillaries in liquid paraffin bath and are uncorrected. The reaction was monitored by TLC. Products were purified by column chromatography. IR spectra were recorded in nujol on Perkin-Elmer 1420 spectrophotometer. ^{1}H NMR spectra were recorded on Varian 300 MHz spectrometer in $CDCl_3$ as a solvent and TMS as an internal standard. Peak values are shown in δ (ppm). Mass spectra were recorded on a Kratos MS 80 mass spectrometer.

1-(2-Hydroxy-phenyl)-3-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-propenone (3a-j): A mixture of 1(0.001 mole) and 2(0.001mole) was dissolved in 40 ml absolute ethanol. To this mixture 3 gms of KOH pelletes were added. The reaction was stirred at room temperature for 48hrs. Then reaction mixture was poured over crushed ice and contents were acidified with concentrated HCl. Product thus obtained was crystallized from acetic acid.

3-Chloro-2-(1-phenyl-3-thiophen-2-yl-1H-pyrazol-4-yl)-chromon-4-one (4a-j): 0.001 mole of 3 was dissolved in 15 ml of DMSO. To this reaction mixture excess of $CuCl_2$ (about 2gm) was added. Contents were heated under mild reflux for 3 hrs and the reaction mixture was left overnight. 100 ml of cold water was slowly added to the flask and the separated product was filtered and washed with cold water followed by dilute HCl for several times again it was washed with cold water. The product was crystallized from ethanol.

2-(1'-Phenyl-3'-thiophen-2-yl-3,4-dihydro-2H,1H'-[3,4]bipyrazol-5-yl)-phenol (5a): A mixture of 3(0.001 mole), hydrazine hydrate (0.003 mole) and ethanol 30 ml were refluxed for 4 hrs. There after acetic acid 5 ml was added to the reaction mixture. Heating was continued further for 4 hrs. Reaction mixture was left overnight. The excess of solvent was removed under vacuum. The contents were cooled and poured over crushed ice. Resultant solid was filtered and crystallized from ethanol.

Table 1: Physical and spectral data of the synthesized compounds

Compd.	R_1	R_2	R_3	M.P. (^{0}C)	Yield (%)	Spectral data (NMR in δ ppm, IR values in cm^{-1} & mass given as M^+
3a	H	H	Cl	170-2	78	IR: 3422, 3045,1684, 1638, NMR: 7.01δ to 8.3δ, m, 13 H, 9.49δ, s, 1H & 12.7δ, s, 1H exchangeable with D_2O Mass M^+= 406.
3b	H	Me	Cl	187-8	73	IR: 3410 3050,1686, 1637, NMR: 2.45 δ, s, 3H, 7.10δ to 8.28δ, m, 12 H, 9.49δ, s, 1H & 12.5, s, δ 1H exchangeable with D_2O Mass M^+= 420.
3c	Me	H	Me	171-2	69	IR: 3417 3052,1688, 1633, NMR: 2.41δ, s, 3H, 2.44δ, s, 3H, 7.12δ to 8.26δ, m, 12 H, 9.43δ, s, 1H & 13.1, s, δ 1H exchangeable with D_2O Mass M^+= 400.
3d	H	H	Br	156	68	IR: 3415 3060,1687, 1635, NMR: 6.99δ to 8.22δ, m, 13 H, 9.45δ, s, 1H & 12.4δ, s, 1H exchangeable with D_2O Mass M^+= 450
3e	H	H	Me	260-2	78	IR: 3416 3050,1682, 1630, NMR: 2.41δ, s, 3H, 6.95δ to 8.20δ, m, 13 H, 9.41δ, s, 1H & 12.9δ, s, 1H exchangeable with D_2O Mass M^+= 386
3f	H	Me	H	163	77	IR: 3417 3052,1680, 1632, NMR: 2.43δ, s, 3H, 6.99δ to 8.26δ, m, 13 H, 9.45δ, s, 1H & 12.97δ, s, 1H exchangeable with D_2O Mass M^+= 386
3g	Cl	H	Cl	171-2	80	IR: 3410, 3070, 1686,

						1634,753,735 NMR: 7.26 δ to 8.12δ, m, 12 H, 9.24δ, s, 1H & 13.2δ, s, 1H exchangeable with D_2O Mass M^+= 440
3h	H	H	Et	193	64	IR: 3412 3055,1685, 1638, NMR: 1.21δ, t, 3H, 2.45 δ, q, 2H, 7.15δ to 8.29δ, m, 13 H, 9.40δ, s, 1H & 12.67δ, s, 1H exchangeable with D_2O Mass M^+= 400
3i	Me	H	H	159	68	IR: 3414 3052,1681, 1633, NMR: 2.40δ, s, 3H, 6.95δ to 8.20δ, m, 13 H, 9.47δ, s, 1H & 12.91δ, s, 1H exchangeable with D_2O Mass M^+= 386
3j	H	H	F	186	73	IR: 3419 3058,1689, 1639, NMR: 7.25δ to 8.34δ, m, 13 H, 9.52δ, s, 1H & 13.61δ, s, 1H exchangeable with D_2O Mass M^+= 390.
4a	H	H	Cl	236	47	IR: 3068,1664, 756, 745. NMR: 7.15δ to 8.01δ, m, 11 H, 9.12δ, s, 1H, Mass M^+= 438.
4b	H	Me	Cl	253	44	IR: 3062,1665, 755, 748. NMR: 2.42δ, s, 3H, 7.28δ to 8.20δ, m, 10 H, 9.18δ, s, 1H, Mass M^+= 452.
4c	Me	H	Me	227	48	IR: 3074,1640, 759.NMR: 2.41δ, s, 3H, 2.46δ, s, 3H, 7.09δ to 8.03δ, m, 10 H, 9.24δ, s, 1H, Mass M^+= 432.
4d	H	H	Br	265	40	IR: 3048,1655, 755. NMR: 7.25δ to 8.18δ, m, 11 H, 9.18δ, s, 1H, Mass M^+= 483.
4e	H	H	Me	221	45	IR: 3072,1648, 753.NMR: 2.42δ, s, 3H, 7.13δ to 8.22δ, m, 11 H, 9.24δ, s, 1H, Mass M^+= 418
4f	H	Me	H	206	42	IR: 3070,1652, 757.NMR: 2.44δ, s, 3H, 7.11δ to 8.21δ, m, 11 H, 9.20δ, s, 1H, Mass M^+= 418
4g	Cl	H	Cl	275	51	IR: 3059,1659, 755, 750, 744 NMR: 7.25δ to 8.32δ, m, 10 H, 9.27δ, s, 1H, Mass M^+= 473
4h	H	H	Et	196	38	IR: 3044,1655, 759. NMR: 1.20δ, t, 3H, 2.43 δ, q, 2H, 7.11δ to 8.09δ, m, 11H, 9.40δ, s, 1H, Mass M^+= 432
4i	Me	H	H	232	42	IR: 3066,1654, 752.NMR: 2.43δ, s, 3H, 7.03δ to 8.09δ, m, 11 H, 9.22δ, s, 1H, Mass M^+= 418
4j	H	H	F	210	44	IR: 3058,1658, 758. NMR: 7.28δ to 8.28δ, m, 11 H, 9.28δ, s, 1H, Mass M^+= 422.
5a	H	H	Cl	112-3	43	IR: 3359, 3318, 3070,1629,756, NMR: 3.18 δ, dd, 1H, 3.71 δ, dd, 1H, 5.11 δ, t, 1H, 6.93δ to 7.97δ, m, 12 H, 8.61δ, s, 1H, exchangeable with D_2O & 11.24δ, s, 1H exchangeable with D_2O Mass M^+= 420.
5b	H	Me	Cl	124-6	45	IR: 3355, 3320, 3067,1625,758, NMR: 2.48δ, s, 3H, 3.16 δ, dd, 1H, 3.75 δ, dd, 1H, 5.17 δ, t, 1H, 6.99δ to 7.99δ, m, 11 H, 8.68δ, s, 1H, exchangeable with D_2O & 11.22δ, s, 1H exchangeable with D_2O Mass M^+= 434.
5c	Me	H	Me	120-2	49	IR: 3345, 3312, 3050,1621, NMR: 2.41δ, s, 3H, 2.43δ, s, 3H, 3.13 δ, dd, 1H, 3.71 δ, dd, 1H, 5.12 δ, t, 1H, 6.98δ to 7.91δ, m, 11 H, 8.61δ, s, 1H, exchangeable with D_2O & 11.10δ, s, 1H exchangeable with D_2O Mass M^+= 414.

5d	H	H	Br	147	46	IR: 3367, 3322, 3062,1621, NMR: 3.14 δ, dd, 1H, 3.68 δ, dd, 1H, 5.16 δ, t, 1H, 6.65δ to 7.88δ, m, 12 H, 8.71δ, s, 1H, exchangeable with D_2O & 11.01δ, s, 1H exchangeable with D_2O Mass M^+= 464.
5e	H	H	Me	109	47	IR: 3342, 3332, 3060,1628, NMR: 2.40δ, s, 3H, 3.12 δ, dd, 1H, 3.70 δ, dd, 1H, 5.10 δ, t, 1H, 6.94δ to 7.90δ, m, 12 H, 8.60δ, s, 1H, exchangeable with D_2O & 11.20δ, s, 1H exchangeable with D_2O Mass M^+= 400.
5f	H	Me	H	115	41	IR: 3366, 3323, 3048,1640, NMR: 2.43δ, s, 3H, 3.10 δ, dd, 1H, 3.72 δ, dd, 1H, 5.17 δ, t, 1H, 6.96δ to 7.91δ, m, 12 H, 8.61δ, s, 1H, exchangeable with D_2O & 11.26δ, s, 1H exchangeable with D_2O Mass M^+= 400.
5g	Cl	H	Cl	167	53	IR: 3355, 3320, 3067,1625,758, NMR: 3.19 δ, dd, 1H, 3.78 δ, dd, 1H, 5.27 δ, t, 1H, 7.03δ to 8.05δ, m, 11 H, 8.79δ, s, 1H, exchangeable with D_2O & 11.42δ, s, 1H exchangeable with D_2O Mass M^+= 454.
5h	H	H	Et	118	32	IR: 3352, 3323, 3062,1621, NMR: 1.16δ, t, 3H, 2.41 δ, q, 2H, 3.11 δ, dd, 1H, 3.69 δ, dd, 1H, 5.12 δ, t, 1H, 7.01δ to 8.01δ, m, 12 H, 8.71δ, s, 1H, exchangeable with D_2O & 11.12δ, s, 1H exchangeable with D_2O Mass M^+= 414.
5i	Me	H	H	121	38	IR: 3340, 3331, 3054,1619, NMR: 2.41δ, s, 3H, 3.13 δ, dd, 1H, 3.71 δ, dd, 1H, 5.12 δ, t, 1H, 6.95δ to 7.97δ, m, 12 H, 8.62δ, s, 1H, exchangeable with D_2O & 11.21δ, s, 1H exchangeable with D_2O Mass M^+= 400.
5j	H	H	F	114	38	IR: 3361, 3324, 3067,1627, NMR: 3.19 δ, dd, 1H, 3.73δ, dd, 1H, 5.15 δ, t, 1H, 6.98δ to 7.99δ, m, 12 H, 8.69δ, s, 1H, exchangeable with D_2O & 11.29δ, s, 1H exchangeable with D_2O Mass M^+= 404.

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