ISSN: 0974 - 7516 Volume 9 Issue 12

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 9(12), 2013 [516-519]

Synthesis and antimicrobial activity of some new cyanopyridone derivatives

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ABSTRACT

The present article reports the synthesis and antimicrobial studies of new cyanopyridone derivatives. The structures of newly synthesized compounds were confirmed by various spectroscopic techniques. The antimicrobial study was carried out by disc diffusion methods. The results of antimicrobial data reveals that compounds **(3c)**, **(3d)**, **(3e)** and **(3g)** were active selected bacterial strains, while **(3c),(3d)** and **(3h)** were shown good activity against fungi strain *A.niger*.

KEYWORDS

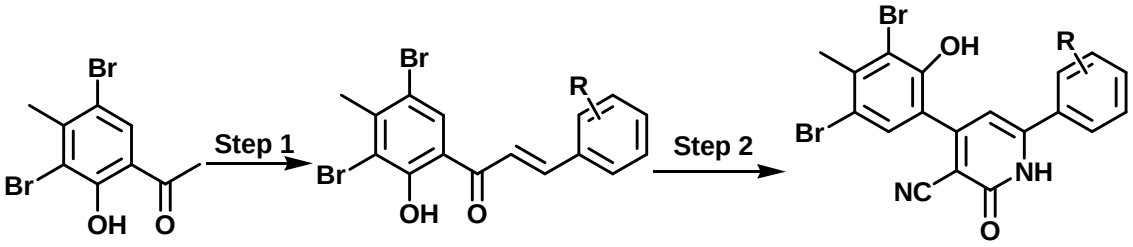
1-(3,5-Dibromo-2-hydroxy-4-methylphenyl)ethanone;
Cyanopyridone;
Chalcone;
Antimicrobial activity.

INTRODUCTION

The resistance towards wide spectrum of antibacterial drugs become serious health hazard. This cause of problem prompted the researcher to discover and modify the current antibacterial and antifungal agents. Pyridones, which belong to important group of heterocylic compound have been extensively explore for their applications in the field of medicine. Pyridine with a carbonyl group at position-2 have been subjected of extensive study due to its diverse range of therapeutic activities like antimicrobial[1], anticancer[2], antiHIV[3] and antiviral[4] etc. Some marketed pyridone belonging drugs are, Amrinone(PDE-3 inhibitor), Ciclopirox(antifungal) and Menthylprylon(treatment of insomnia). As result of broader range of activity of pyridone derivatives, we have selected this class for research and to develop some new derivatives of pyridone and investigate them for antimicrobial activity. Various methods are reported in literature[5-7] for synthesis of cyanopyridone derivatives, but the most common is reaction of α,β-unsaturated carbonyl system(chalcone) with cyanoethylacetate in presence of ammonium acetate.

MATERIAL AND METHODS

The melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 spectrophotometer using KBr disc and 1H NMR spectra in DMSO-d_6 or in CDCl3 (Chemical shift in δ ppm) on Bruker Avance II (400 MHz) using TMS as an internal standard. The results are in good agreement with the structure assigned. The purity of all compounds was checked by thin layer chromatography using TLC plates of silica gel (E. Merck G254) using Ethyl acetate : Hexane solvent system (7:3). Physical Constants synthesized compounds **(3a-3j)** are recorded in TABLE 1.



REACTION SCHEME

Reaction condition: (1) substituted aldehyde (R - CHO), 40% KOH, 25^{0}C, 18hrs, (R= different substitution) (2) cyanoethylacetate, ammonium acetate, reflux, 8 hrs.

TABLE 1 : Physical constants 3-cyano-4-(3,5-dibromo-2-hydroxy-4-methyl phenyl)-6- (4-chlorophenyl)-2-oxo-1,2-dihydropyridine (3a-3j)

Sr No.	Comp.	R	Molecular Formula	M.W.	Yield	M.P^{0}C	R_f
1	3a	C_6H_5-	$C_{19}H_{12}Br_2N_2O_2$	460	70%	>300	0.50
2	3b	3-Br- C_6H_4-	$C_{19}H_{11}Br_3N_2O_2$	539	57%	90	0.45
3	3c	2-Cl-C_6H_4-	$C_{19}H_{11}Br_2ClN_2O_2$	495	61%	88	0.54
4	3d	4-Cl-C_6H_4-	$C_{19}H_{11}Br_2ClN_2O_2$	495	65%	>300	0.60
5	3e	4-N$(CH_3)_2$-C_6H_4-	$C_{21}H_{17}Br_2N_3O_2$	503	62%	152	0.58
6	3f	4-OCH_3-C_6H_4	$C_{20}H_{14}Br_2N_2O3$	490	79%	55	0.57
7	3g	3,4-OCH_3-C_6H_4	$C_{21}H_{16}Br_2N_2O_4$	520	61%	118	0.58
8	3h	2-NO_2-C_6H_4-	$C_{21}H_{16}Br_2N_2O_4$	505	59%	56	0.47
9	3i	3-NO_2-C_6H_4-	$C_{19}H_{11}Br_2N_3O_4$	505	62%	175	0.57
10	3j	2-OH-C_6H_4-	$C_{19}H_{12}Br_2N_2O_3$	476	76%	>300	0.49

General procedure for synthesis of (2E)-1-(3,5-dibromo-2-hydroxy-4-methylphenyl)-3-phenylprop-2-en-1-ones (2a-2j)

To a well stirred solution of 1-(3,5-dibromo-2-hydroxy-4 methyl phenyl) ethanone (1) (0.01 mol) and substituted aldehyde (0.01 mol) in ethanol (25 ml), 40% KOH solution was added till the solution become basic. The reaction mixture was stirred for 24 hrs at 25^{0}C. Completion of reaction was monitored by TLC. Reaction mass was poured onto crushed ice, acidified using concentrated HCl. The product was filtered, dried in vacuo and crystallized using an appropriate solvent.

General procedure for synthesis of 3-cyano-4-(3,5-dibromo-2-hydroxy-4-methyl phenyl)-6- (4-chlorophenyl)-2-oxo-1,2-dihydropyridine (3a-3j)

To a solution of 2a-2j (0.01mol) in 25 ml ethanol, cyanoethyl acetate(0.01 mol), ammonium acetate were added and refluxed for 8 hrs. Completion of reaction was monitored by TLC. The reaction mass was poured onto crushed ice, filtered the product, dried in vacuo and crystallized using an appropriate solvent.

Antimicrobial activity

The antimicrobial activity was assay by using the disc diffusion method. Newly synthesized compounds were screened *in vitro* for their antimicrobial activity against four bacterial strains such *Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and fungi strain *Aspergillus niger* at 40 µg/mL concentration. Standard drugs like Ciprofloxacin and Griseofulvin were used for the comparison purpose. The obtained results for compounds **(3a-3j)** are recorded TABLE 2.

Spectroscopic data of 3-Cyano-4-(3,5-dibromo-2-hydroxy-4-methyl phenyl)-6- (4-chlorophenyl)-2-oxo-1,2-dihydropyridine (3a-3j)

(1)4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile (5a)

1H-NMR($CDCl_3$) δppm : 2.25 (3H,s,-CH_3), 3.43

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TABLE 2 : Antimicrobial screening results of compounds 3a-j

Comp.	R	Antibacterial activity (%)				Antifungal activity (%)
		S.aureus	*S.epider*	*E.Coli*	*P.aerug*	*A.niger*
3a	C_6H_5-	81	40	32	83	53
3b	3-Br-C_6H_4-	62	65	85	89	66
3c	2-Cl-C_6H_4-	71	38	92	71	92
3d	4-Cl-C_6H_4-	83	94	77	92	81
3e	3-N(CH_3).C_6H_4-	64	72	62	88	66
3f	4-OCH_3-C_6H_4-	75	57	76	51	63
3g	3,4-di OCH_3-C_6H_4-	62	71	84	79	46
3h	2-NO_2-C_6H_4-	67	48	37	62	72
3i	3-NO_2 -C_6H_4-	41	62	72	77	38
3j	2-OH-C_6H_4-	82	66	58	33	55
Cipro.	-	100	100	100	100	-
Greseo.	-	-	-	-	-	100

***S.aureus- Streptococcus aureus, S.epidermis- Streptococcus epidermis, E.Coli- Escherichia Coli, P.aerug- Pseudomonas aeruginosa, A.niger- Aspergillus niger,*Cipro.- Ciprofloxacin, Greseo.- Griseofulvin**

(1H,s broad, -NH), 7.35- 7.75 (7H,m,Ar-H), 8.14 (1H,s,-OH), IR(KBr)υcm^{-1} 3480(O-H str.), 3350(N-H str.), 3075(C-H str.), 2975(C- H str.), 2214 (C=N str.), 1690(C=O str), 1580(C=C str.) 1238(C-O-C str.), MS (ESI): m/z = 461 [M+]

(2)6-(3-bromophenyl)-4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-2-oxo-1,2-dihydropyridine -3-carbonitrile (5b)

1H-NMR($CDCl_3$) δppm : 2.28 (3H,s,-CH_3), 3.31 (1H,s broad, -NH), 7.42- 7.73 (6H,m,Ar-H), 8.12 (1H,s,-OH), IR(KBr)υcm^{-1} 3480(O-H str.), 3350(N-H str.), 3075(C-H str.), 2975(C- H str.), 2214 (C=N str.), 1690(C=O str), 1580(C=C str.) 1238(C-O-C str.), MS (ESI): m/z = 540 [M+]

(3)6-(2-chlorophenyl)-4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (5c)

1H-NMR($CDCl_3$) δppm : 2.30 (3H,s,- CH_3), 3.23 (1H,s broad, -NH), 7.41- 7.73 (6H,m,Ar-H), 8.04 (1H,s,-OH), IR(KBr)υcm^{-1} 3490 (O-H str.), 3320(N-H str.), 3020(C-H str.), 2880(C- H str.), 2290(C=N str.), 1687 (C=O str.), 1570(C=C str.) 1290(C-O-C str.), 580(C-Br), 550(C-Cl), MS (ESI): m/z = 495 [M+]

(4)6-(4-chlorophenyl)-4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-2-oxo- 1,2-dihydropyridine-3-carbonitrile (5d)

(5:5) 1H-NMR($CDCl_3$) δppm : 2.33 (3H,s,- CH_3), 3.23 (1H,s broad, -NH), 7.5- 7.72 (6H,m,Ar-H), 8.1 (1H,s,-OH), IR(KBr)cm^{-1} 3480(O-H str.), 3350(N-H str.), 3075(C-H str.), 2975(C- H str.), 2214(C=N str.), 1681(C=O str.), 1580(C=C str.) 1238(C-O-C str.), 610(C-Br), 560(C-Cl), MS (ESI): m/z = 495 [M+]

(5)4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-6-[4-(dimethylamino)phenyl]-2-oxo-1,2-dihydropyridine-3-carbonitrile (5e)

1H-NMR($CDCl_3$) δppm : 2.25 (3H,s,- CH_3), 3.42 (1H,s broad, -NH), 3.82(6H,s,-N(CH_3)$_2$), 7.41- 7.7 (6H,m,Ar-H), 8.22 (1H,s,-OH), IR(KBr)υcm^{-1} 3485(O-H str.), 3350 (N-H str.), 3025(C-H str.), 2950(C- H str.), 2240 (C=N str.), 2240(C=N str.),1634 (C=O str.), 1600(C=C str.),1135(C-O-C str.), 605(C-Br), MS (ESI): m/z = 504 [M+]

(6)4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-6-(4-methoxyphenyl)-2- oxo-1,2-dihydropyridine-3-carbonitrile (5f)

1H-NMR(d_6-DMSO) δppm : 2.22(3H,s,- CH_3), 3.5 (1H,s broad, -NH)3.9 (3H,s,-OCH3), 7.4- 7.7 (6H,m,Ar-H), 8.04 (1H,s,-OH), IR(KBr)cm$_{-1}$ 3382 (O-H str.), 3234 (N-H str.), 2856 (C-H str.), 2858(C-H str.), 2214 (C=N str.), 1614 (C=O str.), 1548(C=C str.) 1238(C-O-C str.) MS (ESI): m/z = 491 [M+]

(7)4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-6-

(3,4-dimethoxyphenyl)-2-oxo-1,2-dihydro pyridine-3-carbonitrile (5g)

1H-NMR($CDCl_3$) δppm : 2.26(3H,s,- CH_3), 3.7 (1H,s broad, -NH) 3.9 (6H,m,(-OCH3)2), 7.3- 7.8 (6H,m,Ar-H), 8.2 (1H,s,-OH), IR(KBr)cm^{-1} 3505(O-H str.), 3355(N-H str.), 3350(C-H str.), 2850(C- H str.), 2240 (C=N str.), 1666 (C=O str.), 1600(C=C str.) 1135(C-O-C str.), 605(C-Br) MS (ESI): m/z = 521 [M+]

(8)4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-6-(2-nitrophenyl)-2-oxo- 1,2-dihydropyridine-3-carbonitrile (5h)

1H-NMR($CDCl_3$)δppm: 2.30 (3H,s,- CH_3), 3.3 (1H,s broad, -NH), 7.4- 7.7 (6H,m,Ar-H), 8.04 (1H,s,-OH), IR(KBr)cm^{-1} 3450(O-H str.), 3355(N-H str.), 3350(C-H str.), 3025(C- H str.), 2880 (C=N str.), 2238(C=N str.), 1682(C=O str.), 1590(C=C str.) 1270(C-O-C str.), 555(C-Br) MS (ESI): m/z = 506 [M+]

(9)4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-6-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (5i)

1H-NMR($CDCl_3$) δppm : 2.35 (3H,s,- CH_3), 3.2 (1H,s broad, -NH), 7.42- 7.74. (6H,m,Ar-H), 8.14 (1H,s,-OH), IR(KBr)υcm^{-1} 3495(O-H str.), 3380(N-H str.), 3033(C-H str.), 2855 (C- H str.), 2240 (C=N str.),1685(C=O str.), 1600(C=C str.), 1555(N=O),579(C-Br), MS (ESI): m/z = 506 [M+]

(10)4-(3,5-dibromo-2-hydroxy-4-methylphenyl)-6-(2-hydroxyphenyl)-2- oxo-1,2-dihydropyridine-3-carbonitrile(5j)

1H-NMR($CDCl_3$) δppm : 2.35 (3H,s,- CH_3), 3.47 (1H,s broad, -NH), 6.75 (1H,s,-OH), 7.36- 7.8 (6H,m,Ar-H), 8.04 (1H,s,-OH), IR(KBr)cm^{-1} 3482(O-H str.), 3376(N-H str.), 3023(C-H str.), 2805(C- H str.), 2263(C=N str.), 1690(C=O str.), 1593(C=C str.), 1520(N=O),569(C-Br) MS (ESI): m/z = 477 [M+]

RESULTS AND DISCUSSION

Cyanopyridones **(3a-3j)** have been synthesized by the reaction of (2E)-1-(3,5-dibromo-2-hydroxy-4-methylphenyl)-3-phenylprop-2-en-1-ones **(2a-2j)** with pyridine-4-carbohydrazide in acetic acid in reflux condition to get the desired product with 60 to 77% of good yield. The structures of compounds are confirmed by IR, NMR and Mass spectral data analysis. From the results of antimicrobial data, compounds **(3c)** and **(3d)** were active and compounds **(3e)** and **(3g)** were moderately active against selected bacterial strains. While **(3c)**,**(3d)** and **(3h)** are shown good activity against fungi strain *A.niger*. From the structure activity relationship table, we found that phenyl ring substituted with chloro(3c, 3d) had shown an excellent result compare to standard drug Ciprofloxacin and Griseofulvin at concentration of 40μg/ml.

CONCLUSION

From the antimicrobial data, it is worthwhile to say that, newly synthesized cyanopyridone derivatives are showing good to moderate activity against bacterial and fungi strains From the structure activity relationship table and the results we found that, halogen substituted phenyl rings shows good activity as compare to other functional groups. This results give us initiative to synthesize more compounds with different halogen substitution on the phenyl ring with different position, which may become good to excellent antimicrobial agents.

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