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Synthesis and Biological evaluation of Some novel Cyanopyridine derivatives of Vanillin analogue.

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ABSTRACT

Some new 6-Aryl-4-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-3-cyano-2- methoxy pyridine derivatives were prepared. All the prepared compounds were characterized by their spectral (I.R., N. M. R., Mass) data and screened for their antimicrobial activities.

Key words : Chalcones & Cyanopyridine derivatives, Antimicrobial activities.

INTRODUCTION

Cyanopyridine derivatives have attracted considerable attention in view of their great therapeutic importance such as anticonvulsant, antiHIV, antiepileptic and antihypertensive agents. In order to develop more therapeutically active compounds, it was considered of interest to synthesize some new cyanopyridine derivatives.

Pyridine derivatives have been found to possess variety of therapeutic activities such as antimicrobial[1], angiotensin II antagonist[2-3], antiviral[4] , antiHIV[5], anticancer[6], antifungal[7], antiepileptic[8], antibacterial[9], analgesic[10], antisoriasis[11] and antihypertensive[12].

Therapeutically importance of Cyanopyridine derivative is used considerable interest to synthesize cyanopyridine derivative like 6-Aryl-4-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-3-cyano-2-methoxy pyridine derivatives of type (2a-l) have been prepared by the cyclocondensation of 1-Aryl-3-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-propenones of type (1a-l) with malononitrile in presence of sodium methoxide.

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 [13] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities[14] 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-2).

Results and Discussion:

The synthesis of 1-Aryl-3-[4'-(o- chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l) and 6-Aryl-4-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-3-cyano-2-methoxy pyridine derivatives (2a-l) was carried out in two steps, first by the condensation of 4-[(2-chlorobenzyl)oxy]-3-methoxy benzaldehyde (1) with different aromatic acetophenone by Claisen-Schmidt condensation in presence base catalyst to give chalcone derivatives (1a-l), which in next step were refluxed with malononitrile and sodium methoxide to yield cyanopyridine derivatives (2a-l). (scheme-1).

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

The screening data indicated that among methoxy cyanopyridine derivatives, tested compounds **2a, 2e, 2f** and **2k** showed greater degree of antibacterial activity against *S.aureus.* However, the compounds **2a, 2d, 2e** and **2k** possess very good activity against *B.subtilis.* The compounds **2a, 2d, 2g** and **2j** significant activity against *E.coli.* However, the compounds **2a, 2f, 2h** and **2i** exhibited moderate to excellent activity against *P.vulgaris*. All the compounds were found to possess moderate to good activity against Gram positive and Gram negative strains.

ANTIFUNGAL ACTIVITY

The screening data indicated that among methoxy cyanopyridine derivatives, tested compounds **2d, 2f, 2g** and **2j** showed greater degree of antifungal activity against *A.niger*. All other compounds exhibit mild to moderate antifungal activity against *A.niger*. The antibacterial activity was compared with standard drug viz. Ampicillin, Amoxicillin, Norfloxacin, Penicillin 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'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l) :

Take a mixture of 4-[(2-chlorobenzyl)oxy]-3-methoxy benzaldehyde (1) (0.01M) and 4-methoxy acetophenone (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 neutralized with dil.HCl and ethanol is added for crystallization.

1-Aryl-3-[4'-(o-chlorobenzyloxy)-3'-methoxyphenyl]-propenones (1a-l) :

Yield 78%, m. p. 70^0 C; IR(KBr) : ν 2951,2874,1466 (Alkane,-CH_3), 1260 (-OCH_3) ,640 (-C-Cl); 1235 (Ar-O-C) , 1672 (C=O) , 1583 (C=C) ,3061,1506,1163,818 (Aromatic) ,cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.88, (s,6H,-OCH_3) , 6.86 & 7.73 (d,2H,-CH=CH-), 5.15(s,2H,-O-CH_2-) ,6.96-8.03(m,11H, Ar-H) , .Mass m/z 408.5 .M.F.:$C_{24}H_{21}O_4Cl$.

General procedure for the preparation of 6-Aryl-4-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-3-cyano-2-methoxy pyridine (2a-l):

To a solution of 1-(p-Methoxyphenyl)-3-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-propenone (4.08g, 0.01M) and malononitrile (0.75ml, 0.012M) in methanol (40ml) add sodium methoxide (1.08g, 0.02M) was added. The content was heated under reflux with stirring for 13 hr. The reaction mixture was converted to orange syrup type suspension, cooled to ambient temperature and solid precipitated out was filtered and residue was crystallized from ethanol. Yield 71%, m.p. 188^0 C, $C_{28}H_{23}ClN_2O_4$.

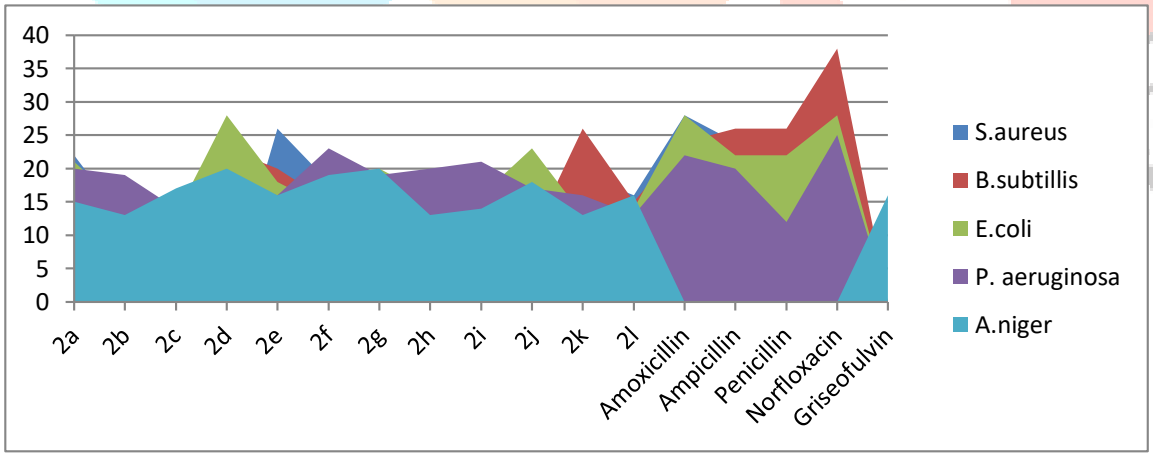
6-Aryl-4-[4'-(o-chlorobenzyloxy)-3'-methoxy-phenyl]-3-cyano-2-methoxy pyridine:

Yield 71 %, m. p. 188^o C; IR (KBr) : ν 2951.46, 1441.19 (Alkane,-CH_3), 1246.59 (-OCH_3) ,750.08 (-C-Cl); 1213.82 (Ar-O-C) , 2217.29 (C=N), 1607.59 (C=C str.), 1542.92 (C=N str.), 3005.3, 1512.47, 1131.89, 825.08 (Aromatic) cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 5.24 (s, 2H,-O-CH_2-) ,6.89-8.00 (m,12H, Ar-H), 3.89 & 3.92 (s,6H,-OCH_3), 4.10 (s, 3H,-OCH_3). Mass m/z **486.5**. M.F.: **$C_{28}H_{23}ClN_2O_4$**.

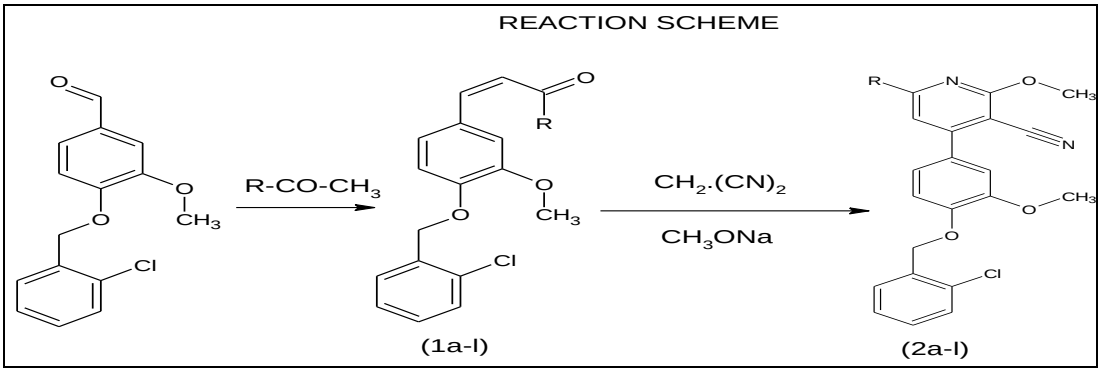
Table-1

compd. no.	R	Molecular formula	Molecular weight	M.P. ^0C	% yield	% of N calc.	found.
2a	-C_6H_5	$C_{27}H_{21}ClN_2O_3$	456.5	130	55	6.13	6.09
2b	-4-NH_2-C_6H_4	$C_{27}H_{22}ClN_3O_3$	471.5	96	59	8.91	8.86
2c	-4-Br-C_6H_4	$C_{27}H_{20}BrClN_2O_3$	535.5	170	67	5.23	5.20
2d	-4-Cl-C_6H_4	$C_{27}H_{20}Cl_2N_2O_3$	491.0	140	60	5.70	5.68
2e	-2,4-(Cl_2)- C_6H_3	$C_{27}H_{19}Cl_3N_2O_3$	525.5	166	66	5.33	5.30
2f	-2-OH- C_6H_4	$C_{27}H_{21}ClN_2O_4$	472.5	83	56	5.93	5.90
2g	-3-OH- C_6H_4	$C_{27}H_{21}ClN_2O_4$	472.5	102	61	5.93	5.91
2h	-4-OH- C_6H_4	$C_{27}H_{21}ClN_2O_4$	472.5	85	66	5.93	5.89
2i	-4-OCH_3- C_6H_4	$C_{28}H_{23}ClN_2O_4$	486.5	188	71	5.76	5.80
2j	-4-CH_3- C_6H_4	$C_{28}H_{23}ClN_2O_3$	470.5	122	72	5.95	5.91
2k	-3-NO_2- C_6H_4	$C_{27}H_{20}ClN_3O_5$	501.5	152	62	8.37	8.33
2l	-4-NO_2- C_6H_4	$C_{27}H_{20}ClN_3O_5$	501.5	160	63	8.37	8.34

Table-2



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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