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SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYL- 3-CYANO-4-[4'-(p-METHYLBENZYLOXY)-3'- METHOXYPHENYL]-2-OXO-1,2-DIHYDROPYRIDINES.

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ABSTRACT

Some new of 6-Aryl-3-cyano-4-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-2-oxo-1,2-dihydropyridines (2a-l) have been prepared by the condensation of chalcones of 1-Aryl-3-[4'-(p-methylbenzyloxy)-3'-methoxyphnyl]prop-2-en-1-ones (1a-l) with ethylcyanoacetate in presence of ammonium acetate. All the prepared Cyanopyridine derivatives compounds were characterized by their spectral (I.R., N.M.R., Mass) data and screened for their antimicrobial activities.

KEYWORDS: Chalcone, Cyanopyridine derivatives, Antimicrobial Activities.

INTRODUCTION

Pyridine is the parent of the series of compounds that is important in Pharmaceutical, agriculture and industrial chemistry. Among a wide range of pyridines, 3-cyanopyridines acquired special attention due to their wide range of therapeutic activities. Most derivatives are prepared by manipulation of pyridine and its simple homologues in a manner similar to chemistry of the benzenoid chemistry.

This inspired us to synthesize 6-Aryl-3-cyano-4-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl] -2-oxo-1,2-dihydropyridines (2a-l) have been prepared by the condensation of chalcones of 1-Aryl-3-[4'-(p-methylbenzyloxy)-3'-methoxyphnyl]prop-2-en-1-ones (1a-l) with ethylcyanoacetate in presence of ammonium acetate. Pyridone derivatives have been found to possess variety of therapeutic activities, like antiviral[1], antimicrobial[2], angiotensin II

antagonist[3-4], anticancer[5], antiHIV[6], pesticidal[7-8], herbicidal.[9] Much research has been carried out with an aim to finding therapeutic values of pyridine skeleton since their discovery. The pyridine derivatives are reported to exhibit a wide variety of biological activities.

Antiepileptic[10], antifungal[11], anticonvulsant[12], antibacterial[13], antisoriasis[14], analgesic[15] insecticidal[16], antihypertensive.[17]

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[18] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities[19] against varieties of bacterial strains such Staphylococcus aureus, *Bacillus subtillis*, *Escherichia coli*, Proteus vulgaris and fungi *Aspergillus niger* at 40 µg concentration. Standard drugs like Ampicillin, Amoxicillin, Norfloxacin, Benzyl penicillin and Griseofulvin were used for comparison purpose (Table-1).

RESULTS AND DISCUSSION

The synthesis of 6-Aryl-3-cyano-4-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-2-oxo-1,2-dihydropyridines (2a-l) have been prepared by the condensation of chalcones of 1-Aryl-3-[4'-(p-methylbenzyloxy)-3'-methoxyphnyl]prop-2-en-1-ones (1a-l) with ethylcyanoacetate in presence of ammonium acetate.

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.

ANTIBACTERIAL ACTIVITY

It has been observed from the microbiological data that all compounds (1a-l) and (2a-l) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains.

ANTIFUNGAL ACTIVITY

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds against A. niger. The antibacterial activity was compared with standard drug viz. and antifungal activity was compared with standard drug viz. Griseofulvin.

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 1-Aryl-3-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-propenones (1a-l).

Take a mixture of 4-[(p-methylbenzyl)oxy]-3-methoxy benzaldehyde (1) (0.01M) and 4-methoxy aceto phenone (0.01) in methanol, add a NaOH (0.002M) to the reaction mixture. The reaction mixture was magnetically stirred for 12 hrs and then left overnight. After it was pour over ice and neutralised with dil. HCl and ethanol is added for crystallisation.

1-Aryl-3-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-propenones (1a-l).

Yield 76%, m.p. 112^{0}C; IR(KBr): ν 2968,2841,1456 (Alkane,-CH_3), 1255 (-OCH_3), 1255 (Ar-O-C), 1663 (C=O), 1591 str. (C=C), 3064,1511,1133,806 (Aromatic), cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.84, (s,6H,-OCH_3), 7.00 & 7.20 (d,2H,-CH=CH-), 5.08(s,2H,-O-CH_2-), 6.96-8.05(m,11H, ArH), .Mass m/z 388 .M.F.:$C_{25}H_{24}O_4$.

General procedure for the preparation of 6-Aryl-3-cyano-4-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-2-oxo-1,2-dihydropyridines (2a-l).

3-[4'-(p-Methylbenzyloxy)-3'-methoxyphenyl]-1-(p-methylphenyl)-prop-2-en-1-one (4.08g 0.01mol) was dissolved in ethanol (50 ml). Then ethylcyanoacetate (1.13g. 0.01mol) and ammonium acetate (1.54g. 0.02 mol) were added to it. The mixture was then heated with reflux for 8 hrs. The product separated was filtered and recrystallized from methanol. Yield 71%, m.p.75^{o}C; Anal. Calcd. for $C_{28}H_{24}N_2O_3$: C, 77.06%; H, 5.50; N, 6.41%; Found: C, 77.02; H, 5.47; N, 6.37%. Similarly, other 6-Aryl-3-cyano-4-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-2-oxo pyridines were prepared. The physical data are recorded in Table No.1.

6-Aryl-3-cyano-4-[4'-(p-methylbenzyloxy)-3'-methoxyphenyl]-2-oxo-1,2-dihydropyridines (2a-l)

Yield 71%, m.p. 75 ^{0}C; IR(KBr) : ν 2970,1446 (Alkane,-CH_3), 1253 (-OCH_3), 1253 (Ar-O-C), 2279 (-CN), 3031,1489,1128 (Aromatic), 3429 NH str., 1625 NH def.1728 C=O str. cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 2.31,2.38 (s,6H,-CH_3), 5.14 (s,2H,-O-CH_2-), 6.80-7.81 (m,13H, ArH), 3.85 (s,3H,-OCH_3) .Mass m/z 436. M.F.$C_{28}H_{24}N_2O_3$.

Table 1.

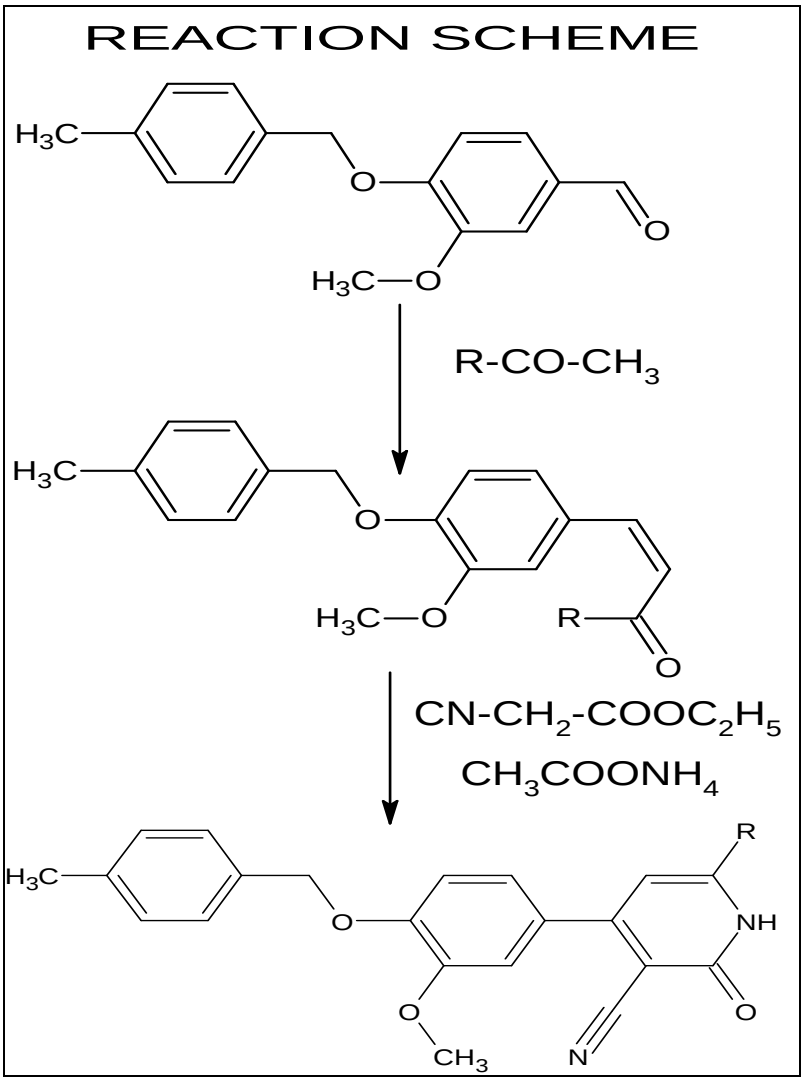
Characterization data of the compounds (1a-l) and (2a-l)						
Compd no.	R	Molecular formula	Mole.Wt.	M.P. (^{0}C)	Nitrogen %	
					Found	Calcd
1a	-C_6H_5	$C_{24}H_{22}O_3$	358	122	-	-
1b	-4-NH_2-C_6H_4	$C_{24}H_{23}NO_3$	373	170	3.75	3.51
1c	-4-Br-C_6H_4	$C_{24}H_{21}BrO_3$	437	112	-	-
1d	-4-Cl-C_6H_4	$C_{24}H_{21}ClO_3$	392.5	108	-	-
1e	-2,4-(Cl_2)- C_6H_3	$C_{24}H_{20}Cl_2O_3$	427	140	-	-
1f	-2-OH- C_6H_4	$C_{24}H_{22}O_4$	374	73	-	-
1g	-3-OH- C_6H_4	$C_{24}H_{22}O_4$	374	78	-	-
1h	-4-OH- C_6H_4	$C_{24}H_{22}O_4$	374	72	-	-
1i	-4-OCH_3- C_6H_4	$C_{25}H_{24}O_4$	388	112	-	-
1j	-4-CH_3- C_6H_4	$C_{25}H_{24}O_3$	372	134	-	-
1k	-3-NO_2- C_6H_4	$C_{24}H_{21}NO_5$	403	92	3.47	3.51
1l	-4-NO_2- C_6H_4	$C_{24}H_{21}NO_5$	403	148	3.47	3.32
2a	-C_6H_5	$C_{27}H_{22}N_2O_3$	422	135	6.63	6.58
2b	-4-NH_2-C_6H_4	$C_{27}H_{23}N_3O_3$	437	158	9.61	9.54
2c	-4-Br-C_6H_4	$C_{27}H_{21}BrN_2O_3$	501	125	5.58	5.55
2d	-4-Cl-C_6H_4	$C_{27}H_{21}ClN_2O_3$	457	122	6.12	6.10
2e	-2,4-(Cl_2)- C_6H_3	$C_{27}H_{20}Cl_2N_2O_3$	491	115	5.70	5.68
2f	-2-OH- C_6H_4	$C_{27}H_{22}N_2O_4$	438	98	6.39	6.35
2g	-3-OH- C_6H_4	$C_{27}H_{22}N_2O_4$	438	72	6.39	6.34
2h	-4-OH- C_6H_4	$C_{27}H_{22}N_2O_4$	438	75	6.39	6.36
2i	-4-OCH_3- C_6H_4	$C_{28}H_{24}N_2O_4$	452	95	6.18	6.01
2j	-4-CH_3- C_6H_4	$C_{28}H_{24}N_2O_3$	436	75	6.41	6.37
2k	-3-NO_2- C_6H_4	$C_{27}H_{21}N_3O_5$	467	110	8.99	8.93
2l	-4-NO_2- C_6H_4	$C_{27}H_{21}N_3O_5$	467	158	8.99	8.93

Table 2.

compd no.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	S.aureus	B.subtillis	E.coli	P.vulgaris	A.niger
1a	10	17	17	15	16
1b	18	14	15	18	15
1c	20	15	15	16	14
1d	16	17	18	13	13
1e	14	10	19	18	20
1f	15	12	13	17	15
1g	18	16	16	15	17
1h	19	18	15	16	18
1i	12	16	19	19	18
1j	13	19	16	15	16
1k	18	15	15	14	17
1l	12	17	17	11	19

2a	11	26	16	13	17
2b	16	16	17	17	14
2c	21	17	14	18	16
2d	18	19	20	16	17
2e	16	13	22	20	20
2f	14	14	20	19	16
2g	17	15	19	18	18
2h	20	20	18	19	20
2i	13	20	23	22	21
2j	13	21	20	20	19
2k	19	17	17	18	18
2l	15	19	18	17	17
Ampicillin	22	20	21	24	0
Amoxicillin	20	23	22	21	0
Norfloxacin	19	20	23	22	0
Benzyl penicillin	21	21	19	18	0
Griseofulvin	0	0	0	0	25

Scheme-1



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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