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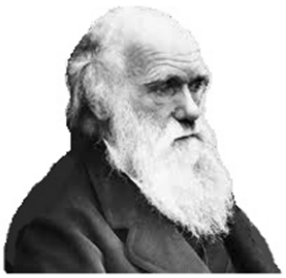

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Synthesis and antimicrobial activity of {2-amino/2-methoxy}-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl nicotinonitriles

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ABSTRACT

2-Amino-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl nicotinonitriles. **(2a-2j)**; 2-Methoxy-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl nicotinonitriles. **(3a-3j)** have been synthesized. The products have been assayed for their antimicrobial activity against Gram +ve bacteria and Gram –ve bacteria and fungi. The products have been characterized by IR, ^{1}HNMR, Mass Spectra and TLC.

Keywords: Cyanopyridines, Amino Nicotinonitriles, Methoxy Nicotinonitriles, Antimicrobial activity

1. INTRODUCTION

Cyanopyridines derivatives have been found to possess wide range of therapeutic activities as Anti-inflammatory [1], Acetylcholinesterase inhibitors [2], Agonist receptor for treating cardio logical or genitourinary disorders [3], Anti-fungal [4], Aurora-A selective kinase inhibitors [5], Anti tubercular [6], Antibacterial [7], Anti tumor [8], Reproduction and development [9], Epidermal growth factor receptor TKI [10], etc. 2-Amino-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl nicotinonitriles **(2a-2j)** have been synthesized by

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condensation of 3-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-1-aryl-prop-2-ene-1-ones with ammonium acetate and malanonitrile; 2-Methoxy-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl nicotinonitriles **(3a-3j)** have been synthesized by condensation of 3-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-1-aryl-prop-2-ene-1-ones with sodium methoxide and malanonitrile.

The products **(2a-2j); (3a-3j)** were assigned by IR, ^{1}HNMR, mass spectral data, TLC, physical data and antimicrobial activity represented in Table 1and Table 2 respectively.

2. ANTIMICROBIAL ACTIVITY

The antimicrobial activity was determined by cup plate method [11] at a concentration of 50 μg/ml using DMF as a solvent. The activity was taken by Gram positive bacteria *B. megaterium, S. aureus,* Gram negative bacteria *Escherichia coli,* and *S. taphimarium* and anti fungal activity against *Aspergillus niger*. The zone of inhibition was measured in mm. The antibacterial activity was compared with the known standard drugs, viz, Ampicillin, Chloramphenicol, Norfloxacin and anti fungal activity was compared with known standard drug viz. Fluconazole. The zone of inhibition that displayed by standard drugs are recorded in Table 3.

3. EXPERIMENTAL

All the melting points were measured by open glass capillary method. IR absorption spectra (in cm^{-1}) were recorded on SHIMADZU-FT-IR-8400 spectrophotometer, frequency range: 4000-400 cm^{-1} using KBr disc pallet method, ^{1}H NMR on 400 MHz Bruker Avance-III spectrometer using DMSO-d6 as a solvent and TMS as instrument standard and mass spectra on SHIMADZU-GC-MS QP-2010 Ultra. The purity of the compounds were routinely checked by TLC using silica gel-G.

4. REACTION SCHEME

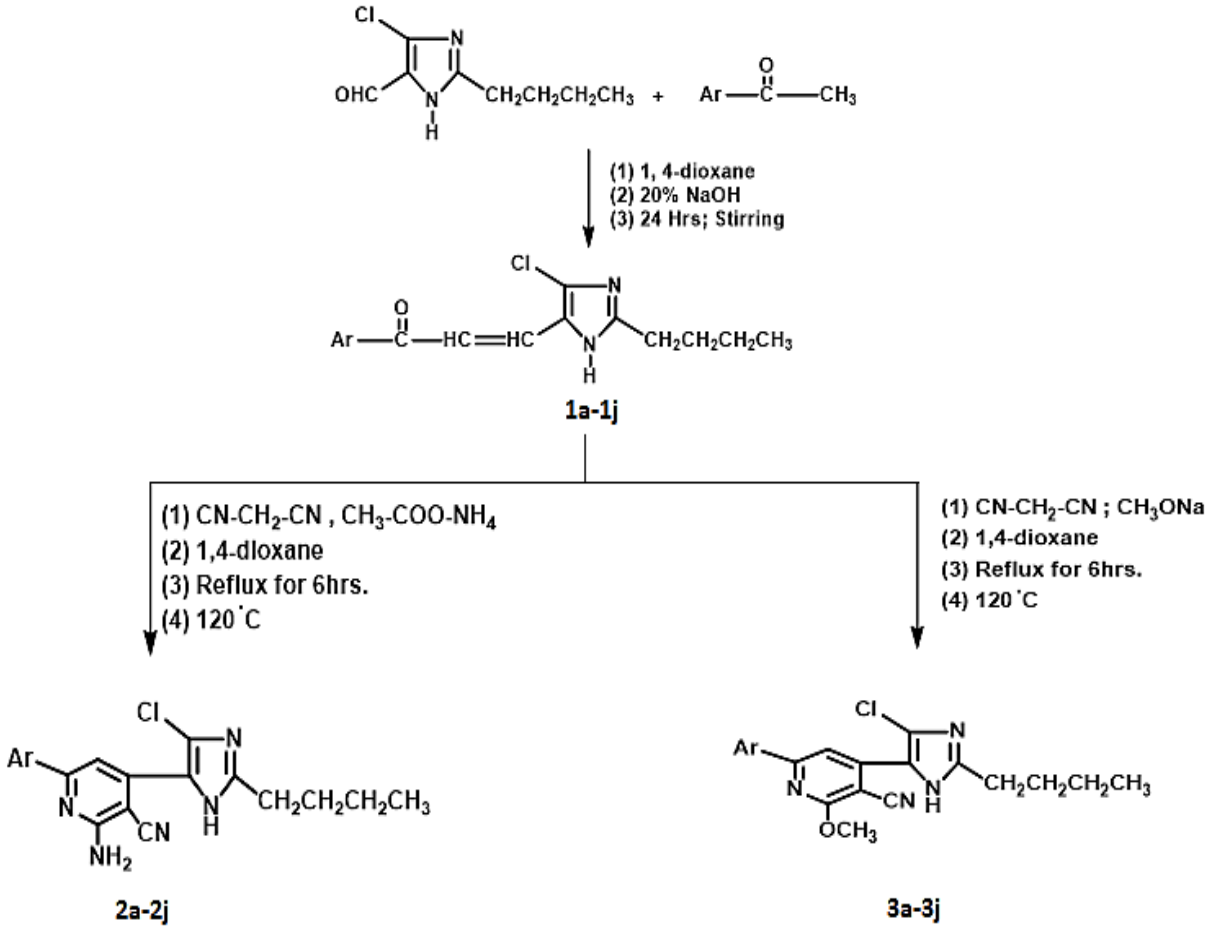
4. 1. Synthesis of 3-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-1-(4''-methoxy phenyl)-prop-2-ene-1-one (1i)

A mixture of 2-(n-butyl)-4-chloro-5-carboxaldo-1H-imidazole (1.87 gm, 0.01M); 4-Methoxy acetophenone (1.50 gm, 0.01M); 1,4-dioxane (20 ml); 20% NaOH (20 ml) was stirred for 24 hrs. at room temperature. Completion of reaction was checked with TLC. The reaction mixture was poured into crushed ice, filtered it, dried it. The product was crystallized in 1, 4-dioxane.

Yield: 77%; M.P.: 87 °C; (Required: C: 64.05; H: 6.01; N: 8.79%; $C_{17}H_{19}ClN_2O_2$; Found: C: 64.05; H: 6.01; N: 8.70%). IR (KBr): 2968 (C-H str. asym); 2864 (C-H str. sym); 1459 (C-H str. Def) 3060 (C-H str. aromatic); 1558 (C=C ring skeletal); 1166 (C-H i.p. (def)); 751 (C-H-str.def); 1600 (C-N str.); 1515 (C=N str.); 3415 (N-H str); 1600 (N-H bending); 1653 (C=O str.); 1459 (CH=CH); 728 (C-Cl); 1250 (C-O-C str.). ^{1}H NMR: 0.9 (T, 3H, -C$\underline{H_3}$); 1.2-1.3 (m, 2H, -C$\underline{H_2}$-CH_3); 1.5-1.6 (m, 2H, -C$\underline{H_2}$-CH_2-CH_3); 2.6 (T, 2H, -C$\underline{H_2}$-CH_2-CH_2-CH_3); 12.8 (S,

1H, -NH); 7.4 (d, 1H, -CH=CH-) 7.6 (d, 1H, -CH=CH-); 7.1 (d, 2H, Ar-H); 8.0 (d, 2H, Ar-H); 3.8 (S, 3H, -OCH_3). m/z: 318, 283, 268, 253, 240, 225, 211, 200, 184, 167, 145, 135, 115, 107, 92, 77, 64, 43, 41, 40.

Similarly, other compounds (1a-1j) were synthesized. Chalcones physical data and antimicrobial activities are published in another journal.



Scheme 1

4. 2. Synthesis of 2-Amino-4-(2'-n-butyl-4'-chloro-1'-H-imidazol- 5'-yl)-6-(4''-methoxy phenyl) nicotinonitrile (2i)

A solution of 3-(2'-n-Butyl-4'-chloro-1'-H-imidazol-5'-yl)-1-(4''-methoxy phenyl)-prop-2-ene-1-one (3.19 gm, 0.01M); 1,4-dioxane (20 ml); malanonitrile (0.66 gm, 0.01M) and ammonium acetate (0.77 gm, 0.01M) was refluxed in an oil bath for 6 hrs. at 120 ℃ temp. Completion of reaction was checked with TLC. After the completion of reaction, the reaction mixture was poured into crushed ice, the product formed was filtered and dried. The product was crystallized in 1,4-dioxane.

Yield: 75%; M.P.: >300 °C. (Required: C: 62.91; H: 5.28; N: 18.34%; $C_{20}H_{20}ClN_5O$; Found: C: 62.90; H: 5.26; N: 18.29%). IR (KBr): 2957 (C-H str. asym); 2867 (C-H str. sym);

1438 (C-H str. Def); 3046 (C-H str. aromatic); 1599 (C=C ring skeletal); 1168 (C-H i.p. def); 715 (C-H- str.o.o.p.def); 1438 (C-N str.); 1649(C=N str.); 3477 (N-H str.); 1401 (N-H bending); 697 (C-Cl); 2111 (-C≡N str.);1228 (C-O-C str.). ^{1}H NMR: 0.8 (t, 3H, -C<u>H</u>$_3$); 1.2-1.3 (m, 2H, -C<u>H</u>$_2$-CH$_3$); 1.6-1.7 (m, 2H, -C<u>H</u>$_2$-CH$_2$-CH$_3$); 2.6 (t, 2H, -C<u>H</u>$_2$-CH$_2$-CH$_2$-CH$_3$); 12.8 (s, 1H, -N<u>H</u>); 3.8 (s, 3H, -OC<u>H</u>$_3$); 7.6-7.7 (s, 2H, -N<u>H</u>$_2$); 7.4 (s, 1H, Ar-C<u>H</u>); 7.1 (d, 2H, Ar-<u>H</u>); 8.0 (d, 2H, Ar-<u>H</u>); m/z: 382, 338, 324, 298, 283, 274, 235, 224, 157, 146, 107, 98, 83, 77, 57, 43, 41, 40, 31.

Similarly, other compounds (2a-2j) were synthesized. The physical data and antimicrobial activity of (2a-2j) represented in Table 1.

Table 1. The physical data and antimicrobial activity of compounds (2a-2j). Zone of inhibition in mm.

Sr. No.	Ar	Molecular Formula	M.P. (°C)	% Nitrogen yield		Antibacterial activity				Anti fungal activity
						Gram +ve bacteria		Gram –ve bacteria		
				Calcd.	Found	*B. mega.*	*S. aureus*	*S. taphi.*	*E. coli.*	*A. niger*
2a	C_6H_5-	$C_{19}H_{18}ClN_5$	191	19.91	19.88	10	19	18	16	15
2b	3-OH.C_6H_4-	$C_{19}H_{18}ClN_5O$	230	19.04	19.00	19	17	**23**	18	12
2c	4-OH.C_6H_4-	$C_{19}H_{18}ClN_5O$	287	19.04	19.38	**22**	18	17	19	11
2d	3-NH_2.C_6H_4-	$C_{19}H_{19}ClN_6$	>300	22.91	22.88	**20**	19	18	17	**23**
2e	4-Cl.C_6H_4-	$C_{19}H_{17}Cl_2N_5$	251	18.13	18.05	18	**20**	19	**21**	**20**
2f	4-Br.C_6H_4-	$C_{19}H_{17}BrClN_5$	192	16.26	16.20	17	13	**21**	18	19
2g	3-NO_2.C_6H_4-	$C_{19}H_{17}ClN_6O_2$	290	21.18	21.12	19	17	**22**	**20**	18
2h	4-NO_2.C_6H_4-	$C_{19}H_{17}ClN_6O_2$	>300	21.18	21.09	**23**	15	18	19	**24**
2i	4-OCH_3.C_6H_4-	$C_{20}H_{20}ClN_5O$	>300	18.34	18.29	15	19	17	16	19
2j	3-NH_2, 2-OH.C_6H_3-	$C_{19}H_{19}ClN_6O$	>300	21.95	21.90	18	**24**	**24**	17	**23**

4. 3. Synthesis of 2-Methoxy-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-(4''-methoxy phenyl) nicotinonitrile (3i)

A solution of 3-(2'-n-butyl-4'-chloro-1'-H-imidazol-5' yl)-1-(4''-methoxy phenyl)-prop-2-ene-1-one (3.19 gm, 0.01M), 1,4-dioxane (20 ml); malanonitrile (0.66 gm, 0.01M) and

sodium methoxide (0.54 gm, 0.01M) was taken in a RBF. The reaction mixture was refluxed in oil bath for 6 hrs. at 120 ℃ temperature. After completion of the reaction, the reaction mixture was poured into crushed ice. The product formed was filtered and dried. The product was crystallized in 1,4-dioxane.

Yield: 81%; M.P.: >300 °C; (Required: C: 63.55; H: 5.33; N: 14.12%; $C_{21}H_{21}ClN_4O_2$; Found: C: 63.51; H: 5.31; N: 14.07%). IR (KBr): 2957 (C-H str. asym); 2855 (C-H str. sym); 1459 (C-H str. Def); 3065 (C-H str. aromatic); 1600 (C=C ring skeletal); 1105 (C-H i.p. def); 715 (C-H- str.o.o.p.def); 1401 (C-N str.); 1571(C=N str.); 3334 (N-H str.); 1459 (N-H bending); 2208 (-C≡N str.); 833 (C-Cl); 1250 (C-O-C str.). ^{1}H NMR: 0.8 (T, 3H, -C<u>H</u>$_3$); 1.2-1.3 (m, 2H, -C<u>H</u>$_2$-CH$_3$); 1.6-1.7 (m, 2H, -C<u>H</u>$_2$-CH$_2$-CH$_3$); 2.6 (t, 2H, -C<u>H</u>$_2$-CH$_2$-CH$_2$-CH$_3$); 12.8 (s, 1H, -N<u>H</u>); 3.7 (s, 3H, O-C<u>H</u>$_3$); 3.8 (s, 3H, Cyano Pyridine O-C<u>H</u>$_3$); 7.6-7.7 (s, 1H, -C<u>H</u>); 7.1 (d, 2H, Ar-<u>H</u>); 8.0 (d, 2H, Ar-<u>H</u>). m/z: 397, 365, 339, 334, 315, 298, 289, 239, 207, 189, 157, 107, 98, 81, 77, 62, 57, 43, 41, 40, 31.

Similarly, other compounds (3a-3j) were synthesized. The physical data and antimicrobial activity of (3a-3j) represented in Table 2.

Table 2. The physical data and antimicrobial activity of compounds (3a-3j). Zone of inhibition in mm.

Sr. No.	Ar	Molecular Formula	M.P. (°C)	% Nitrogen yield		Antibacterial activity				Anti fungal activity
						Gram +ve bacteria		Gram –ve bacteria		
				Calcd.	Found	*B. mega.*	*S. aureus*	*S. taphi.*	*E. coli.*	*A. niger*
3a	C_6H_5-	$C_{20}H_{19}ClN_4O$	152	15.27	15.20	11	12	14	19	13
3b	3-OH.C_6H_4-	$C_{20}H_{19}ClN_4O_2$	232	14.63	14.59	16	15	19	**20**	12
3c	4-OH.C_6H_4-	$C_{20}H_{19}ClN_4O_2$	245	14.63	14.55	19	**22**	**20**	18	14
3d	3-NH_2.C_6H_4-	$C_{20}H_{20}ClN_5O$	289	18.34	18.30	11	16	19	**22**	19
3e	4-Cl.C_6H_4-	$C_{20}H_{18}Cl_2N_4O$	>300	13.96	13.90	**20**	13	18	19	**21**
3f	4-Br.C_6H_4-	$C_{20}H_{18}BrClN_4O$	295	12.57	12.51	13	15	**23**	18	**23**
3g	3-NO_2.C_6H_4-	$C_{20}H_{18}ClN_5O_3$	263	17.00	16.91	14	16	19	**21**	**20**
3h	4-NO_2.C_6H_4-	$C_{20}H_{18}ClN_5O_3$	280	17.00	16.98	12	18	17	19	19
3i	4-OCH_3.C_6H_4-	$C_{21}H_{21}ClN_4O_2$	>300	14.12	14.07	**23**	**20**	19	**22**	**24**
3j	3-NH_2, 2-OH.C_6H_3-	$C_{20}H_{20}ClN_5O_2$	287	17.60	17.55	19	**24**	18	**23**	18

Table 3. Compounds showing comparable antimicrobial activity with known standard drugs.

Compounds	Antibacterial activity				Anti fungal activity
	Gram +ve Bacteria		Gram -ve Bacteria		
	B. mega.	***S. aureus***	***S. taphi.***	***E. coli.***	***A. niger***
(2a-2j)	2c	2e	2b	2e	2d
	2d	2j	2f	2g	2e
	2h	-	2g	-	2h
	-	-	2j	-	2j
(3a-3j)	3e	3c	3c	3b	3e
	3i	3i	3f	3d	3f
	-	3j	-	3g	3g
	-	-	-	3i	3h
	-	-	-	3j	-
Activity of Standard Drugs:					
Ampicillin (50 µg/ml)	27	26	25	28	-
Chloramphenicol (50 µg/ml)	29	28	27	25	-
Norfloxacin (50 µg/ml)	32	30	24	27	-
Fluconazole (50 µg/ml)	-	-	-	-	26

5. CONCLUSIONS

2-Amino-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl nicotinonitriles **(2a-2j)** and 2-Methoxy-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl nicotinonitriles **(3a-3j)** have been synthesized. The compounds 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i and 3j showed good remarkable antibacterial and anti fungal activity with compared to known standard drugs e.g., Ampicillin, Chloramphenicol, Norfloxacin and Fluconazole at same concentration 50 µg/ml.

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