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Research Article

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Synthesis and biological evaluation of some new cyano pyridine derivatives

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ABSTRACT

Some new 3-cyanopyridine 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: Isoindoline derivatives, Cyanopyridine, antimicrobial activities

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INTRODUCTION

The pyridine skeleton is of great importance to chemists as well as to biologists as it is found in a large variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities. Cyanopyridine are important intermediates in the pharmaceutical industry for the synthesis of nicotinamide, nicotinic acid and isonicotinic acid etc [1]. The importance of cyanopyridines in organic synthesis has increased over the past few decades because they are among the most versatile organic synthetic intermediates [2].

It has been demonstrated that molecules containing 3-cyanopyridine moiety may be able to work as ligands towards transition-metal ions [3], drug substances [4], and significant intermediates for the synthesis of important vitamins [5] such as nicotinic acids [6] and nicotinamides [7].

The pharmacological and physiological activity of 3-cyanopyridines has attracted much attention in recent years with the synthesis and the study of the nonglycosidic cardiotonic agent milrinone [8], as well as with a number of 3-cyanopyridine derivatives which proved to be active against the herpes virus and the human immunodeficiency virus [9]. Furthermore Cyanopyridine derivatives found to possess a wide range of biological activity such as anti-tubercular [10], antimicrobial [11], anti-cancer [12], antihypertensive [13], anti-histaminic [14], Anti-inflammatory, analgesic & antipyretic properties [15], Cardiotonic [16] and Anti-HIV [17].

Cyanopyridine have attracted attention of medicinal chemistry for both with regard to heterocyclic chemistry and the pharmacological activities associated with them, inspired us to synthesize isoindoline bearing 3- cyanopyridine derivatives (5a – 5l) and (6a – 6l).

EXPERIMENTAL SECTION

All melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on a FTIR - 8400 spectrophotometer. ^{1}H NMR spectra recorded on a Bruker 300 MHz spectrometer with DMSO as a solvent and tetra methyl silane (TMS) as internal standard. The chemical shifts are expressed in parts per million (ppm) downfield from the internal standard and signals are quoted as *s* (singlet), *d* (doublet) and *m* (multiplate). Thin Layer Chromatography (TLC) analytical separation was conducted with Silica Gel 60 F-254 (Merck) plates of 0.25mm thickness eluted with Hexanes : Ethyl acetate (7 : 3 v/v) and visualized with UV (254 nm) or iodine to check the purity of the synthesised compounds.

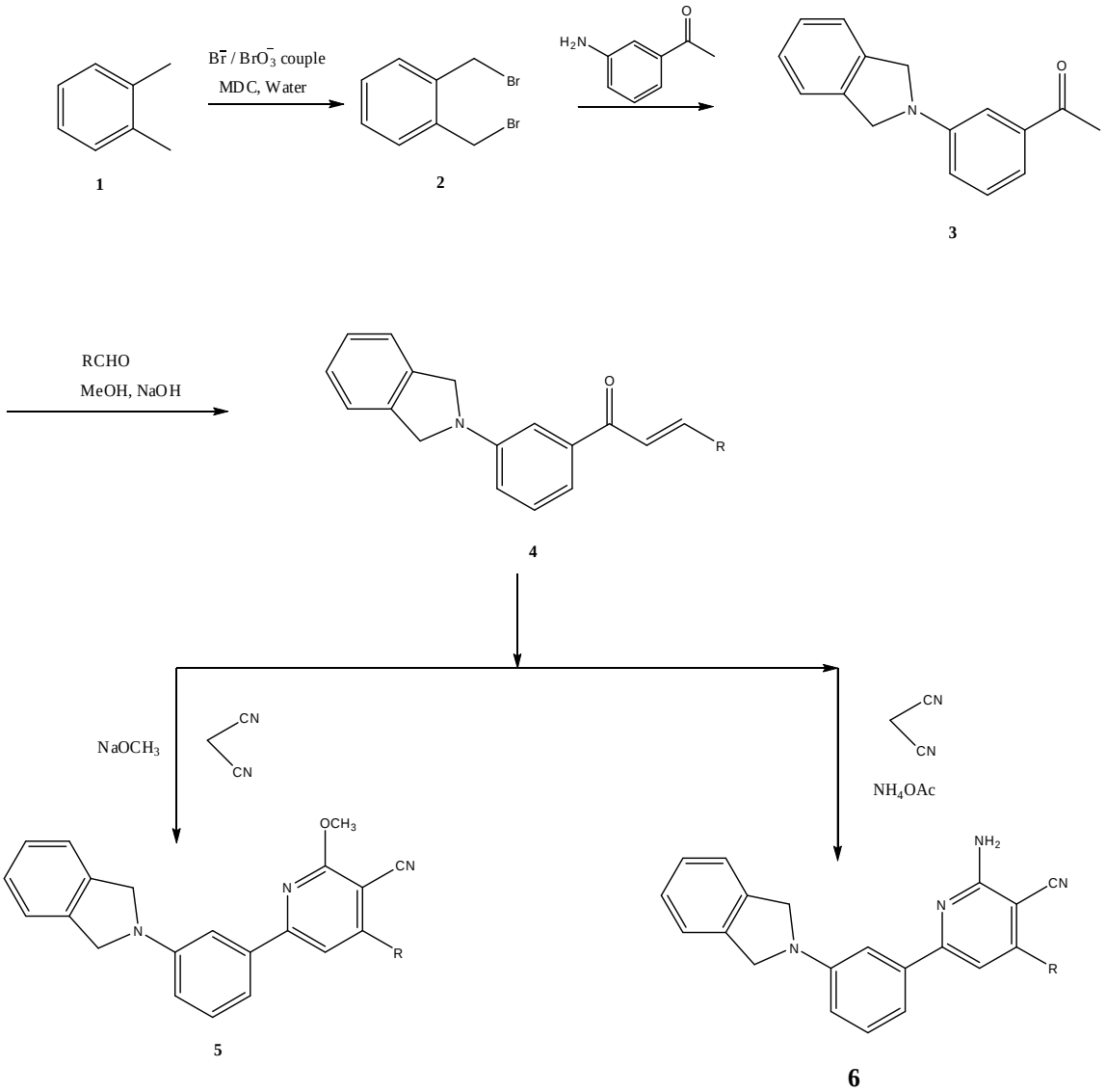
The antimicrobial activity was assayed by using the cup-plate agar diffusion method [18] by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities against varieties of bacterial strains such Staphylococcus aureus, Escherichia coli, Bacillus megaterium, Salmonella taphimurium and fungi Aspergillus niger at 50 µg concentration. Standard drugs like Amoxycillin, Chloramphenicol, ciprofloxacin and Griseofulvin were used for comparison purpose (Table-2).

General procedure for the synthesis of compounds (2), (3), (4), (5) and (6). Compounds (2), (3) and (4) were prepared by the reported method [19].

Preparation of 4-(2'"-Chlorophenyl)-2-methoxy-6-[3'-(1", 3"-dihydro-1H-oisoindol-2"-yl) phenyl] nicotinonitrile (5b):
To a solution of 1-[3'-(1",3"-dihydro-1H-isoindol-2"-yl)phenyl]-3-(2'"-Chlorophenyl) prop-2-en-1-one (3.0gm, 0.01 mol), malononitrile (0.66gm, 0.01 mol) and freshly prepared sodium methoxide in methanol (25ml). The content was heated under reflux with stirring for 12 hrs. The reaction mixture was diluted with water and filtered the precipitated solid and crystallized from methanol to give **5b**.

Similarly, the remaining compounds (5a-l) were prepared by this method. Their physical data are given in Table-1.

Compound (5b) IR (KBr,cm^{-1}) : 2227 (-C≡N str.), 3016 (C=CH str.), 1575 (C=N str, cyano group), 1321 (C-N str, isoindoline moiety), 678 (C-Cl str.) ; ^{1}H NMR (CDCl3, δ, ppm): 4.134 (3H, *s*, -OCH_3), 4.73 (4H, s, -$(CH_2)_2$-N-, Isoindoline ring), 6.8 (2H, s, Ar-H),7.19 – 7.55 (11H, *m*, Ar-H); Mass m/z = 438.3, 440.3, 413.3 370.3, 184.0, 160.4



Scheme – 1

Synthesis of 2-Amino-4-(2'"-Chlorophenyl)-6-[3'-(1", 3"-dihydro-1H-isoindol-2"-yl) phenyl] nicotinonitrile (6b):
A mixture of 1-[3'-(1",3"-dihydro-1H-isoindol-2"-yl)phenyl]-3-aryl prop-2-en-1-one. (3.40 g, 0.01 mol), malononitrile (0.66g, 0.01 mol) and ammonium acetate (2.31 g, 0.03 mol) in DMF (30 ml) was refluxed for 8 hrs. The content was poured in to crushed ice. The solid was obtained by filtration, washed with water and crystallised from dioxane to give **6b**.

Similarly, the remaining compounds (6a-l) were prepared by this method. Their physical data are given in Table-1.
Compound (6b) IR (KBr,cm^{-1}) : 3410 (N-H str.), 3053 (C=CH str.), 1373 (C-N str., isoindoline moiety), 2212 (C≡N str.), 702 (C-Cl str.) ; ^{1}H NMR (DMSO – d_6, δ, ppm): 4.67 (4H, *s*, -$(CH_2)_2$-N-, Isoindoline moiety), 6.81 – 7.02 (2H, *m*, -NH_2), 7.17 – 7.28 (2H, s, Ar-H), 7.33 – 7.65 (11H, m, Ar-H), 7.68 – 7.79 (1H, m, Ar-H). Mass m/z = 425.5, 423.4, 279.3. 214.3.

RESULTS AND DISCUSSION

The IR spectrum of compound **5b** and **6b** in KBr shows the characteristic band in the region of 1550-1580 cm^{-1} and 2120 – 2240cm^{-1} which indicate the presence of -C=N group while compound 6b also shows band in region the of 3500-3300 cm^{-1} due to –NH2 group. The ^{1}H NMR spectrum of compound **5b** shows sharp singlet of –OCH_3 at δ 4.13 confirmed the present of methoxy group in cyanopyridine derivatives while the ^{1}H NMR spectrum of compound **6b** shows singlet of –NH_2 group at δ 6.8 confirmed the amino group in Cyanopyridine moiety. Result of IR and 1H NMR analysis confirmed formation of desired products.

Antibacterial activity
From the screening results (Table – 2), The result shows that compounds 5d, 5e, 6e and 6g exhibited good activity against S. Taphimurium; compounds 5b, 5e, 5j, 6f and 6k exhibited good activity against B. megaterium. In Gram negative bacterial strains compounds 5c, 5f, 5l, 6d and 6h showed good to moderate activity against E. coli; whereas compounds 5a, 5b, 5h, 5l, 6d, 6h and 6l showed good activity against S. aureus compared with Amoxycillin, Ciprofloxacine and Chloramphenicol. All others compound show moderately active or less active against all bacterial strains.

Antifungal activity
From the screening results (Table – 2), Compounds 5g, 5i, 6b and 6k showed good activity against A Niger compared with Griseofulvin.

Table -1 Characterisation data of compounds (5a-l) and (6a-l)

Com. No.	Ar	Molecular Formula	M.P. (°C)	Nitrogen %	
				Calcd	Found
5a	C_6H_5	$C_{27}H_{21}N_3O$	212	10.41	10.38
5b	2-Cl C_6H_4	$C_{27}H_{20}ClN_3O$	236	9.60	9.66
5c	3-Cl C_6H_4	$C_{27}H_{20}ClN_3O$	240	9.60	9.57
5d	4-Cl C_6H_4	$C_{27}H_{20}ClN_3O$	238	9.60	9.62
5e	2,3-Cl_2 C_6H_3	$C_{27}H_{19}Cl_2N_3O$	268	9.90	9.87
5f	2-F C_6H_4	$C_{27}H_{20}FN_3O$	226	9.97	10.01
5g	4-OCH_3 C_6H_4	$C_{28}H_{23}N_3O_2$	190	9.69	9.72
5h	4-CH_3 C_6H_4	$C_{28}H_{23}N_3O$	184	10.06	10.10
5i	4-OH C_6H_4	$C_{27}H_{21}N_3O_2$	260	10.02	10.06
5j	3-OH C_6H_4	$C_{27}H_{21}N_3O_2$	263	10.02	9.98
5k	2-C_4H_3S	$C_{25}H_{19}N_3OS$	233	10.26	10.29
5l	4-$(CH_3)_2N$ C_6H_4	$C_{29}H_{26}N_4O$	207	12.55	12.59
6a	C_6H_5	$C_{26}H_{20}N_4$	254	14.42	14.46
6b	2-Cl C_6H_4	$C_{26}H_{19}N_4Cl$	274	13.25	13.21
6c	3-Cl C_6H_4	$C_{26}H_{19}N_4Cl$	278	13.25	13.26
6d	4-Cl C_6H_4	$C_{26}H_{19}N_4Cl$	271	13.25	13.18
6e	2,3-Cl_2 C_6H_3	$C_{26}H_{18}N_4Cl_2$	288	12.25	12.31
6f	2-F C_6H_4	$C_{26}H_{19}N_4F$	266	13.78	13.82
6g	4-OCH_3 C_6H_4	$C_{27}H_{22}N_4O$	241	13.39	13.41
6h	4-CH_3 C_6H_4	$C_{27}H_{22}N_4$	255	13.92	13.89
6i	4-OH C_6H_4	$C_{26}H_{20}N_4O$	290	13.85	13.88
6j	3-OH C_6H_4	$C_{26}H_{20}N_4O$	292	13.85	13.83
6k	2-C_4H_3S	$C_{24}H_{18}N_4S$	298	14.20	14.22
6l	4-$(CH_3)_2N$ C_6H_4	$C_{28}H_{25}N_5$	281	16.23	16.26

Table 2 – Antibacterial and antifungal activity data of compounds (5a - l) and (6a-l)

Com. No.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	Salmonella taphimurium	*Bacillus megaterium*	*Escherichia coli*	*Staphylococcus aureus*	*Aspergillus niger*
5a	16	12	12	20	12
5b	17	19	14	18	11
5c	13	12	18	14	15
5d	22	10	15	13	11
5e	24	20	13	17	15
5f	13	14	20	12	13
5g	16	15	11	11	20
5h	12	11	15	18	13
5i	12	10	12	16	20
5j	13	20	13	14	14
5k	16	12	16	16	11
5l	17	23	20	19	15
6a	15	16	12	14	13
6b	13	13	09	11	20
6c	15	11	13	14	12
6d	14	15	22	20	11
6e	23	13	17	12	13
6f	14	20	13	10	12
6g	20	13	17	10	10
6h	14	14	24	19	09
6i	15	15	14	12	13
6j	15	11	13	13	12
6k	12	20	12	13	18
6l	11	13	13	23	12
Amoxycillin	26	28	27	29	--
Ciprofloxacine	33	34	33	34	--
Chloramphenicol	18	20	19	19	--
Griseofulvin	--	--	--	--	20

CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds which shows 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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