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Synthesis, Characterization and Antimicrobial Activity of Some New Dihydropyridine Derivatives

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Abstract Synthesis of 4-(3-(aryl)–1–phenyl-1*H*–pyrazol–4–yl)-3,5–dimethyl-1,4,7,8–tetrahydro dipyrazolo [3,4-b:4',3'-e] pyridine by the reaction of different substituted 3-(aryl)–1-phenyl-1*H*-pyrazole-4-carbaldehyde with 2 mole of 3-methyl-1*H*-pyrazol-5(4*H*)-one in presence of ammonium acetate and methanol as a solvent. 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 3-(aryl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde, 3-methyl-1*H*-pyrazol-5(4*H*)-one, ammonium acetate, methanol

1. Introduction

1,4-Dihydropyridine derivatives (1,4-DHPs) form a class of heterocyclic compounds with interesting pharmacological and biological properties [1]. It is well known that the 1,4-DHP nucleus serves as the scaffold of important cardiovascular drugs and it has been well established that the calcium modulator activity of this family of compounds is determined by structural requirements [2]. The systematic structural modification of the 1,4-DHP ring yields different compounds used in the treatment of hypertension and angina pectoris. The most prominent of these compounds is nifedipine, which was the first generation calcium channel blocker, marketed by Bossert, F. *et. al;* [3]. Since then, a wide variety of novel compounds belonging to the second and third generations of new biologically active substances from the 1,4-DHP class have been developed in order to obtain larger bioavailability or greater tissue selectivity. Felodipine, lercanidipine, And clinidipine are examples of newer DHP-calcium antagonists, which are effective antihypertensive compounds.so the pharmacological properties of 1,4-DHP have been extensively studied for several decades. The first synthesis of a dihydropyridine is attributed to Arthur Hantzsch for work done a century ago [4]. Interestingly, the product from the condensation of 2 mol of ethyl aceto acetate and 1 mol of aldehyde and 1 mol of ammonia was assigned the 2,3- dihydropyridine structure by Hantzsch.

Some of dihydropyridine compounds are characterized by longer bioactivity of greater tissue selectivity.1,4-dihydropyridine derivatives are associated with diverse biological activities like as Antiarrythemic [5], Antiinflammatory [6], Antiallergic [7], Antiulcer [8], Antitumor [9], Vasodilator [10], Enzymetic [11-12], Calcium channel antagonist [13-15], Antihypertensive [16], Antihypolipemic [17], Antimayocardic [18], Cardiovascular [19], Photo induced relaxation [20-21].

2. Experimental

All the chemicals and solvents are used of AR grade and without purification. 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 ^{1}H 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. All the reactions are monitored by TLC. The physical data of synthesized compounds are given in table 1.

2.1. Synthesis of int- 1

Take a mixture of 2-Methoxy acetophenone (0.02mol), phenylhydrazine (0.02mol), 2-3 drops of glacial acetic acid in 20 ml methanol was refluxed on water bath for 3-4 hrs at 65 ºC. After reaction completion cooled the reaction mixture solid observed. Filter the solid and wash with methanol. Dry the solid and use for further reaction. Similarly various substituted phenyl hydrazine were synthesized using similar reaction procedure.

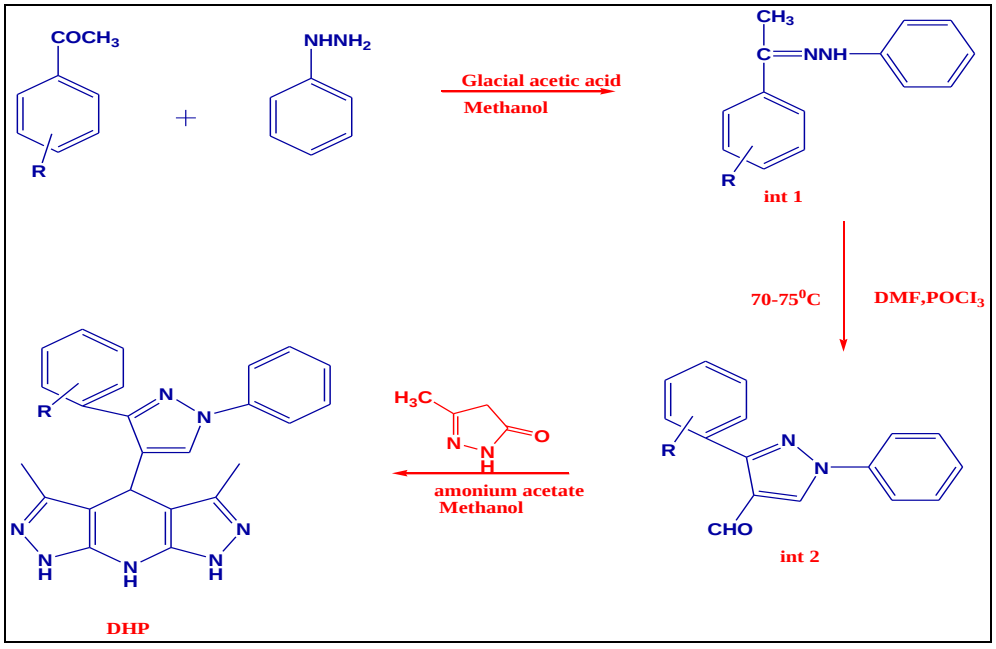
2.2. Synthesis of int- 2

First prepared Vilsmier-hack reagent from DMF (20ml) and $POCl_3$ (1.2ml, 0.024mole) at 0 ºC stir for 30 min. In this reagent add a lot wise small amount of 1-(1-2-Methoxyphenyl) ethylidene) 2-phenyl hydrazine (0.01mole) and stir the reaction mixture at 70-75o 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. Similarly various substituted pyrazole carbaldehyde were synthesized using similar reaction procedure.

2.3. Synthesis of 4-(3-(2-Methoxyphenyl)–1–phenyl-1H–pyrazol–4–yl)-3,5–dimethyl-1,4,7,8–tetrahydro dipyrazolo[3,4,–b: 4',3', -e] pyridine

Take a mixture of 3-(2-methoxyphenyl)-1-phenyl-1H pyrazole-4-carbaldehyde (2.77gm,0.01 mole) and 3-methyl 1H-pyrazole -5(4H)-one (1.97 gm,0.021 mole) and 20 ml methanol as solvent and ammonium acetatate. 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, wash with ice cold water. Dry the solid and recrystallised from ethanol. Check the MP and characterized it from various spectroscopic method. Yield 52%.

2.4. Reaction Scheme



3. Result and Discussion

All the synthesized compounds confirmed by spectroscopic techniques like IR, ^{1}H NMR and mass spectra.

3.1. Spectral Data of the Synthesized Compounds

4-(3-(2-Methoxyphenyl)–1–phenyl-1h–pyrazol–4–yl)-3,5–dimethyl-1,4,7,8–tetrahydrodipyrazolo[3,4,–*b*:4',3'-*e*] pyridine(Vb_{11})

M.P. 155°C; IR (KBR pallet) cm^{-1}, 2985 (C-H str.in Alkane), 3063 (C-H str.in Aromatic), 771 (o-substituted benzene), 1674 (C=N str. Pyrazole), 1234 (C-O-C linkage in ether), 3410 (NH str. In amine); 1H NMR (DMSO) in δ ppm; 6.93-8.20 (multiplet, 10H, Ar-H), 1.77-2.00 (singlet, 6H, 2-CH_3), 3.81 (singlet, 3H, OCH_3), 4.79 (singlet, 1H, CH), 10.16-11.29 (singlet, 3H, NH); MS (m/z): 437 (M^+); Element analysis Calculated: C (68.63%), H (5.30%), N (22.41%), Found: C (68.05%), H (5.06%), N (22.06%).

4-(3-(4-Chlorophenyl)–1–phenyl-1*H*–pyrazol–4–yl)-3,5–dimethyl-1,4,7,8–tetrahydrodipyrazolo[3,4,–*b*:4',3,'-*e*] pyridine (Vb_1)

M.P. 168°C; IR (KBR pallet) cm^{-1}, 2975 (C-H str.in Alkane), 3028 (C-H str.in Aromatic), 780 (*p*-substituted benzene), 1690 (C=N str. Pyrazole), 840 (C-Cl in str.), 3310 (NH str. In amine); ^{1}H NMR (DMSO) in δ ppm; 7.06-8.26 (multiplet, 10H, Ar-H), 2.2 (singlet, 6H, 2-CH_3), 4.79 (singlet, 1H, CH), 10.02-11.35 (singlet, 3H, NH); MS (m/z): 442 (M^+); Element analysis Calculated: C (65.23%), H (4.56%), N (22.19%), Found: C (64.29%), H (4.26%), N (21.56%).

Table 1: Physical constant of synthesized compounds

S. No.	R=	Molecular Formula	MP (°C)	Molecular Weight	Yield %
Vb_1	4-Cl	$C_{24}H_{20}ClN_7$	168	442	65
Vb_2	4-Br	$C_{24}H_{20}BrN_7$	195	486	58
Vb_3	2-OCH_3	$C_{25}H_{23}N_7O$	155	437	52
Vb_4	4-CH_3	$C_{25}H_{23}N_7$	142	421	62
Vb_5	2-Cl	$C_{24}H_{20}ClN_7$	159	442	56
Vb_6	2-Br	$C_{24}H_{20}BrN_7$	186	486	59
Vb_7	4-NO_2	$C_{24}H_{20}N_8O_2$	178	452	48
Vb_8	4-OCH_3	$C_{25}H_{23}N_7O$	158	437	61
Vb_9	2-NO_2	$C_{24}H_{20}N_8O_2$	165	452	45
Vb_{10}	H	$C_{24}H_{21}N_7$	148	407	55
Vb_{11}	2-CH_3	$C_{25}H_{23}N_7$	152	421	59

3.2 Antimicrobial activity synthesized compounds

All the compounds have been evaluated for their antibacterial activity against Gram Positive bacteria like *Staphylococcus aureus, Bacillus subtilis* and Gram Negative bacteria like *Escherichia coli, Salmonella para typhosa B* and they were also evaluated for antifungal activity against *Candida albicans and Aspergillus niger* at different concentrations: i.e. Primary screening at 2000 to 1000, Secondary screening at 1000 to 250 and tertiary screening at 250 to 15.62 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The antimicrobial activities of the synthesized compounds (Va_1-Va_{13}) have been compared with standard drugs. Their antimicrobial effect was determined in higher dilution using Agar Dilution Method (Approved by NCCLs).The MIC of synthesized compounds recorded in table-2.

Table-2 MIC of synthesized compounds

S. No.	Antibacterial Activity				Antifungal Activity	
	Gram Positives		Gram Negative			
	S. aureus (µg/ml	*B. subtilis (µg/ml)*	*E. coli (µg/ml)*	*S. peratyphi B (µg/ml*	*A. niger (µg/ml)*	*C. albicans (ug/ml)*
Vb_1	62.5	125	125	125	62.5	62.5
Vb_2	62.5	62.5	125	125	125	125
Vb_3	125	125	125	125	125	125
Vb_4	62.5	31.25	62.5	62.5	31.25	31.25
Vb_5	125	62.5	125	125	62.5	62.5
Vb_6	125	62.5	250	125	62.5	62.5
Vb_7	500	500	250	250	500	250
Vb_8	125	62.5	125	125	62.5	62.5
Vb_9	500	500	250	250	500	500
Vb_{10}	62.5	62.5	125	62.5	62.5	62.5
Vb_{11}	62.5	62.5	125	125	62.5	31.25
Reference drugs:	*S. aureus*	*B. subtilis*	*E. coli*	*S. peratyphi B*	*A. niger*	*C. albicans*
Ciprofloxacin	1.9	7.8	1.4	0.4	*	*
Fluconazole	*	*	*	*	0.7	0.4

4. Conclusion

From the activity data we have predicted that some of the synthesized compounds shows excellent activity as compared of standard drug. Out of all compounds some shows remarkable antibacterial and antifungal activity. So these compounds can be used as potent antimicrobial agent after further investigation.

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