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Synthesis, spectral studies and antimicrobial activity of 2-amino-4-(2'-n-butyl-4'-chloro-1'-h-imidazol-5'-yl)-6-aryl-4-h-pyran-3-carbonitriles

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Abstract
The study focuses on the synthesis, spectral studies and antimicrobial activity of 2-Amino-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl-4-H-pyran-3-carbonitriles derivatives against Gram +ve bacteria, Gram –ve bacteria and fungi. The products have been characterized by IR, ^{1}H NMR, Mass Spectra and TLC.

Keywords: 4-H-Pyran, carbonitrile, cyanopyran, antimicrobial activity, spectral study

Introduction

The most important heterocyclic moieties bearing a single oxygen atom such as 4H-pyran and 2H-pyran in a six-membered doubly unsaturated ring system are the key building materials of uncountable natural products and expresses a drug-like structure motif with a wide range of applications in the field of organic synthesis and medicinal chemistry. Pyran constitute the most important class of pharmacologically active naturally occurring and synthetic compounds, playing a vital role in the field of bio-organic chemistry. Pyran and analogues of pyrans occupies the top position in Bio-organic chemistry due to varied applications.

Over 50 derivatives of 2-amino-3-cyano-4H-pyran scaffolds have been synthesized by the condensation reaction of a series of aromatic aldehydes with different 1, 3-dicarbonyl compounds and malononitrile [1]. J. Svete and co-workers [2] reported solid and solution phase preparation of fused amino-2H-pyranones. N. M. Abed et. al. [3] documented synthesis of novel Pyran derivatives. H. A. Ghany and co-workers [4] prompted that condensation reaction of 2-coumarylidene malanonitrile with active methylene compound produced novel Pyran derivatives in a good yield.

N. R. Kamdar and co-workers [5] reported synthesis of new pyrano based pyrimidine molecules and screened their in-vitro anti-tubercular, anti-bacterial and anti-fungal activities. M. M. Ghorab et. al. [6] have been reported anticancer and radio sensitizing characteristics of derivatives of novel pyrano-thiazole-schiff base linked with pharmacologically active sulfonamide group. I. V. Magedov and co-worker [7] have been synthesized amino Cyanopyran bearing naphthoquinones and evaluated their anti-cancer activity. S. Uzzaman and co-workers [8] documented synthesis, structural modeling and anti-microbial evaluation of novel steroidal aminopyran scaffolds. M. S. Vasava et. al. [9] have been synthesized novel 1, 4-dihydropyrano [2, 3-c] pyrazole derivatives and evaluated their biological and in silico study. V. P. Sheverdov et. al. [10] have been synthesized Antiproliferative activity of Nitrile containing pyrans and 1, 2, 5, 6, 7, 8-Hexahydroquinoline-3, 3, 4, 4-Tetracarbonitriles.

A series of novel Cyanopyran derivatives (2a-2j) i.e. 2-Amino-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl-4-H-pyran-3-carbonitriles have been synthesized by the condensation reaction of 3-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'- yl)-1-aryl-prop-2-ene-1-ones, malanonitrile and pyridine. The products (2a-2j) were assigned by IR, ^{1}H NMR, mass spectral data, TLC. The physical data and antimicrobial activity is represented in Table 1.

Antimicrobial Activity

The antimicrobial activity was determined by cup plate method 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 antifungal 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 antifungal activity was compared with known standard drug viz. Fluconazole. The zone of inhibition that displayed by standard drugs are recorded in Table 2.

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: 4000-400cm^{-1} using KBr disc pallet method, ^1H 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.

Reaction Scheme

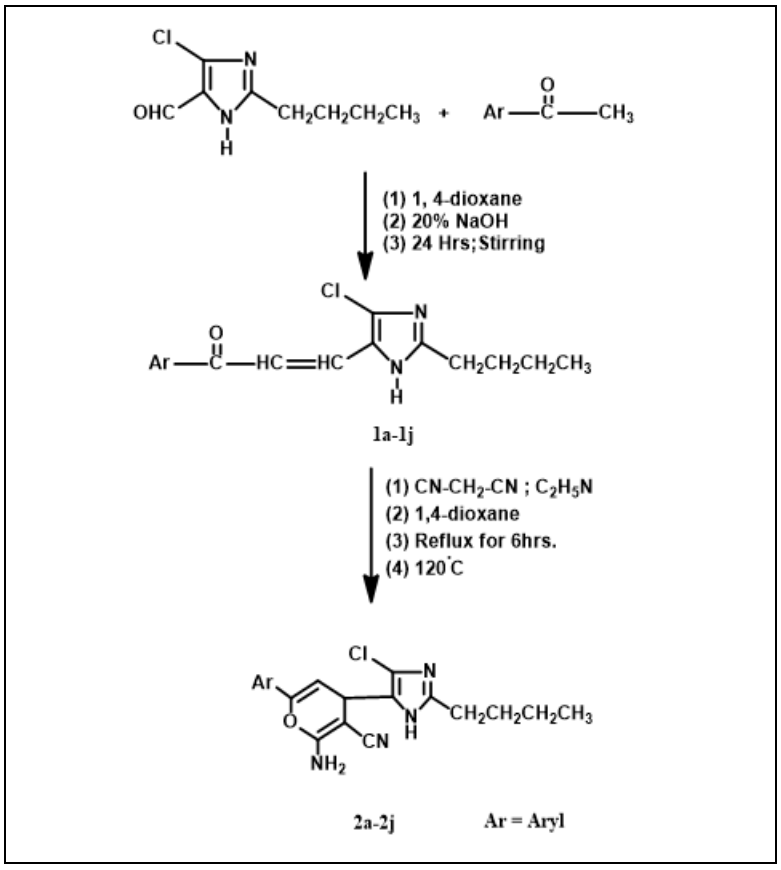

Fig 1

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 (1.87gm, 0.01M); 4-Methoxy acetophenone (1.50gm, 0.01M); 1, 4-dioxane (20ml) and 20% NaOH (20ml) was stirred for 24 hours at room temperature. Completion of reaction was checked with TLC. The reaction mixture was poured into crushed ice, filtered and dried. 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.).

^1H NMR: 0.9 (t, 3H, -C<u>H</u>$_3$); 1.2-1.3 (m, 2H, -C<u>H</u>$_2$-CH$_3$); 1.5-1.6 (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>); 7.4 (d, 1H, -CH=C<u>H</u>-) 7.6 (d, 1H, -C<u>H</u>=CH-); 7.1 (d, 2H, Ar-<u>H</u>); 8.0 (d, 2H, Ar-<u>H</u>); 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.

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

Synthesis of 2-Amino-4-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-6-aryl-4-H-pyran-3-carbonitriles (2i).

A mixture of 3-(2'-n-Butyl-4'-chloro-1'-H-imidazol-5'-yl)-1-(4''-methoxy phenyl)-prop-2-ene-1-one (3.19gm, 0.01M); 1,4-dioxane (20ml); malanonitrile (0.66gm, 0.01M) and pyridine (1ml) was taken in a RBF. The reaction mixture was refluxed in oil bath for 6 hours at 120˚C. On successful completion of the above reaction, the solution was poured into ice cold water. The products were formed, filtered and dried. Completion of reaction was checked with TLC. Crystallization of products was carried out in 1, 4-dioxane.

Yield: 75%; M.P.: >300˚C; (Required: C: 62.42; H: 5.50; N: 14.56%; $C_{20}H_{21}ClN_4O_2$; Found: C: 62.41; H: 5.49; N: 14.50%).
IR (KBr): 2924 (C-H str. Asym.); 2857 (C-H str. Sym.); 1459 (C-H str. def.); 3085 (C-H str.); 1599 (C=C ring skeletal); 1172 (C-H i.p. def.); 736 (C-H o.o.p. str. def.); 1561 (C-N str.); 1511 (C=N str.); 3372 (N-H str.); 1422 (N-H bending); 669 (C-Cl); 2208 (-C≡N str.); 1239 (C-O-C str.).
^{1}H NMR: 0.8-0.9 (t, 3H, -C<u>H</u>$_3$); 1.2-1.3 (m, 2H, -C<u>H</u>$_2$-CH$_3$); 1.5 (m, 2H, -C<u>H</u>$_2$-CH$_2$-CH$_3$); 2.5 (t, 2H, -C<u>H</u>$_2$-CH$_2$-CH$_2$-CH$_3$); 12.1 (s, 1H, -N<u>H</u>); 3.8 (s, 3H, -OCH$_3$); 8.0 (s, 2H, N<u>H</u>$_2$-); 4.9 (d, 1H, Ar-<u>H</u>); 3.4 (d, 1H, Ar-<u>H</u>); 7.6 (d, 2H, Ar-<u>H</u>); 8.2 (d, 2H, Ar-<u>H</u>).
m/z: 353, 342, 327, 286, 277, 249, 201, 185, 157, 135, 107, 98, 77, 57, 43, 41, 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 antimmicrobial activity of compounds (2a-2j). Zone of inhibition in mm.

Sr. No.	Ar	Molecular Formula	M.P. (°C)	% Nitrogen yield		Antibacterial activity				Antifungal activity
						Gram +ve bacteria		Gram –ve bacteria		
				Calcd.	Found	*B. mega.*	*S. aureus*	*S. taphi.*	*E. coli.*	*A. niger*
2a	C_6H_5-	$C_{19}H_{19}ClN_4O$	181	15.79	15.70	11	10	13	17	17
2b	3-OH.C_6H_4-	$C_{19}H_{19}ClN_4O_2$	231	15.11	15.09	16	13	17	19	16
2c	4-OH.C_6H_4-	$C_{19}H_{19}ClN_4O_2$	220	15.11	15.01	10	15	18	20	19
2d	3-NH_2.C_6H_4-	$C_{19}H_{20}ClN_5O$	>300	18.94	18.89	15	17	24	19	19
2e	4-Cl.C_6H_4-	$C_{19}H_{18}Cl_2N_4O$	142	14.39	14.31	20	19	18	21	16
2f	4-Br.C_6H_4-	$C_{19}H_{18}BrClN_4O$	163	12.92	12.88	16	14	17	22	15
2g	3-NO_2.C_6H_4-	$C_{19}H_{18}ClN_5O_3$	287	17.52	17.49	17	15	20	19	22
2h	4-NO_2.C_6H_4-	$C_{19}H_{18}ClN_5O_3$	271	17.52	17.42	23	19	18	20	17
2i	4-OCH_3.C_6H_4-	$C_{20}H_{21}ClN_4O_2$	>300	14.56	14.50	19	23	22	22	18
2j	3-NH_2,2-OH.C_6H_3-	$C_{19}H_{20}ClN_5O_2$	>300	18.15	18.10	17	25	19	24	23

Table 2: Compounds showing comparable antimicrobial activity with known standard drugs.

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

Conclusions

The study emphasis on the synthesis, spectral studies and antimicrobial activity of novel cyano pyran derivatives. The compounds- 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j have showed good remarkable antibacterial and antifungal activity with compared to known standard drugs e.g., Ampicillin, Chloramphenicol, Norfloxacin and Fluconazole at same concentration 50 µg/ml.

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