Synthesis, Characterization and antimicrobial activity of Cyanopyridine derivatives with Vanillin.

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Abstract:

Cyanopyridines play a vital role owing to their range of biological and physiological activities. In the light of these biological activities and variety of industrial applications, some new of 6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-methoxy-3-cyanopyridines (1a-l) & 6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-ethoxy-3-cyanopyridine (2a-l) have been prepared, by the cyclocondensation of 1-Aryl-3-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-propenones type (I) with malononitrile in presence of Sodiummethoxide & Sodiumethoxide. All the prepared compounds were characterized by their spectral (I.R., N.M.R. ,Mass) data and screened for their antimicrobial activities.

Key words : Chalcone, cyanopyridine, antimicrobial activities.

INTRODUCTION

Cyanopyridine derivatives[1] have attracted considerable attention in view of their great therapeutic importance as anticonvulsant [2], antifungal [3], antibacterial [4], herbicidal[5] . antihypertensive[6], antiepileptic[7], antitubercular[8], analgesic[9] , insecticidal[10-11], antisoriasis[12] , antiallergic[13], antiinflamatory[14], properties. The synthesis of cyanopyridines are of current interest owing to their enormous occurrence in biologically active derivatives. Hence, considerable attention has been focused on the study of efficient and pharmaceutical important cyanopyridines bearing benzimidazole nucleus. 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[15] acquired a 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. However the simple pyridine compounds are prepared by the cyclization of aliphatic raw materials. The pyridine nucleus is found in a large number of commonly used drugs which have diverse pharmacological activities. Interests in the synthesis of multicyclic pyridine containing compounds have increased in recent years because of their biological and pharmacological activities. In our continuation work in the chemistry of pyridine nucleus, This inspired us to synthesize 6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-methoxy-3-cyanopyridines (1a-l) & 6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-ethoxy-3-cyanopyridine (2a-l) .

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 [16] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities[17] 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-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-methoxy-3-cyanopyridines (1a-l) & 6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-ethoxy-3-cyanopyridine (2a-l) was prepared by the cyclocondensation of 1-Aryl-3-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-propenones of type (I) with malononitrile in presence of sodiummethoxide & sodiumethoxide respectively. (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

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. How ever the maximum activity was observed in compounds (1a),(1h),(2a),(2j) against S.aureus. The significant activity was observed in compounds (1e),(1h),(2h),(2i) against B.subtillis. The maximum activity was displayed by the compounds (1d),(1j),(2c),(2f), against E.coli. The compounds (1c),(1g),(2a), and (2e) were comparatively more effective against P.vulgaris.

ANTIFUNGAL ACTIVITY

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds (1a),(1c),(1e),(2b),(2g),(2h), against **A.niger.**

The antibacterial activity was compared with standard drug viz. Ampicillin, Amoxicillin, Norfloxacin, Benzyl 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'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-propenones (Type-I) :

Take a mixture of 4-[(4-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 neutralised with dil.HCl and ethanol is added for crystallisation.

4-[(4-chlorobenzyl)oxy]-3-methoxy benzaldehyde:

Yield 90%, M.P. 58 ^{0}C; IR(KBr) : ν 2922 (-CHO), 1260 (-OCH_3) ,640 (-C-Cl); 1235 (Ar-O-C) cm^{-1}, ^{1}H-NMR ($CDCl_3$) : δ 9.86 (s,1H,-CHO) , 5.15(s,2H,-O-CH_2-) 6.96-8.03(m,7H, Ar-H) 3.94 (s,3H,-OCH_3) .Mass m/z 276 . M.F.:$C_{15}H_{13}O_3Cl$

1-Aryl-3-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-propenones (Type-l) :

Yield 72%, 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'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-methoxy-3-cyanopyridines (1a-l) :

Take the 1-(p-Methoxyphenyl)-3-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-propenone (4.08g, 0.01M), malononitrile (0.75ml ,0.012M) in methanol (40ml) add Sodiummethoxide (1.08g, 0.02M). The content was heated under reflux with stirring for 12 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 85%, M.P. 175^0 C, M.F.C_{28} $H_{23}ClN_2O_4$; Similarly, other 6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-methoxy-3-cyanopyridines were prepared.

6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-methoxy-3-cyanopyridines (1a-l) :

Yield 85%, M.P. 175^{0}C; IR(KBr) : ν 2950,2874,1455 (Alkane,-CH_3), 1260 (-OCH_3) ,793.9 (-C-Cl); 1221.8 (Ar-O-C) , 2218 (C=N) , 1546.9 (C=C) ,3082,1513,1132,823.8 (Aromatic) ,cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.88, (s,6H,-OCH_3) , 6.86 & 7.73 (d,2H,-CH=CH-), 5.18(s,2H,-O-CH_2-) ,6.95-8.07(m,12H, Ar-H) , .Mass m/z 486.13 .M.F.: C_{28} $H_{23}ClN_2O_4$. .

General procedure for the preparation of 6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-ethoxy-3-cyanopyridine (2a-l):

Take the 1-(4-Methoxyphenyl)-3-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-propenone (4.08g, 0.01M), malononitrile (0.75ml, 0.012M) in methanol (40ml) add Sodiumethoxide (1.36g, 0.02M). The content was heated under reflux with stirring for 12 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 55%, M.P. 150^0 C, M.F. C_{29} $H_{25}ClN_2O_4$; Similarly, other 6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-ethoxy-3-cyanopyridines were prepared.

6-Aryl-4-[4'-(p-chlorobenzyloxy)-3'-methoxyphenyl]-2-ethoxy-3-cyanopyridine (2a-l):

Yield 55%, M.P. 150 ^{0}C; IR(KBr) : ν 2960.95,2868.4,1455.75 (Alkane,-CH_3), 1258.47 (-OCH_3) ,773.27 (-C-Cl); 1242 (Ar-O-C) , 1545.14 (C=N) , 3084.85,1492,1138.85,809.93 (Aromatic), 1574.92 (-C=C,pyridine), cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ ppm 1.52, (t,3H,-CH_2-CH3) , 5.51 (dd,1H,-CH-,pyr), 5.18 (s,2H,-O-CH_2-) ,6.95-8.05 (m,12H, Ar-H) , 3.87 & 3.97 (s,6H,-OCH_3), 4.64 (q,2H,-CH2CH_3) .Mass m/z 500.5 . M.F.:$C_{26}H_{25}N_2O_4Cl$.

Table-1

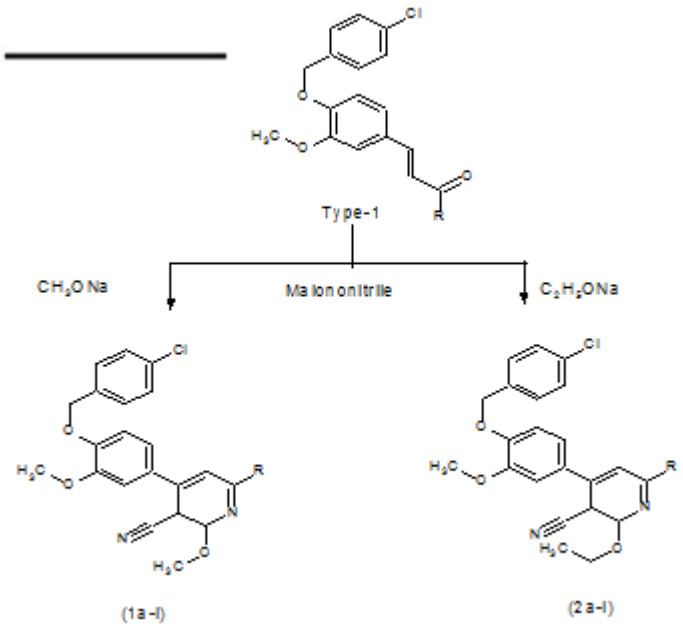
Characterization data of the compounds 1a-l and 2a-l

compd. no.	R	Molecular formula	Mole. Wt.	M.P. (^{0}C)	Nitrogen %	
					Calcd.	Found
1a	-C_6H_5	$C_{27}H_{21}ClN_2O_3$	456.5	170	6.13	6.10
1b	-4-OCH_3-C_6H_4	$C_{28}H_{23}ClN_2O_4$	486.5	175	5.75	5.72
1c	-4-Cl-C_6H_4	$C_{27}H_{20}Cl_2N_2O_3$	491.0	156	5.70	5.75
1d	-2,4-$(Cl)_2$-C_6H_3	$C_{27}H_{19}Cl_3N_2O_3$	525.5	185	5.33	5.26
1e	-4-OH-C_6H_4	$C_{27}H_{21}ClN_2O_4$	472.5	200	5.92	5.93
1f	-4-Br-C_6H_4	$C_{27}H_{20}BrClN_2O_3$	535.5	225	5.23	5.28
1g	-4-NO_2-C_6H_4	$C_{27}H_{20}ClN_3O_5$	501.5	232	8.37	8.40
1h	-4-NH_2-C_6H_4	$C_{27}H_{22}ClN_3O_3$	471.5	196	8.90	8.95
1i	-2-OH-C_6H_4	$C_{27}H_{21}ClN_2O_4$	472.5	185	5.92	5.85
1j	-4-CH_3-C_6H_4	$C_{28}H_{23}ClN_2O_3$	470.5	156	5.95	5.92
1k	-2,4-$(OCH3)_2$-C_6H_3	$C_{29}H_{25}ClN_2O_5$	516.5	201	5.42	5.40
1l	-4-(O-CH_2-C_6H_5)-C_6H_4	$C_{34}H_{27}ClN_2O_4$	563.0	226	4.98	4.92
2a	-C_6H_5	$C_{28}H_{23}ClN_2O_3$	470.5	163	5.95	5.90
2b	-4-OCH_3-C_6H_4	$C_{29}H_{25}ClN_2O_4$	500.5	150	5.59	5.65
2c	-4-Cl-C_6H_4	$C_{28}H_{22}Cl_2N_2O_3$	505.0	174	5.54	5.60
2d	-2,4-$(Cl)_2$-C_6H_3	$C_{28}H_{21}Cl_3N_2O_3$	539.5	192	5.19	5.25
2e	-4-OH-C_6H_4	$C_{28}H_{23}ClN_2O_4$	486.5	210	5.75	5.80
2f	-4-Br-C_6H_4	$C_{28}H_{22}BrClN_2O_3$	549.5	230	5.09	5.10
2g	-4-NO_2-C_6H_4	$C_{28}H_{22}ClN_3O_5$	515.5	196	8.14	8.20
2h	-4-NH_2-C_6H_4	$C_{28}H_{24}ClN_3O_3$	485.5	200	8.65	8.60
2i	-2-OH-C_6H_4	$C_{28}H_{23}ClN_2O_4$	486.5	189	5.75	5.72
2j	-4-CH_3-C_6H_4	$C_{29}H_{25}ClN_2O_3$	484.5	160	5.78	5.73
2k	-2,4-$(OCH3)_2$-C_6H_3	$C_{30}H_{27}ClN_2O_5$	530.5	220	5.28	5.21
2l	-4-(O-CH_2-C_6H_5)-C_6H_4	$C_{35}H_{29}ClN_2O_4$	577.0	230	4.85	4.82

Table-2

compd. no.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	S.aureus	B.subtillis	E.coli	P.vulgaris	A.niger
1a	20	21	21	18	20
1b	12	18	17	15	18
1c	19	14	19	21	21
1d	19	19	22	18	18
1e	15	22	14	12	20
1f	18	21	18	19	18
1g	16	17	13	20	21
1h	21	19	17	17	20
1i	17	23	19	19	19
1j	17	22	20	13	18
1k	20	17	14	20	17
1l	15	21	19	14	20
2a	20	19	12	20	18
2b	17	12	19	18	20
2c	15	18	21	14	17
2d	19	20	20	17	18
2e	12	23	14	20	12
2f	18	17	22	18	19
2g	17	15	13	20	22
2h	12	21	17	17	20
2i	19	22	20	13	17
2j	20	10	10	18	18
2k	19	16	18	17	18
2l	20	18	20	12	18
Ampicillin	20	24	22	21	0
Amoxicillin	21	24	25	25	0
Norfloxacin	18	17	24	25	0
Benzyl penicillin	20	18	18	15	0
Griseofulvin	0	0	0	0	24

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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REFERENCES

[1] Krivokolysko S. G.; Chem. Heterocyclic. Compd. (N. Y.) (1999).
[2] M. R. Pavia, C. P. Taylor, F. M. Hershenson and S.J. Lobbestael; J. Med. Chem., 30, 1210 (1987).
[3] N. Latif, N. Mishrky and N. S. Girgis; Indian J. Chem., 20B, 147-149 (1981).
[4] L. Castedo, J. M. Quintela and R. Riguers; Eur. J. Med. Chem. Chim. Ther., 19(6), 555 (1984); Chem. Abstr., 103, 37337 (1985).
[5] Devries Keith Michael, D. R. Lee, W. S. Wayne; PCT Int. Appl. WO 98, 21, 184; Chem. Abstr., 129, 27896r (1998).
[6] J. J. Baldwin, A. Scrialrine, G. S. Ponticeello, E. L. Engelhardt and C. S. Sweeti; J. Heterocycl. Chem., 17(3), 425 (1980); Chem. Abstr., 93, 186222, (1980).
[7] W. von Behenburg, J. Engel, J. Heese and K. Thiele; Ger. Often., D.E., 3, 337, 593 (Cl C07D 213/72) 1984; Chem. Abstr., 101, 130595n (1984).
[8] W. L. Hoefling, D. Elhaner and E. Reckling; VEB Leund-Werke “Walter Ulbricht” Ger. 1, 193, 506 (1965); Chem. Abstr., 63, 6979 (1965).
[9] Thiele Kurt, Von Be Benburg and Walter E.; S. African 6, 905, 06, 13 Feb. (1970).
[10] B. John ED., Freeman and Peter F. M.; Ger. Often., 2, 029, 079 (Cl. A 01 N007d) (1971); Brist. Appl. (1969); Chem. Abstr., 74,99891d (1971).
[11] K. M. Hussain, H. Ruzial, S. Ahmed, Nizamuddin; Ind. J. Chem. Sect. B Org. Incl. Med. Chem., 37B(10), 1069-1074 (1998); Chem. Abstr.,(131), 237504h (1999).
[12] V. Scott and Joseph; Jap. Pat., 2, 803, 592 (1979); Chem. Abstr., 92, 47216 (1980).
[13] Yoshida Hirashi, O. Kiyoshi, Y. Yasujuki, F. Kensaku; Jpn. Kokai Tokkyo Koho JP 10, 120, 677; Chem. Abstr., 129, 16062q (1998).
[14] Mama Fedele, C. Franco, B. Adriana, B. Bruna, F. Walter, F. Amelia; Eur. J. Med. Chem., 34(3), 245-254 (1999); Chem. Abstr., 131, 352178s (1999).
[15] Hammama Abou Elfatoon G., El-Hafeza N. A., M. Wandall; Z. Naturforsch B.; Chem. Sci., 2000.
[16] A. L. Barry; The antimicrobial susceptibility test: Principle and practices, edited by llluslea & Febiger , (Philadelphia), USA, 180; Biol. Abstr., 1977, 64, 25183
[17] Panda J. Srinivas S. V., Rao M. E.; J. Indian Chem. Soc., 79(9), 770-1 (2002); Chem. Abstr., 138, 153499n (2003).