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Synthesis, Characterization and Biological Screening of some novel heterocyclic compounds

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ABSTRACT

New Benzodizepine derivative was prepared by reaction of chalcone with 5-bromo o-phenylenediamine in presence of pyridine. First Chalcones were prepared by treatment of 4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3H-pyrazol-3-one with different substituted aldehyde by claisen-schimidt condensation. The structures of the newly synthesized Benzodiazepine derivatives have characterized by IR, ^{1}H-NMR, Mass spectroscopy and elemental analysis. The synthesized compounds were evaluated for their antimicrobial activities.

Keywords: Synthesis, Chalcone, Benzodiazepine, Spectral studies and Antibacterial activity.

INTRODUCTION

The chemistry of heterocyclic compounds is as logical as that of aliphatic or aromatic compounds. Their study is of great interest both from the theoretical as well as practical importance. Hetrocyclic compounds have been synthhtized meanly due to wide range of biological activities. [1,2] Chalcones are natural and synthetic products that have been reviewed for their wide range of biological activities as antibacterial , anti-tumor, anti-inflammatory, antioxidant agents, antibacterial, and antifungal activities [3-8]. The another heterocyclic compound, benzodiazepines and their derivatives exhibits numerous pharmaceutical as well as biological applications such as, anti–convulsion, anticonvulsant, anti–inflammatory, analgesic, antianxiety, sedative, antidepressive, hypnotic and neuroleptic agents[9-13]. In continuation of over previous research work on novel biologically active molecules, we have designed and synthesized some novel benzodiazepine derivatives has describe in scheme-1. The synthesized compounds were evaluated for its antifungal and antibacterial activity.

MATERIALS AND METHODS

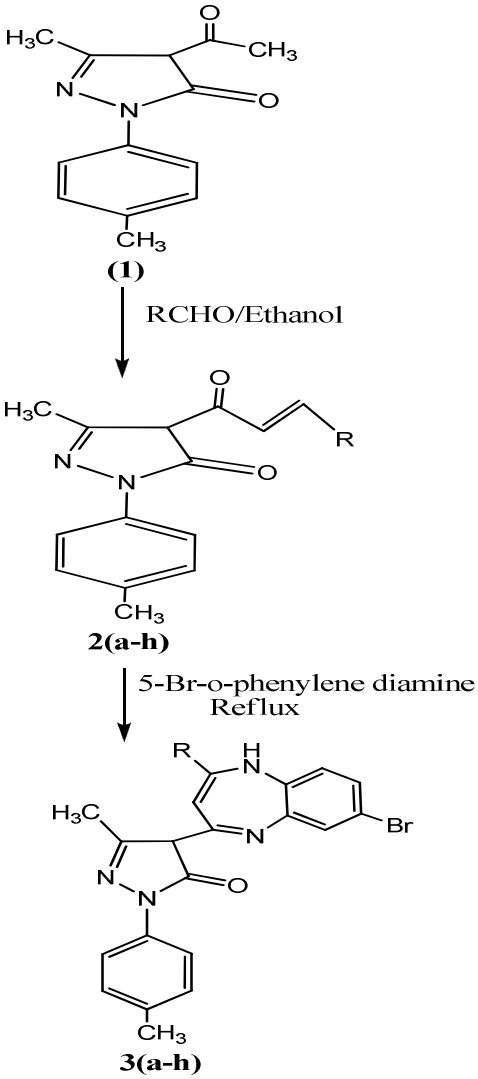
Experimental

4-acetyl-5-methyl-2-(4-methylphenyl)-2,4-dihydro-3H-pyrazol-3-one was prepared by reported method.[14] The reactions were followed up and the purity of compounds was checked on pre-coated TLC plates. All the synthesized compounds were purified by recrystallization method. 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.

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

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.



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

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

Compd.	Molecular formula (Mol.wt.)	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)	84	141-143	75.43	75.45	5.69	5.70	8.78	8.80
2b	$C_{21}H_{20}N_2O_2$ (332)	78	135-136	75.87	75.88	6.04	6.06	8.41	8.43
2c	$C_{20}H_{18}N_2O_3$ (334)	80	156-158	71.82	71.84	5.41	5.43	8.37	8.38
2d	$C_{20}H_{18}N_2O_3$ (334)	77	152-153	71.83	71.84	5.42	5.43	8.38	8.38
2e	$C_{21}H_{20}N_2O_3$ (348)	79	236-238	72.38	72.40	5.78	5.79	8.03	8.04
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	$C_{20}H_{17}N_2O_2Cl$	199-200	75	68.09	68.07	4.86	4.84	7.94	7.93

	(352)								
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*

Synthesis of 4-(7-bromo-2-aryl-1H-benzo[b][1,4]diazepin-4-yl)-3-methyl-1-p-tolyl-1H-pyrazol-5(4H)-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 5-bromo-o-phynelendiamine(0.01mol) in pyridine (10 ml) was refluxed in oil bath on with constant stirring with magnetic stirrer for 4-4.5 hrs. 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 50% aq. 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:-2 Analytical Data and Elemental Analysis of Compounds 3(a-h)

Compd.	Molecular formula (Mol.wt.)	Yield	M.P.* ^{0}C	Elemental Analysis					
				%C		% H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	$C_{26}H_{21}N_4OBr$ (484)	72	211-213	64.32	64.34	4.35	4.36	11.52	11.54
3b	$C_{27}H_{23}N_4OBr$ (498)	75	226-228	64.93	64.94	4.63	4.64	11.21	11.22
3c	$C_{26}H_{21}N_4O_2Br$ (500)	68	194-195	62.26	62.28	4.21	4.22	11.16	11.17
3d	$C_{26}H_{21}N_4O_2Br$ (500)	73	199-201	62.27	62.28	4.20	4.22	11.15	11.17
3e	$C_{27}H_{23}N_4O_2Br$ (514)	75	203-204	62.90	62.92	4.49	4.50	10.86	10.87
3f	$C_{27}H_{23}N_4OBr$ (498)	78	209-211	64.93	64.94	4.63	4.64	11.20	11.22
3g	$C_{26}H_{20}N_4OClBr$ (518)	69	187-189	60.06	60.07	3.86	3.88	10.77	10.78
3h	$C_{27}H_{23}N_4OBr$ (562)	74	202-205	55.32	55.34	3.56	3.57	9.91	9.93

***** *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 3e and 3g 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	54	56	58	62
3b	57	58	59	63
3c	57	60	62	64
3d	60	62	61	67
3e	66	68	69	69
3f	62	66	63	66
3g	71	69	76	73
3h	64	65	64	67

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 Fusarium oxyporium*. 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 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***	***Botrydepladia Thiobromine***	***Nigrospora Sp.***	***Fusarium oxyporium***
3a	57	59	57	56
3b	59	60	62	58
3c	61	62	59	62
3d	64	63	63	59
3e	66	68	65	62
3f	67	65	63	65
3g	71	73	74	71
3h	65	66	64	67

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-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.), 1720-1750 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),1080(ArC-Cl), 1055(ArC-Br). ^{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),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 4-(7-bromo-2-aryl-1H-benzo[b][1,4]diazepin-4-yl)-3-methyl-1-p-tolyl-1H-pyrazol-5(4H)-one 3(a-h) were supported by the elemental analysis and IR spectra showing an absorption bands at 1620-1656 (C=N),3336-3347(NH),3030-3080 cm^{-1}(C-H, of Ar.),1720-1750cm^{-1} (-CO),2950,1370 cm^{-1}(-CH_3), 3345-3325(OH),2815-2850cm^{-1}(-OCH_3), 1080 (ArC-Cl), 1055(ArC-Br).^{1}H NMR: 6.82 –7.74 (13H,m,Ar-H),5.46(1H,s,CH of benzo diazepine ring), 1.96(3H,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; 2.37 (3H,s,CH_3). The C, H, N, S 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,^{1}H-NMR and IR.

REFERENCES

[1] CHL Praveena,VE Rani,Y N Spoorthy and L K Ravindranath,*Journalof Chemical and Pharmaceutical Research*,**2013**,5(5),280-292.
[2] P J Shah, H S Patel and B P Patel, *Journal of Saudi Chemical Society*,**2013,**17,307.
[3] C.J. Zheng, S.M. Jiang, Z.H. Chen, B.J. Ye, H.R. Piao,*Arch. Pharm. Chem. Life Sci.* **2011**, 344, 689–695.
[4] B. Tiwari, A.S. Pratapwar, A.R. Tapas, S.R. Butle, B.S. Vatkar,*Int. J. ChemTech Res.* **2010**, 2, 499–503.
[5] G. Eumkeb, S. Siriwong, S. Phitaktim, N. Rojtinnakorn, S. Sakdarat,*J. Appl. Microbiol.* **2012**,112, 55–64.
[6] P J Shah, P N Patel, K D Patel and H S Patel, *heteroletters*,**2014**,4(4),537-547.
[7] T.N. Doan, T.D.Tran,*Pharmacol. Pharm*. **2011**, 2, 282–288.
[8] J.M. Talia, N.B. Debattista, N.B. Pappano,*Braz. J Microbiol.* **2011**,42, 470–475.
[9] E. A. Younes, Q. Hussein, M. A. May, F. R. Fronczek,*Arkivoc*, **2011**,ii, 322.
[10] F.Ahmadia, S. Dabirianb,M. Faizic, S. A.Tabatabaib,D. Beikid and S. Shahhosseinib, *Iranian Journal of Pharmaceutical Research*,**2014**,13(supplement),79-86.
[11] M. Faizi,M. Sheikhha,A. Ahangar,G. H. Tabatabaei,B. Shafaghi,A. Shafiee and S. A. Tabatabai, *Iran. J. Pharm. Res.*,**2012**,11, 83.
[12] T. I. Saari, M. Uusi-Oukari, J. Ahonen, K. T. Olkkola, *Pharmacol*. *Rev*. **2011**, 63, 243

[13] E Lager, J Nilsson,E Q Nielsen,M Nielsen,T Liljefors and O Sterner,*Bioorg. Medicin. Chem.*, **2008**,11,6936-6948.
[14] P.J. Shah and J.D. Patel, *Asian Journal of Chemistry*,**2010,**22(4),3069-3075.