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Synthesis, Characterization and Antimicrobial Activity (MIC) of Some Substituted Pyranopyrazole Derivatives

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ABSTRACT

Synthesis of 4-(3-(4-chlorophenyl)-1 phenyl-1H pyrazol-4-yl)3,5-dimethyl 4,7-dihydro 1H-pyrano[2,3-c;6,5-c'] dipyrazole by well-known knoevenagel condensation reaction of 3-methyl pyrazole 5-one and 3-(4-chlorophenyl)-1-phenyl-1H pyrazole 4-carbaldehyde in presence of piperidine as catalyst and acetonitrile as solvent. Various pyrazolecarbaldehyde were synthesized from substituted acetophenone and phenylhydrazine reaction and followed by vilsmier hack reaction. We synthesized different substituted pyrazolecarbaldehyde. The constitution of all the synthesized compounds has been characterized by using IR, MASS,^{1}H NMR spectroscopy. All synthesized compounds were screened for their antimicrobial activity.

Keywords: Knoevenagel condensation, 3-methyl pyrazole 5-one, vilsmier hack reaction, pyrazolecarbaldehyde, piperidine, acetonitrile.

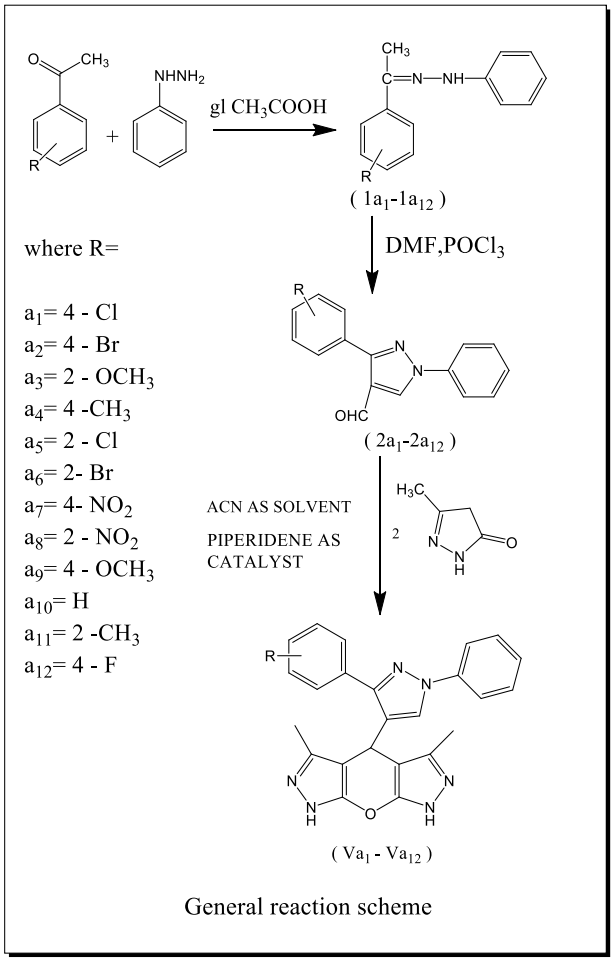
I. INTRODUCTION

In recent times diseases due to antimicrobial infection have been reported to increase considerably World-wide and one of the major caused for that is supressed immunity. So, it is important to synthesize new antimicrobial compounds. Most of heterocyclic compounds are well known due to their biological importance. Out of these pyran nucleus is fertile source of biological importance molecules. Possessing a wide spectrum of biological and pharmacological activities such as antimicrobial [1-3], antiviral[4], antitumor[5], cancer therapy[6]. Also when pyran molecules fused with pyrazole it is more biologically active and pyranopyrazole are also an important class of fused heterocyclic compounds that are known for their wide range of biological activities such as fungicidal [7-8], bactericidal[9] and also reported to exhibit enzyme inhibition[10]. Previously Wang shu-xiang and co-workers synthesized 1, 4-dihydropyrano[2,3-c]pyrazole by ultrasound irradiation,2005[11].Nilesh.j.thumar et.al synthesized 4-H pyrazolopyran and evaluate for antimicrobial activity,2009[12].Vijay P. Pagore and co-workers synthesized pyranopyrazoles derivatives by ammonium chlorides in water,2015[13].Younis M. Badawi and co-workers synthesized some new annulated pyranopyrazole derivatives and evaluated it herbicidal activity.2016[14].

Due to biological importance of pyranopyrazole derivatives our interest to synthesized new pyranopyrazole derivatives by knoevengel condensation of different carbaldehyde and 3-methyl pyrazole 5-one and take a piperidene as a catalyst and a carbaldehyde synthesized by reaction of different acetophenone with phenyl hydrazine and followed by vilsmier-hack reaction using DMF,$POCl_3$.

II. METHODS AND MATERIAL

All the melting points were determined in open capillary tubes and are uncorrected.IR spectral were recorded in solid state using KBr pellet method and recorded on Shimadzu-spectrophotometer and ^1H NMR spectral on broker advance 400 MHz spectrometer with DMSO as a solvent and TMS as internal standard. Mass spectra of synthesized compounds taken on GSMS-GP mass spectrometer. The physical data of synthesized compounds are given in table 1.



General reaction scheme

1. Preparation of 1-(1-4-chlorophenyl)ethylidene)2phenylhydrazine(1a1-12a1).

A mixture of 4-chloro acetophenone (3.09gm,0.02mol),phenylhydrazine(2.16gm,0.02mol), 2-3 drops of glacial acetic acid in 20 ml methanol was refluxed o ware bath for 3-4 hrs.at 65^{0}c.after reaction completion cooled the reaction mixture solid observed. Filter the solid and wash with methanol. Dry the solid and use for further reaction.

Yield% 68% M.P. 146^{0}C

Similarly various substituted phenyl hydrazine were synthesized using similar reaction procedure.

2. Preparation of 3-(4-chlorophenyl)-1-phenyl-1H pyrazole-4-carbaldehyde (2a1-2a12).

Vilsmier-hack reagent prepared from DMF (20ml) and $POCl_3$(1.2ml,0.024 mole)at 0^{o}c stir for 30 min.in this reagent add a lot wise small amount of 1-(1-4-chlorophenyl)ethylidene)2-phenyl hydrazine (2.44 gm,0.01 mole and stir the reaction mixture at 70-75^o c for 6-7 hrs. After completion of reaction cooled the reaction mass and poured into ice cold water. The solid separated on neutralization with $NaHCO_3$ was filtered and washed the solid with water and dry it. Use it for next reaction.

Yield% 58 M.P. 158^{0}C

Similarly various substituted pyrazolecarbaldehyde were synthesized using similar reaction procedure.

3. Preparation of 4-(3-(4-chlorophenyl)-1 phenyl-1H pyrazol-4-yl)3,5-dimethyl 4,7-dihydro 1H-pyrano[2,3-c;6,5-c']dipyrazole (va1-va12).

A mixture of 3-(4-chlorophenyl)-1-phenyl-1H pyrazole-4-carbaldehyde (2.83gm,0.01 mole) and 3-methyl 1H-pyrazole -5(4H)-one (1.96 gm,0.02 mole) and 20 ml acetonitrile as solvent and piperidine as a catalyst. Reflux the reaction mass for 6-7 hrs. After completion of reaction cool the reaction mass and poured into ice cold water and filter the solid with sodium bisulfite solution. Dry the solid. Check the MP and characterized it from various spectroscopic method.

Yield%64% M.P. 166^{0}c

Similarly various substituted pyranopyrazole synthesized using similar reaction proceed.

III. RESULT AND DISCUSSION

Spectral data of the synthesized compounds

4-(3-(4-chlorophenyl)-1 phenyl-1H pyrazol-4-yl)3,5-dimethyl 4,7-dihydro 1H-pyrano[2,3-c;6,5-c']dipyrazole Va_1

IR(KBr)3008,2970,3350,1150,660,3080,1450.1210,770,780,1360 cm^{-},^1H NMR δ ppm,1.85 (s,6H,CH_3*2) 7.26 to 8.74 (m,10H,Ar-H),4.5(s,CH)10.01 (NH) 400 MHz DMSO,MS (m/z)443 (M^+),409,77

4-(3-(4-bromophenyl)-1 phenyl-1H pyrazol-4-yl)3,5-dimethyl 4,7-dihydro 1H-pyrano[2,3-c;6,5-c']dipyrazole Va_2

IR(KBr)3020,2960,3345,580,3060,1480,1210,800,820,1320 cm^{-},^1H NMR δ ppm,1.6 (s,6H,CH_3*2) 7.24 to 7.89 (m,10H,Ar-H),4.93(s,CH)10.1 to 11.1 (NH) 400 MHz DMSO,MS (m/z)487 (M^+),429,77,340

4-(3-(2-methoxy phenyl)-1 phenyl-1H pyrazol-4-yl) 3, 5-dimethyl 4, 7-dihydro 1H-pyrano [2, 3-c; 6,5-c,] dipyrazole Va3

IR(KBr)3010,1490,1550,750,2980,1370,3380,1280,1080,750 cm^{-},^1H NMR δ ppm,1.5 to 1.7 (s,6H,CH3*2) 2.03 (s,OCH3) 7.06 to 7.87 (m,10H,Ar-H),4.82(s,CH)8.2 to 10.17 (NH) 400 MHz DMSO,MS (m/z)438 (M+),329,217,41,77

4-(3-(1-phenyl-3(o-tolyl)-1 phenyl-1H pyrazol-4-yl) 3,5-dimethyl 4,7-dihydro 1H-pyrano[2,3-c;6,5-c']dipyrazole Va_4

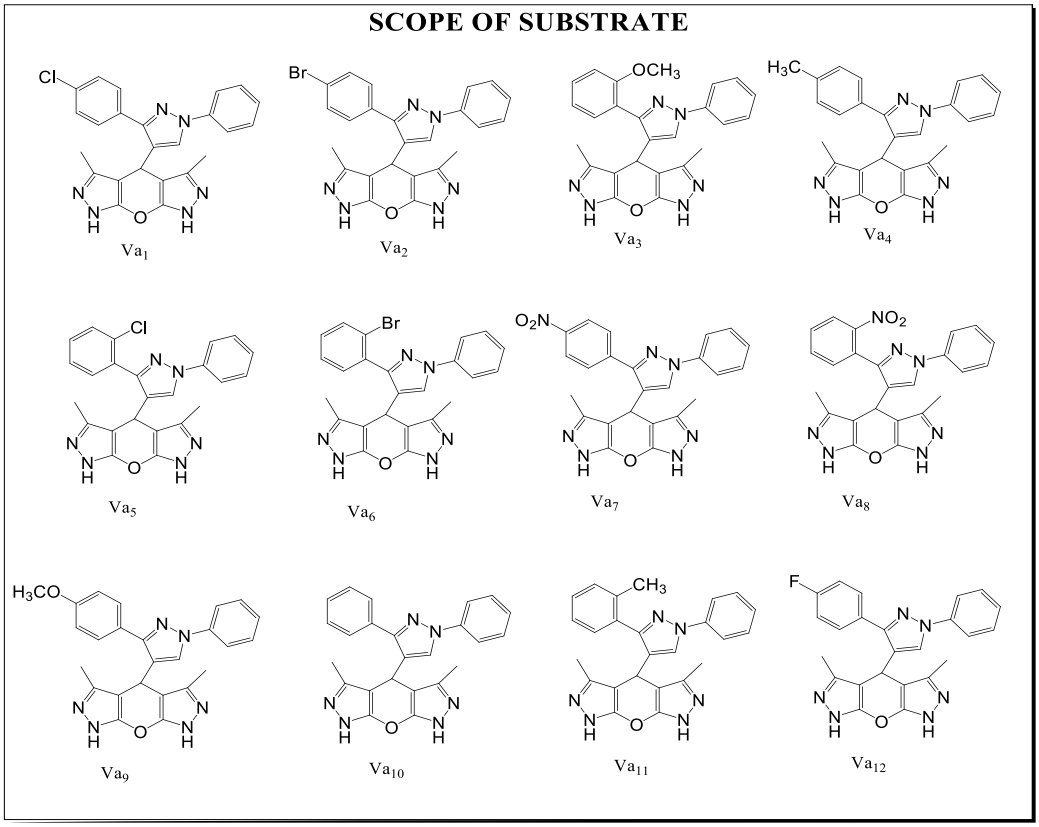
IR(KBr)3020,1530,1580,820,2960,1360,3345,1245,1090,672,720 cm^{-},^1H NMR δ ppm,1.89 (s,6H,CH_3*2) 2.35(s,Ar-CH_3) ,7.2 to 8.34 (m,10H,Ar-H),4.74(s,CH)10.01 to 11.19 (NH) 400 MHz DMSO,MS (m/z)422 (M^+),409,348,280,77,41

4-(3-(4-flurophenyl)-1 phenyl-1H pyrazol-4-yl) 3, 5-dimethyl 4,7-dihydro 1H-pyrano[2,3-c;6,5-c'] dipyrazole Va_{12}

IR(KBr)3006.2955,3305,665,1480,1283,764,3085,590 cm^{-},^1H NMR δ ppm,1.78(s,6H,CH_3*2) 7.2 to 7.8 (m,10H,Ar-H),4.74(s,CH) 9.5 to 11.1 (NH) 400 MHz DMSO,MS (m/z)426 (M^+),378,226,77

Table 1. Physical Data of Synthesized Compounds

Compound name	R=	MOLECULAR FORMULA	MP (C^0)	MOLECULAR WEIGHT	YIELD %
VA_1	4-Cl	$C_{24}H_{19}ClN_6O$	166	443	64
VA_2	4-Br	$C_{24}H_{19}BrN_6O$	175	487	59
VA_3	2-OCH_3	$C_{25}H_{22}N_6O_2$	159	438	67
VA_4	4-CH_3	$C_{25}H_{22}N_6O$	157	422	62
VA_5	2-Cl	$C_{24}H_{19}ClN_6O$	170	443	69
VA_6	2-Br	$C_{24}H_{19}BrN_6O$	182	487	54
VA_7	4-NO_2	$C_{24}H_{19}N_7O_3$	169	453	63
VA_8	2-NO_2	$C_{24}H_{19}N_7O_3$	172	453	67
VA_9	4-OCH_3	$C_{25}H_{22}N_6O_2$	162	438	65
VA_{10}	H	$C_{24}H_{20}N_6O$	154	408	68
VA_{11}	2-CH_3	$C_{25}H_{22}N_6O$	161	422	63
VA_{12}	4-F	$C_{24}H_{19}FN_6O$	156	426	60



Antimicrobial screening

The compounds va1-va12 were screened for their antibacterial against Escherichia coli, salmonella Typhosapara B, staphylococcus aureus, bacillus subtillis as well as antifungal activity against Aspergillusniger and candida albicans.In table no 2 showed antibacterial activity and antifungal activity of compounds va1-va12.

Table 2. Antimicrobial Activity Of Synthesized Compounds

Compound	Antibacterial Activity												Antifungal Activity					
	Gram Positive Bacteria						Gram Negative Bacteria						A.niger (µg/ml)			C.albicans (µg/ml)		
	S.aureus (µg/ml)			B.subtillis (µg/ml)			E.coli (µg/ml)			S.peratyphi B (µg/ml)								
	500	250	125	500	250	125	500	250	125	500	250	125	500	250	125	500	250	125
Va1	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Va2	+	-	-	+	-	-	+	-	-	+	+	-	+	+	-	+	+	-
Va3	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+
Va4	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-
Va5	+	+	-	+	+	-	+	-	-	+	-	-	+	+	-	+	-	-
Va6	+	+	-	+	+	-	+	+	-	+	-	-	+	-	-	+	+	-
Va7	+	+	-	+	-	-	+	-	-	+	-	-	+	+	-	+	+	-
Va8	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-
Va9	+	+	-	+	+	-	+	-	-	+	-	-	+	+	-	+	-	-
Va10	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+
Va11	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Va12	+	+	-	+	+	-	+	+	-	+	+	-	+	+	+	+	+	+
C. Floxacin	1.9			7.8			0.4			1.4								
fluconazole													0.7			0.4		

IV. CONCLUSION

The examination of the data of table 2 reveals that most of the compounds showed moderate antibacterial and antifungal activity as compared to standard drug ciprofloxacin and fluconazole. from the above data we says that $va_{1,}va_{3,}va_{4,}va_{8,}va_{10,}va_{11}$ active against gram positive bacteria s.aureus and B.subtillis till 125 ug/ml concentration and va_{11} is active against gram negative bacteria E.coli and s.peratyphin B at 125 (µg/ml) concentration.$va_{1,}va_{3,}va_{11,}va_{12}$ Active against aspergillums niger and candida albicans fungal at lower concentration.so from all data it is concluded that $va_{10,}$ va_{11} are active against all bacteria and fungal.

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