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Synthesis, Characterization & Antimicrobial Activity of Some New Dihydropyridine Derivatives Derived From 3-Aryl-2-Isobutanoyl-N-Phenyl-Acrylamide

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ABSTRACT

1,4-Dihydropyridine is the significant subclass of pyridines, the best known heterocyclic compounds which are associated with good number of pharmacological activities. 1,4-Dihydropyridines whether symmetrical or asymmetrical are expected for their cardiovascular and other pharmacological properties. Some new 4-Aryl-2,6-diisopropyl-3,5-bis[N-phenyl-aminocarbonyl]-1,4-dihydropyridines.The Dihydropyridine derivatives of Type (1a-j) have been synthesized by the condensation of 3- Aryl-2-isobutanoyl-N-phenyl-acrylamide and 4-Methyl-3-oxo-N-phenyl-pentanamide and ammonia. All the prepared compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.

Key words : 3-Aryl-2-isobutanoyl-N-phenyl-acrylamide, Pyrazoles, Antimicrobial activities.

I. INTRODUCTION

The DHP nucleus is common to numerous bioactive compounds which passes various type of activity like vasodilator, antihypertensive, bronchodilator, antiatherosclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective and antidiabetic.[1-6] Many drug molecules bearing 1,4-dihydropyridine nucleus are specifically related with calcium channel antagonism[7] and antihypertensive.[8] Very wide range of literature regarding the structure, synthesis, stereochemistry and hydrogen transfer mechanism of dihydropyridine is available.[9-14].Typical examples of which are nifedipine, verapamil and diltiazem respectively[15,16] .

This inspired us to synthesize 4-Aryl-2,6-diisopropyl-3,5-bis[N-phenyl-aminocarbonyl]-1,4-dihydropyridines. The DHP derivatives of Type **(1a-j)**. The structure of synthesized compounds were assigned based on Elemental analysis , I.R. ^{1}H-NMR and Mass spectral data. The antimicrobial activity was assayed by using the cup-plate agar diffusion method [17] by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities[18] against varieties of bacterial strains and fungi at 40 µg concentration. Standard drugs like Amoxicillin, Benzoylpenicillin, Ciprofloxacin, Erythromycin and Griseofulvin were used for comparison purpose (Table-1).

II. RESULTS AND DISCUSSION

4-Aryl-2,6-diisopropyl-3,5-bis[N-phenyl-aminocarbonyl]-1,4-dihydropyridines.The Dihydropyridine derivatives of Type **(1a-j)** have been synthesized by the condensation of 3- Aryl-2-isobutanoyl-N-phenyl-acrylamide and 4-Methyl-3-oxo-N-phenyl-pentanamide and ammonia. The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR ,^{1} H-NMR , and mass spectral data.

III. ANTIBACTERIAL ACTIVITY

It has been observed from the microbiological data that all compounds **(1a-j)**, were found to be mild to moderately active against Gram positive and Gram negative bacterial strains and fungi. All the compounds were found to possess moderate to good activity against Gram positive and Gram negative strains.

IV. EXPERIMENTAL SECTION

Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm^{-1}) were recorded on Shimadzu-435-IR Spectrophotometer and , ^{1}H-NMR spectra on Bruker spectrometer(300MHz) using TMS as an internal standard, chemical shift in δ ppm.

General procedure for the preparation of (A) 4-Methyl-3-oxo-N-phenyl-pentanamide :

Take the mixture of Methyl-4-methyl-3-oxo-pentanoate (1.44 gm, 0.01 mol) and aniline (0.93 gm, 0.01 mol) in toluene, containing few drops of ethylene diamine. The solution was refluxed for 12 hrs. collect methanol using dean & stark. The resulting reaction mass was washed with dilute HCl and finaly with water. Separated toluene was layer was distilled out under vacuum. Yield 71%, m. p. 32oC, Anal.Calcd. for $C_{12}H_{15}NO_2$ Calcd: C, 70.22; H, 7.37; N, 6.82%, Found: C, 70.71; H, 7.36; N, 6.81%.

General procedure for the preparation of (B) 3- Aryl-2-isobutanoyl-N-phenyl-acrylamide :

The mixture of toluene, 4-Methyl-3-oxo-N-phenyl-pentanamide(2.05 gm, 0.01mol), benzaldehyde (1.06 gm, 0.01 mol), morpholine and acetic acid was heated to the reflux temperature for 14-16 hrs. Water was removed from the reaction mixture by Dean and Stark. The mixture was cooled at room temperature. Washed the reaction mass with sodiumbisulphite solution and finally washed with distilled water. Distilled out solvent and collect the product, purified in hexane. Yield 80%, MP. 144oC, Anal. Calcd. for $C_{19}H_{18}NO_2$ Calcd: C, 77.79; H, 6.53; N, 4.77%, Found: C, 77.07; H, 6.11; N, 4.09%.

General procedure for the preparation of 4-Aryl-2,6-diisopropyl-3,5-bis[N-phenyl-aminocarbonyl]-1,4-dihydropyridine (1a-l) :

To a mixture of 2-Isobutanoyl-3-phenyl-N-phenyl-acrylamide(2.93gm 0.01mol) and 4-Methyl-3-oxo-N-phenylpentanamide (2.05gm, 0.01mol) in methanol, add liq. ammonia and reflux on water bath for 12 hrs. Cool the reaction mixture at room temperature and stand by for a day. The resulting solid mass was filtered and washed with methanol. The product was recrystalized into DMF and methanol. Yield 56% m.p. 210-212oC Anal.Calcd. for $C_{31}H_{33}N_3O_2$ Calcd: C, 77.63; H, 6.94; N, 8.76 %, Found: C, 77.56; H, 6.88; N, 8.70%. Similarly, other 4-Aryl-2,6-diisopropyl-3,5-bis[N-phenyl-aminocarbonyl]-1,4-dihydropyridines were prepared. The physical data are recorded in Table No.1

4-Aryl-2,6-diisopropyl-3,5-bis[N-phenyl-aminocarbonyl]-1,4-dihydropyridine :

Yield 56%, m.p. 210-212^{o}C; IR(KBr) : ν 2951,1435 (Alkane,-CH_3), 1384(–C(CH_3)$_2$), 3068 (Ar, =C-H Str.) , 1606 (C=C str.) , 1172 (Aromatic, C-H i.p.), 1579 pyridine (C=Cstr.) 1295 (C-N Str.),) 3428 (N-H str.) , Carboxamide 1685 (C=O), 3256 (N-H str.)cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 1.20-1.26 (dd, 6H, -CH-(CH_3)$_2$, 3.50-3.58 (m, 1H-(CH_3)$_2$-CH) , 5.49 (s,1H, pyrz-H), 7.16-7.58, (overlapped, 15H, Ar-H) , 7.65 (s, 1H, N-H). , 8.72 (s, 2H, N-H) Mass m/z 479 . M.F.: $C_{31}H_{33}N_3O_2$.

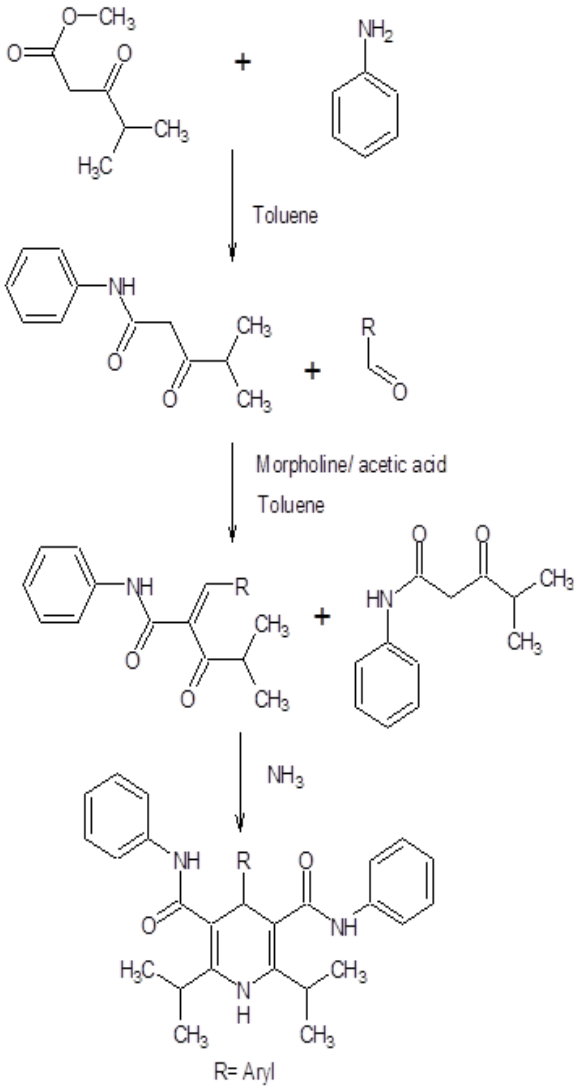
Table 1

Characterization data of the compounds (1a-l) :						
compd no.	R	Molecular formula	Mole.Wt.	M.P. (^{0}C)	Nitrogen %	
					Calcd	Found
1a	-C_6H_5	$C_{31}H_{33}N_3O_2$	479	210	8.76	8.70
1b	-4-Cl-C_6H_4	$C_{31}H_{32}N_3O_2Cl$	514	249	8.17	8.20
1c	-2-Cl-C_6H_4	$C_{31}H_{32}N_3O_2Cl$	514	256	8.17	8.16
1d	-2-Cl-C_6H_4	$C_{31}H_{32}N_3O_2Cl$	514	239	8.44	8.41
1e	-2-OH- C_6H_4	$C_{31}H_{33}N_3O_3$	495	258	7.99	7.95
1f	-2-OH- C_6H_4	$C_{31}H_{33}N_3O_3$	495	235	8.48	8.46
1g	-4-CH_3- C_6H_4	$C_{32}H_{35}N_3O_2$	493	223	8.51	8.47
1h	-4- OCH_3- C_6H_4	$C_{31}H_{33}N_3O_3$	509	229	8.25	8.24
1j	-4-NO_2- C_6H_4	$C_{31}H_{32}N_4O_4$	524	244	10.68	10.62
1k	-3-NO_2- C_6H_4	$C_{31}H_{32}N_4O_4$	524	253	10.68	10.59

Table 2

compd no.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	S.aureus	B.subtillis	Aero genes	P. aeruginosa	A.niger
1a	15	12	17	18	17
1b	14	13	15	17	19
1c	13	10	16	21	18
1d	17	24	15	14	16
1e	11	9	12	10	16
1f	12	8	10	13	17
1g	14	12	17	18	25
1h	18	14	23	13	17
1i	14	15	15	15	18
1j	25	16	18	18	17
Amoxicillin	25	25	20	22	0
Benzyl penicillin	18	19	21	21	0
Ciprofloxacin	20	15	22	16	0
Griseofulvin	0	0	0	0	26

Scheme 1



V. CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds. Which show significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

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