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Synthesis, characterization and antimicrobial screening of some novel heterocyclic compounds derived from chalcone

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ABSTRACT

In the present research work a synthesized series of pyrazole derivatives. The pyrazole derivatives are prepared starting from chalcone and this chalcone were prepared by 4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3H-pyrazol-3-one condense with various substituted aromatic aldehyde. Further this chalcone converted into pyrazole followed by condensation of chalcone with phenyl hydrazine hydrochloride and semicarbazide hydrochloride in presence of pyridine. The structures of newly synthesized compounds are characterized on the basis of IR, ^{1}H-NMR, Mass spectroscopies and elemental analysis. The newly synthesized compounds were screened for antimicrobial activity.

Key words: Synthesis, Chalcone, Pyrazole, Spectral studies and Antibacterial activity.

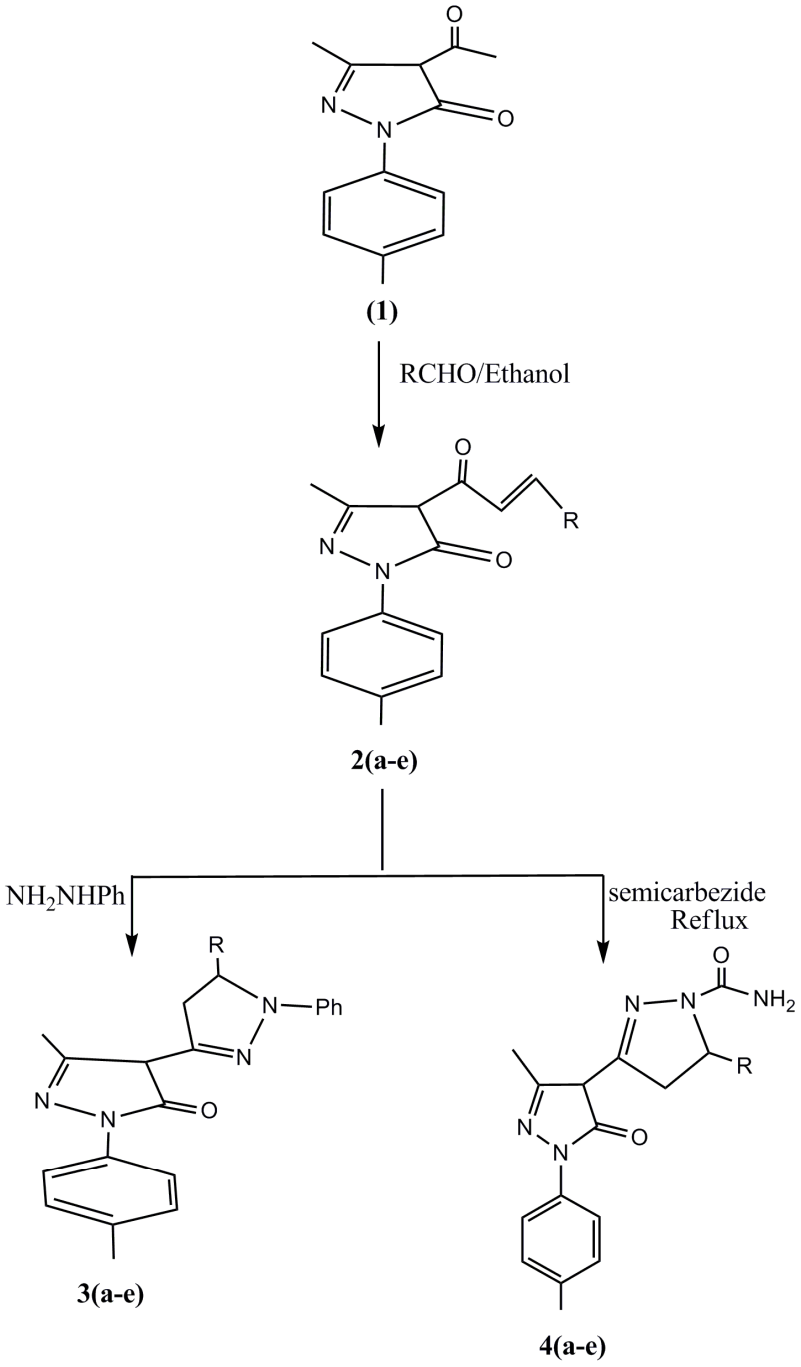
INTRODUCTION

In the present days the heterocyclic ring system continues to attract considerable interest due to a wide variety of biological activities like, antibacterial, antifungal, antitubercular, anticancer, analgesic, anti-inflammatory, anticonvulsant antidepressant and anti-arrhythmic activities.[1,2] The chemistry of chalcones has generated intensive scientific interest due to their biological and industrial applications. Chalcones are natural biocides and are well known intermediates in the synthesis of heterocyclic compounds exhibiting various biological activities.[3,4] One such class of compounds like five membered heterocyclic containing two nitrogen as hetero atoms in its ring structure i.e. Pyrazoles are an important class of hetero aromatic systems that find extension use in the pharmaceutical industry. Pyrazoles occupy unique positions and they have so far been synthesized mainly due to their higher pharmacological activities. They possess antibiotic, antiviral, anti-inflammatory and anti-amoebic properties[5-8]. Pyrazole is dihydropyrazole, a five membered heterocyclic compound containing two nitrogen atoms in adjacent positions and possessing only one endocyclic double bond. Considerable interest has been focused on the pyrazoline structure, which is known to possess a broad spectrum of biological activities, such as antitumor, immune-suppressive,antibacterial, anti-inflammatory, anticancer, antidiabetic and antidepressant [9-11].In continuation of our research on the synthesis of pyrazole a facile synthesis of a range of pyarazole derivatives from α,β-unsaturated ketones (chalcones) and phenylhydrazine hudrochloride and semicarbazide hydrochloride in the presence of pyridine is described in Scheme 1.The synthesized compounds were evaluated for its antifungal and antibacterial activity.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded by a Perkin-Elmer 237 spectrophotometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker AM 400 instrument (at 400 MHz). Mass spectra (MS) were recorded on M S route JMS 600-H. All the synthesized compounds were purified by recrystallization method. The reactions were followed up and the purity of

compounds was checked on pre-coated TLC plates. 4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3H-pyrazol-3-one was prepared by reported method.[12]



Where R=(a) Ph (b) 2-$CH_3C_6H_4$ (c) 2-OHC_6H_4

(d) 4-OHC_6H_4 (e) 4-$OCH_3C_6H_4$

Scheme-1

Synthesis of 3-methyl-1-p-tolyl-4-(3-arylacryloyl)-1H-pyrazol-5(4H)-one 2(a-e):

A mixture of various substituted aromatic aldehydes (0.001 mol) and 4-acetyl-3-methyl-1-(tolyl)-pyrazol-5(4H)-one(1) (0.001 mol) in 95% ethanol(20 mL) were mix in a round bottom flask, 10 mL of 60% aqueous sodium hydroxide solution added drop wise. Resulting mixture was stirred for 2 hrs at 5–10^{0}C, poured into crushed ice and acidified with dilute HCl. The precipitate obtained was filtered and washed twice with cold water. The resulting

solid was allowed to air dry and recrystallized from ethanol. The yields, melting points and other characterization data of these compounds are given in Table -1.

Synthesis of 3'-methyl-1-phenyl-5-aryl-1'-p-tolyl-4,5-dihydro-1H,1'H-3,4'-bipyrazol-5'(4'H)-one 3(a-e):
The reaction mixture of 3-methyl-1-p-tolyl-4-(3-arylacryloyl)-1H-pyrazol-5(4H)-one 2(a-e) (0.01mol) and phenyl hydrazine(0.01mol) in pyridine (10 ml). The reaction mixture was refluxed in oil bath on magnetic stirrer for 3 h. completion of the reaction observed by TLC using hexane/ethyl acetate. The reaction mixture was cooled to room temperature and poured into ice-cold water, then neutralized by dilute HCl. The obtained solid was filtered, washed with water and recrystallyzed from ethanol.The yields, melting points and other characterization data of these compounds are given in Table-2.

Table:-1 Analytical Data and Elemental Analysis of Compounds 2(a-e)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis					
					%C		% H		%N	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	$C_{20}H_{18}N_2O_2$ (318)	343	84	141-143	75.43	75.45	5.69	5.70	8.78	8.80
2b	$C_{21}H_{20}N_2O_2$ (332)	359	78	135-136	75.87	75.88	6.04	6.06	8.41	8.43
2c	$C_{20}H_{18}N_2O_3$ (334)	358	80	156-158	71.82	71.84	5.41	5.43	8.37	8.38
2d	$C_{20}H_{18}N_2O_3$ (334)	362	77	152-153	71.83	71.84	5.42	5.43	8.38	8.38
2e	$C_{21}H_{20}N_2O_3$ (348)	367	79	236-238	72.38	72.40	5.78	5.79	8.03	8.04

***** *Uncorrected*

Table:-2 Analytical Data and Elemental Analysis of Compounds 3(a-e)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis					
					%C		% H		%N	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{26}H_{24}N_4O$ (408)	429	79	163-164	76.44	76.45	5.90	5.92	13.71	13.72
3b	$C_{27}H_{26}N_4O$ (422)	451	74	168-170	76.73	76.75	6.18	6.20	13.24	13.26
3c	$C_{26}H_{24}N_4O_2$ (424)	455	72	165-167	73.55	73.56	5.68	5.70	13.18	13.20
3d	$C_{26}H_{24}N_4O_2$ (424)	459	75	171-173	73.54	73.56	5.68	5.70	13.19	13.20
3e	$C_{27}H_{26}N_4O_2$ (438)	463	73	157-159	73.93	73.95	5.96	5.98	12.76	12.78

***** *Uncorrected*

Table:-3 Analytical Data and Elemental Analysis of Compounds 4(a-e)

Compd.	Molecular formula (Mol.wt.)	LC-MS Data	Yield	M.P.* ^{0}C	Elemental Analysis					
					%C		% H		%N	
					Found	Calcd.	Found	Calcd.	Found	Calcd.
4a	$C_{21}H_{21}N_5O_2$ (375)	391	60	148-149	67.17	67.18	5.62	5.64	18.64	18.65
4b	$C_{22}H_{23}N_5O_2$ (389)	416	57	152-153	67.83	67.85	5.94	5.95	17.97	17.98
4c	$C_{21}H_{21}N_5O_3$ (391)	420	54	157-159	64.43	64.44	5.40	5.41	17.87	17.89
4d	$C_{21}H_{21}N_5O_3$ (391)	419	58	144-146	64.42	64.44	5.39	5.41	17.88	17.89
4e	$C_{22}H_{23}N_5O_3$ (405)	428	53	153-155	65.16	65.17	5.70	5.72	17.26	17.27

***** *Uncorrected*

Synthesis of 3'-methyl-5'-oxo-5-aryl-1'-p-tolyl-4,4',5,5'-tetrahydro-1H,1'H-3,4'-bipyrazole-1-carboxamide 4(a-e):
The reaction mixture of 3-methyl-1-p-tolyl-4-(3-arylacryloyl)-1H-pyrazol-5(4H)-one 2(a-e) (0.01mol) and semicarbazide hydrochloride (0.01mol) in pyridine (10 ml) was refluxed in oil bath on magnetic stirrer for 3 hrs. The completion of the reaction observed by TLC using hexane/ethyl acetate. The reaction mixture was cooled to room temperature and poured into ice-cold water, then neutralized by dilute HCl. The obtained solid was filtered,

washed with water and recrystallyzed from ethanol. The yields, melting points and other characterization data of these compounds are given in Table-3.

BIOLOGICAL SCREENING

Antibacterial activities

The antibacterial activities of all the compounds were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/ML by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used standard for comparison. The area of inhibition of zone measured in mm. Compounds 4e and 4c were found more toxic for microbes. Other compounds found to be less or moderate active shown in Tables -4.

Table:-4 Antibacterial Activity of Compounds 2(a-e), 3(a-e) and 4(a-e)

Compounds	Gram +Ve		Gram –Ve	
	Bacillus subtilis	***Staphylococcus aureus***	***E. coli***	***Klebsiella promioe***
2a	49	54	58	51
2b	52	55	57	53
2c	56	61	60	60
2d	54	58	59	55
2e	50	54	62	51
3a	49	56	57	53
3b	53	57	58	55
3c	58	66	60	63
3d	56	60	62	56
3e	67	67	71	74
4a	50	54	59	51
4b	52	55	61	53
4c	56	64	63	62
4d	54	58	63	55
4e	66	66	70	76

Table:-5 Antifungal Activity of Compounds 2(a-e), 3(a-e) and 4(a-e)

Compounds	Zone of Inhibition at 1000 ppm (%)			
	Aspergillus Niger	***Botrydepladia Thiobromine***	***Nigrospora Sp.***	***Rhizopus Nigricum***
2a	53	59	53	52
2b	56	59	58	53
2c	61	61	62	58
2d	60	62	61	55
2e	66	68	69	66
3a	55	58	54	57
3b	58	58	59	58
3c	63	60	63	63
3d	62	61	62	60
3e	68	67	70	71
4a	59	59	57	60
4b	60	61	61	61
4c	67	63	68	66
4d	64	62	64	63
4e	70	70	73	76

Antifungal Activities

The fungicidal activity of all the compounds was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Aspergillus niger, Botrydepladia thiobromine, Nigrospora Sp, and Rhizopus nigricum*. The antifungal activities of all the compounds (5a-d) were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120^{o} C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. The percentage inhibition for fungi was calculated after five days using the formula given below:

Percentage of inhibition = 100(X-Y) / X

Where,
X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activity displayed by various compounds **2(a-e), 3(a-e) and 4(a-e)** is shown in Tables-5.

RESULTS AND DISCUSSION

It was observed that 4-acetyl-3-methyl-1-(tolyl)-pyrazol-5(4H)-one(1), on condensation with aromatic aldehydes, yields 3-methyl-1-p-tolyl-4-(3-arylacryloyl)-1H-pyrazol-5(4H)-one 2(a-e). The structures of 2(a-e) were confirmed by elemental analysis and IR spectra showing an absorption band at 1620-1640 (C=N), 3030-3080 cm^{-1} (C-H, of Ar.), 1720-1750 cm^{-1} (-CO),1665-1650 cm^{-1}(α,β-unsaturated ketones),1600-1548 cm^{-1}(conjugated C=C), 2950, 1370 cm^{-1} (-CH_3), 3345-3325 (OH), 2815-2850 cm^{-1} (-OCH_3). ^{1}H NMR : 7.23–7.67(9H,m,Ar-H), 6.94, 7.64 (2H, d, CH=CH),3.4(1H,s,CH),1.96(3H,s,CH_3),2b;2.38(3H,s,CH_3),2c,4.22(1H,s,-OH),2d;4.18 (1H,s,-OH), 2e:3.68(3H, s, CH_3). The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 3'-methyl-1-phenyl-5-aryl-1'-p-tolyl-4,5-dihydro-1H,1'H-3,4'-bipyrazol-5'(4'H)-one 3(a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 1620-1656 (C=N), 3030-3080 cm^{-1} (C-H, of Ar.), 1720-1750 cm^{-1} (-CO),1275(C-O),2950, 1370 cm^{-1} (-CH_3), 3345-3325 (OH), 2815-2850 cm^{-1} (-OCH_3). ^{1}H NMR:6.82–7.51(14H,m,Ar-H),1.96,2.42(2H,d,CH of pyrazolone ring), 3.16-2.92(2H,d,CH_2),5.23(1H,t,CH), 2.56,1.96(6H,s,CH_3),3b;2.38 (3H, s, CH_3), 3c,4.22 (1H, s,-OH),3d;4.18(1H,s,-OH), 3e:3.68 (3H,s,CH_3). The C, H, N, S analysis data of all compounds are presented in Table-2.

The structures assigned to 3'-methyl-5'-oxo-5-aryl-1'-p-tolyl-4,4',5,5'-tetrahydro-1H,1'H-3,4'-bipyrazole-1-carboxamide 4(a-e) were supported by the elemental analysis and IR spectra showing an absorption bands at 1620-1656 (C=N),3362-3354(NH_2),3030-3080 cm^{-1}(C-H, of Ar.),1720-1750cm^{-1} (-CO),1656-1628(N-H)2950,1370 cm^{-1}(-CH_3), 3345-3325 (OH), 2815-2850cm^{-1}(-OCH_3).^{1}H NMR: 7.51–7.23(9H,m,Ar-H),2.47(1H,s,CH of pyrazoleone ring),7.4(2H,s,NH_2), 2.56,1.96 (6H,s,CH_3),3.18,2.93(2H,d,CH_2),5.2(1H,t,CH),4b; 2.38(3H,s,CH_3),4c,4.22(1H,s,-OH), 4d; 4.18 (1H,s,-OH),4e:3.68 (3H,s,CH_3). The C, H, N, S analysis data of all compounds are presented in Table-3.

The examination of elemental analytical data reveals that the elemental contents are consistence with the predicted structure shown in Scheme-1. The IR data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS. LC-MS data of all compounds are presented in Tables-1,2 and 3.

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