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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5-(2'-n-BUTYL-4'-CHLORO-1-H-IMIDAZOL-5'-YL)-3-ARYL ISOXAZOLES

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ABSTRACT

5-(2'-n-butyl-4'-chloro-1-H-imidazol-5'-yl)-3-aryl isoxazoles. (2a-2j) 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 characterised by IR, ^{1}HNMR, Mass Spectra and TLC.

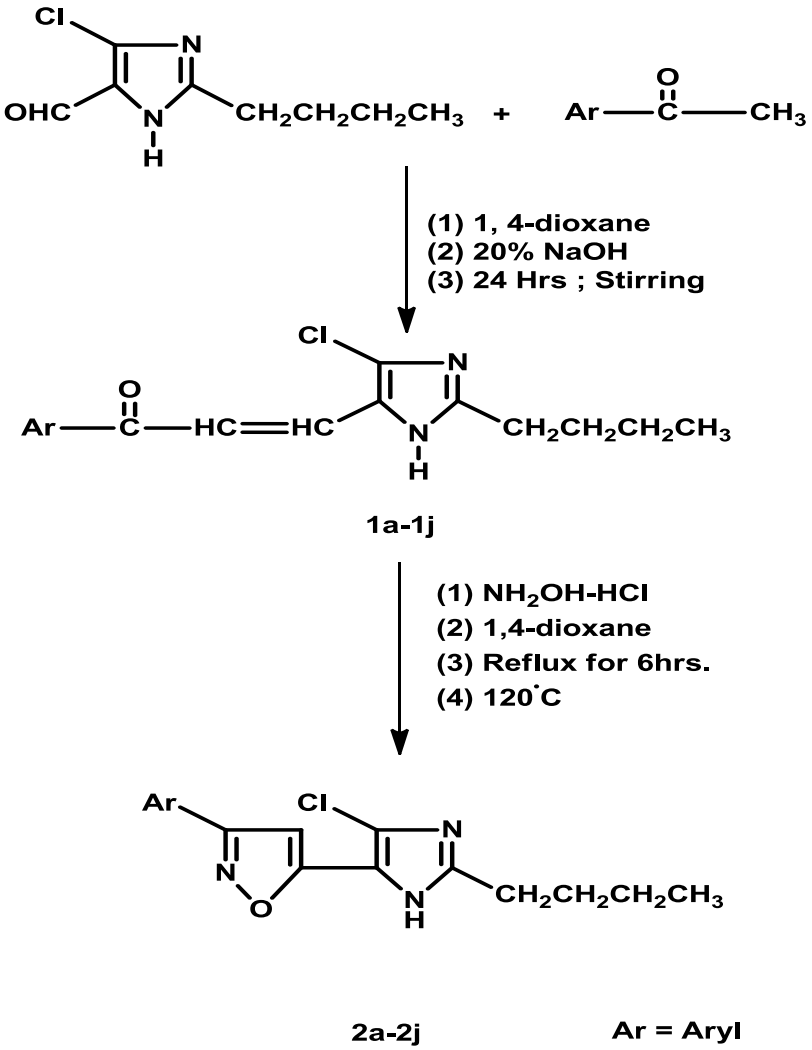
KEYWORDS: Isoxazoles, Anti-microbial activity: (Heterocyclic Compounds).

INTRODUCTION

Isoxazoles derivatives have been found to possess wide range of therapeutic activities as Antibacterial,[1-2] Anticonvulsant,[3-4] Anti-cholestermic,[5] Anticancer,[6] Anti-helmintics,[7] Anti-inflammatory,[8-11] Adenosine antagonist,[12] Fungicidal,[13-16] Herbicidal,[17-18] Hypoglycaemic,[19] Muscle relaxant,[20-21] Nematocidal,[22] Insecticidal,[23] Antiviral,[24] Antimicrobial[25] activity etc. 5-(2'-n-butyl-4'-chloro-1-H-imidazol-5'-yl)-3-aryl isoxazoles (2a-2j) 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 hydroxylamine hydrochloride.

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

Reaction scheme



Scheme I

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, ^{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.

Antimicrobial activity

The antimicrobial activity was determined by cup plate method[26] 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 and the comparable antimicrobial activity, are recorded in TABLE II.

[A] 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); 20% NaOH (20ml) 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 crystallised 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<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, 40.

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

[B] Synthesis of 5-(2'-n-butyl-4'-chloro-1-h-imidazol-5'-yl)-3-(4''-methoxy phenyl)-isoxazole. (2i)

A solution of 3-(2'-n-butyl-4'-chloro-1-H-imidazol-5'- yl)-1-(4''-methoxy phenyl)-prop-2-ene-1-one (3.19gm, 0.01M), Hydroxylamine Hydrochloride (1.39gm, 0.02M) and 1, 4-dioxane (20ml) was refluxed in an oil bath for 6 hrs. at 120˚C temp. Completion of reaction

was checked with TLC. After the completion of reaction, the reaction mixture was poured into crushed ice. Filtered it, dried it. The product was crystallised in 1, 4-dioxane.

Yield: 75%; M.P.: >300°C; (Required: C: 61.54; H: 5.47; N: 12.66%; $C_{17}H_{18}ClN_3O_2$; Found: C: 61.50; H: 5.43; N: 12.56%).

IR (KBr): 2957 (C-H str. asym); 2867 (C-H str. sym); 1438 (C-H str. Def) 3059 (C-H str. aromatic); 1597 (C=C ring skeletal); 1107 (C-H i.p. def); 751 (C-H- str.o.o.p.def); 1509 (C-N str. aromatic); 1438(C=N str. aromatic); 3415 (N-H str. aromatic); 1600 (N-H bending); 792 (C-Cl); 1239 (C-O-C str.).

^{1}H NMR: 0.8-0.9 (T, 3H, -C$\underline{H_3}$); 1.3 (m, 2H, -C$\underline{H_2}$-CH_3); 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, -N$\underline{H}$); 3.8 (S, 3H, -OC$\underline{H_3}$); 7.6 (S, 1H, -C$\underline{H}$); 8.0 (d, 2H, Ar-$\underline{H}$); 7.1 (d, 2H, Ar-$\underline{H}$).

m/z: 332, 317, 300, 289, 275, 233, 224, 199, 175, 168, 157, 133, 107, 98, 77, 68, 57, 43, 41, 40, 31.

Similarly, other compounds (2a-2j) were synthesized.

Table I: The physical data and antimmicrobial activities 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-	$C_{16}H_{16}ClN_3O$	289	13.92	13.90	20	16	15	17	19
2b	3-OH.C_6H_4-	$C_{16}H_{16}ClN_3O_2$	>300	13.22	13.20	18	19	17	20	18
2c	4-OH.C_6H_4-	$C_{16}H_{16}ClN_3O_2$	281	13.22	13.15	14	17	18	19	15
2d	3-NH_2.C_6H_4-	$C_{16}H_{17}ClN_4O$	>300	17.69	17.58	17	23	16	18	17
2e	4-Cl.C_6H_4-	$C_{16}H_{15}Cl_2N_3O$	282	12.50	12.45	14	17	14	16	16
2f	4-Br.C_6H_4-	$C_{16}H_{15}BrClN_3O$	271	11.04	11.00	18	19	23	21	21
2g	3-NO_2.C_6H_4-	$C_{16}H_{15}BrClN_3O_3$	245	16.16	16.10	20	15	17	15	18
2h	4-NO_2.C_6H_4-	$C_{16}H_{15}ClN_4O_3$	260	16.16	16.05	17	18	15	19	17
2i	4-OCH_3.C_6H_4-	$C_{17}H_{18}ClN_3O_2$	>300	12.66	12.56	15	20	18	21	18
2j	3-NH_2, 2-OH.C_6H_3-	$C_{16}H_{15}ClN_4O_4$	298	15.44	15.40	18	21	19	17	23

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

	Compounds	Antibacterial activity Zone of inhibition in mm.				Antifungal activity Zone of inhibition in mm.
		Gram +ve Bacteria		Gram -ve Bacteria		
		B. mega.	***S. aureus***	***S. taphi.***	***E. coli.***	***A. niger***
	(2a-2j)	2a	2d	2f	2b	2f
		2g	2i	2j	2f	2j
		-	2j	-	2i	
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

CONCLUSION

5-(2'-n-butyl-4'-chloro-1-H-imidazol-5'-yl)-3-aryl isoxazoles (2a-2j) have been synthesized. The compounds 2a, 2b, 2d, 2f, 2g, 2i, 2j 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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