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Synthesis, characterization and antimicrobial study of some pyrazole compounds derived from chalcone

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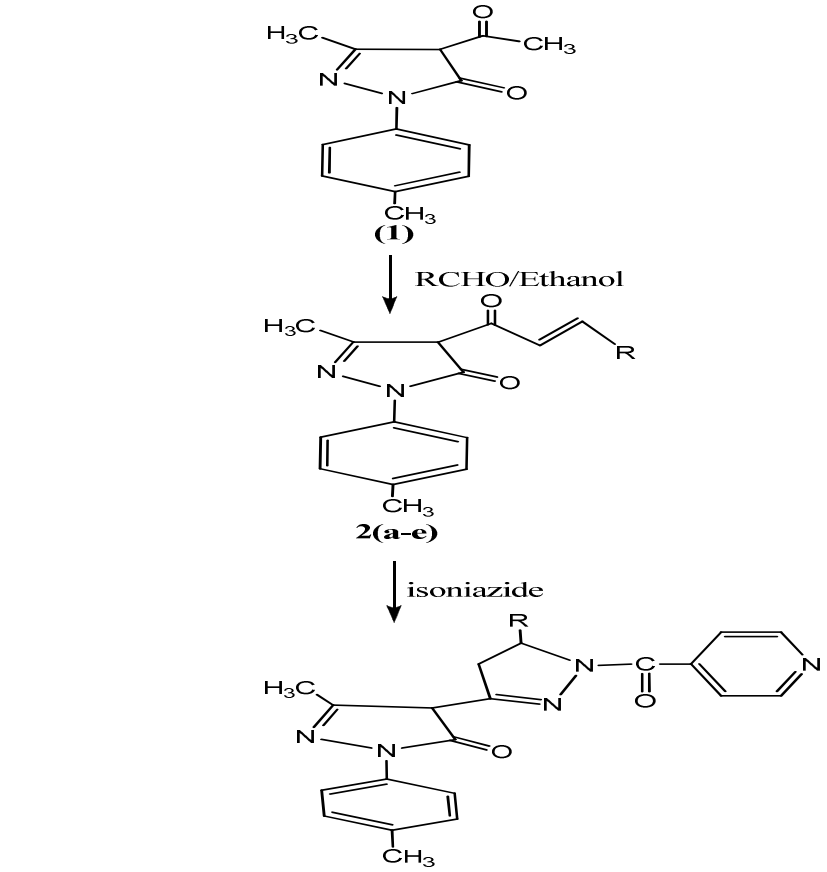
ABSTRACT

The 4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3H-pyrazol-3-one condense with various substituted aromatic aldehyde were yield various chalcone. Further this chalcone converted into pyrazole by condensation of various synthesized chalcone with isoniazide. In the present research article a new series of pyrazole derivatives have been synthesized. 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 studied for antimicrobial activity.

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

INTRODUCTION

Heterocyclic ring system containing nitrogen becomes most interest field in research area due to their wide variety of biological activities like, antibacterial, antifungal, antitubercular, anticancer, analgesic, anti-inflammatory, anticonvulsant, antidepressant and anti-arrhythmic activities[1,2]. Pyrazolines are distinguished and important nitrogen containing five membered heterocyclic compounds. Pyrazoline are compounds with remarkable applications. Various pyrazoline and its derivatives have been found to hold considerable biological activities such as antibiotic, antiviral, anti-inflammatory and anti-amoebic properties[3-8]. Pyrazoline possess a broad spectrum of biological activities, such as antitumor, immune -suppressive, antibacterial, anti-inflammatory, anticancer, antidiabetic and anti depressant[9-11]. The chemistry of chalcones has generated intensive scientific interest due to their biological and industrial applications. Chalcones are exhibit various biological activities, such as antioxidant, anti inflammatory, antimalarial, antileishmanial, anticancer and antitumor[10-14]. In addition, chalcones are very important compounds as a Michael acceptor in organic syntheses. In continuation of our earlier research work, the facile synthesis of pyrazole derivatives from chalcones and isoniazide in the presence of pyridine is described in scheme 1. The synthesized compounds were evaluated for its antifungal and antibacterial activity.



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

Where R= (a) Ph (b) 2-$CH_3C_6H_4$ (c) 2-OHC_6H_4 (d) 4-OHC_6H_4 (e) 4-$OCH_3C_6H_4$ (f) 4-$CH_3C_6H_4$ (g) 4-ClC_6H_4 (h) 4-BrC_6H_4

Scheme-1

MATERIALS AND METHODS

The 4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3H-pyrazol-3-one was prepared by reported method[15]. 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 400MHz). Mass spectra (MS) were recorded on M S route JMS 600-H. Melting points were determined in open capillary tubes and were uncorrected. 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.

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

A mixture of substituted aromatic aldehydes (0.001 mol) and 4-acetyl-3-methyl-1-(p-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 1-isonicotinoyl-3'-methyl-5-aryl-1'-p-tolyl-4,5-dihydro -1H,1'H-3,4' -bipyrazol-5'(4'H)-one 3(a-h):

The reaction mixture of 3-methyl-1-p-tolyl-4-(3-arylacryloyl)-1H-pyrazol-5(4H)-one 2(a-h) (0.01mol) and isoniazide (0.01mol) in pyridine (10 ml) was refluxed in oil bath on magnetic stirrer for 2.5hrs. The completion of

the reaction observed by TLC using cyclohexane/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 R-spirit. 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-h)

Compd.	Molecular formula (Mol.wt.)	M.P.* ^{0}C	Yield	Elemental Analysis					
				%C		% H		%N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
2a	$C_{20}H_{18}N_2O_2$ (318)	141-143	84	75.45	75.43	5.70	5.69	8.80	8.78
2b	$C_{21}H_{20}N_2O_2$ (332)	135-136	78	75.88	75.87	6.06	6.04	8.43	8.41
2c	$C_{20}H_{18}N_2O_3$ (334)	156-158	80	71.84	71.82	5.43	5.41	8.38	8.37
2d	$C_{20}H_{18}N_2O_3$ (334)	152-153	77	71.84	71.83	5.43	5.42	8.38	8.38
2e	$C_{21}H_{20}N_2O_3$ (348)	236-238	79	72.40	72.38	5.79	5.78	8.04	8.03
2f	$C_{21}H_{20}N_2O_2$ (332)	194-195	75	75.88	75.86	6.06	6.05	8.43	8.41
2g	$C_{20}H_{17}N_2O_2Cl$ (352)	199-200	75	68.09	68.07	4.86	4.84	7.94	7.93
2h	$C_{20}H_{17}N_2O_2Br$ (396)	202-204	72	60.47	60.46	4.31	4.30	7.05	7.03

***** *Uncorrected*

Table 2. Analytical Data and Elemental Analysis of Compounds 3(a-h)

Compd.	Molecular formula (Mol.wt.)	M.P.* ^{0}C	Yield	Elemental Analysis					
				%C		% H		%N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	$C_{26}H_{23}N_5O_2$ (437)	156-157	74	71.38	71.36	5.30	5.28	16.01	16.00
3b	$C_{27}H_{25}N_5O_2$ (451)	162-164	71	71.82	71.81	5.58	5.57	15.51	15.49
3c	$C_{26}H_{23}N_5O_3$ (453)	154-156	70	68.86	68.84	5.11	5.10	15.44	15.43
3d	$C_{26}H_{23}N_5O_3$ (453)	167-169	76	68.86	68.85	5.11	5.09	15.44	15.42
3e	$C_{27}H_{25}N_5O_3$ (468)	149-151	74	69.36	69.35	5.39	5.398	14.98	14.96
3f	$C_{27}H_{25}N_5O_2$ (451)	152-153	71	71.82	71.80	5.58	5.57	15.51	15.50
3g	$C_{26}H_{22}N_5O_2Cl$ (471)	146-148	73	66.17	66.16	4.70	4.68	14.84	14.82
3h	$C_{26}H_{22}N_5O_2Br$ (515)	148-149	76	60.47	60.45	4.29	4.28	13.56	13.54

***** *Uncorrected*

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 3g and 3e were found more toxic for microbes. Other compounds found to be less or moderate active shown in Tables -3.

Table 3. Antibacterial Activity of Compounds 3(a-h)

Compounds	Gram +Ve		Gram –Ve	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E. coli***
3a	52	58	52	59
3b	54	59	56	60
3c	56	62	58	61
3d	57	63	57	60
3e	62	66	65	64
3f	54	57	57	59
3g	64	66	69	68
3h	58	61	58	61

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 3(a-h) 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 **3(a-h)** is shown in Tables-4.

Table 4. Antibacterial Activity of Compounds 3(a-h)

Zone of Inhibition at 1000 ppm (%)				
Compounds	***Aspergillus Niger***	***Rhizopus Nigricum***	***Nigrospora Sp.***	***Botrydepladia Thiobromine***
3a	54	58	55	56
3b	57	59	58	58
3c	60	61	61	62
3d	61	63	62	62
3e	62	66	64	65
3f	58	60	60	59
3g	65	69	67	64
3h	59	62	63	60

RESULTS AND DISCUSSION

It was observed that 4-acetyl-3-methyl-1-(p-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-h). The structures of 2(a-h) 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.),1720-1750cm^{-1}(-CO),1665-1650cm^{-1}(α,β-unsaturated ketones), 1600-1548 cm^{-1}(conjugated C=C), 2950,1370cm^{-1} (-CH_3), 3345-3325(OH),2815-2850cm^{-1}(-OCH_3),1075 (ArC-Cl), 1060(ArC-Br). ^{1}HNMR: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).2f; 2.35 (3H,s,CH_3).The C, H, N analysis data of all compounds are presented in Table -1.

The structures assigned to 1-isonicotinoyl-3'-methyl-5-aryl-1'-p-tolyl-4,5-dihydro-1H,1'H-3,4'-bipyrazol-5'(4'H)-one3(a-h) 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),1075(ArC-Cl),1060(ArC-Br). ^{1}H NMR:6.82–8.92(13H,m,Ar-H),2.42 (1H,s, 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), 3f;2.35 (3H,s,CH_3). The C, H, N analysis data of all compounds are presented in Table-2.

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 and 2. Compounds 3g and 3e were shows good antimicrobial activity.

CONCLUSION

In conclusion, in present we prepared new pyrazoline derivatives says, 1-isonicotinoyl-3'-methyl-5-aryl-1'-p-tolyl-4,5-dihydro-1H,1'H-3,4'-bipyrazol-5'(4'H)-one. All the synthesized compounds were studied for antimicrobial activity which shows good activity.

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