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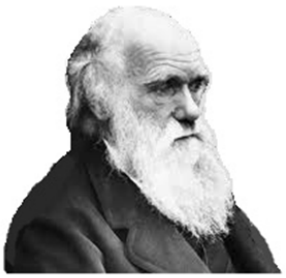

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Synthesis and antimicrobial activity of 5-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-3-aryl-4,5-dihydro-{1-H/1-acetyl/1-phenyl}-pyrazoles

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ABSTRACT

5-(2'-n-butyl-4'-chloro 1'-H-imidazol- 5'-yl)-3-aryl-4, 5-dihydro-1-H-pyrazoles. **(2a-2j)**; 1-[5'-(2"-n-butyl-4"- chloro-1"-H-imidazol-5"-yl)-3'-Aryl-4', 5'-dihydro-1'-H-pyrazol-1-yl]-ethanones. **(3a-3j)**; 5-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-3-Aryl-1-phenyl-4, 5-dihydro-1-H-pyrazoles. **(4a-4j)** have been synthesized. The products have been assayed for their antimicrobial activity against Gram +ve bacteria and Gram –ve bacteria and antifungal activity. The products have been characterised by IR, [1]HNMR, Mass Spectra and TLC.

Keywords: Simple Pyrazoles, Acetyl Pyrazoles, Phenyl Pyrazoles, Antimicrobial activity

1. INTRODUCTION

Pyrazoles derivatives have been found to possess wide range of therapeutic activities as Antimicrobial [1], Anti-inflammatory [2-3], Anti-allergic [4], Anticonvulsant and Antidepressant [5], Anti-diabetic [6], Anti-implantation [7], Antitumor [8], Antineoplastic [9], Analgesic [10-11], Fungicidal [12-13], Bactericidal [14-15], Herbicidal [16], Cardiovascular [17], Anti-amoebic [18], Tranquilizer [19] etc. 5-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-3-aryl-4,5-dihydro-1-H-pyrazoles **(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 hydrazine hydrate; 1-[5'-(2"-n-butyl-4"-chloro-1"-H-imidazol-5"-yl)-3'-Aryl-4',5'-dihydro-1'-H-pyrazol-1-yl]-ethanones **(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

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glacial acetic acid and hydrazine hydrate; 5-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-3-Aryl-1-phenyl-4, 5-dihydro-1-H-pyrazoles **(4a-4j)** 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 phenyl hydrazine.

The products **(2a-2j); (3a-3j); (4a-4j)** were assigned by IR, ^{1}HNMR, mass spectral data, TLC, physical data and antimicrobial activity represented in Table 1, Table 2 and Table 3 respectively.

2. ANTIMICROBIAL ACTIVITY

The antimicrobial activity was determined by cup plate method [20] 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 4.

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.

3. 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, 0.01 M); 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 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 physical data and antimicrobial activities are published in another journal.

3. 2. Synthesis of 5-(2'-n-butyl-4'-chloro 1'-H-imidazol-5'-yl)-3- (4''-methoxy phenyl)-4, 5-dihydro-1-H-pyrazole (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, 0.01 M), hydrazine hydrate (4.8ml, 0.15M) 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: 79%; M.P.: 290 °C; (Required: C: 61.35; H: 6.36; N: 16.83%; $C_{17}H_{21}ClN_4O$; Found: C: 61.31; H: 6.32; N: 16.78%).

IR (KBr): 2927 (C-H str. asym); 2864 (C-H str. sym); 1465 (C-H str. Def); 3019 (C-H str. aromatic); 1597 (C=C ring skeletal); 1179 (C-H i.p. def); 752 (C-H- str.o.o.p.def); 1511 (C-N str.); 1543(C=N str.); 3472 (N-H str.); 1561 (N-H bending); 752 (C-Cl); 1230 (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>); 7.0 (S, 1H, -N<u>H</u>); 4.9 (d, 2H, -C<u>H</u>$_2$); 3.4 (T, 1H, -C<u>H</u>); 8.2 (d, 2H, Ar-<u>H</u>); 7.4 (d, 2H, Ar-<u>H</u>); 3.8 (S, 3H, -OC<u>H</u>$_3$).

m/z: 333, 317, 303, 289, 275, 233, 224, 199, 175, 168, 157, 133, 107, 92, 77, 68, 57, 43, 41, 40.

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-	$C_{16}H_{19}ClN_4$	229	18.50	18.49	14	17	14	12	19
2b	3-OH.C_6H_4-	$C_{16}H_{19}ClN_4O$	152	17.57	17.50	15	15	17	16	**20**
2c	4-OH.C_6H_4-	$C_{16}H_{19}ClN_4O$	280	17.57	17.45	16	13	**20**	15	**22**

2d	3-NH_2.C_6H_4-	$C_{16}H_{20}ClN_5$	>300	22.04	22.00	14	16	**23**	18	**23**
2e	4-Cl.C_6H_4-	$C_{16}H_{18}Cl_2N_4$	219	16.61	16.58	**23**	**20**	18	**23**	19
2f	4-Br.C_6H_4-	$C_{16}H_{18}BrClN_4$	239	14.68	14.60	17	**22**	16	19	17
2g	3-NO_2.C_6H_4-	$C_{16}H_{18}ClN_5O_2$	213	20.14	20.10	18	17	19	15	16
2h	4-NO_2.C_6H_4-	$C_{16}H_{18}ClN_5O_2$	173	20.14	20.05	16	19	18	**20**	15
2i	4-OCH_3.C_6H_4-	$C_{17}H_{21}ClN_4O$	290	16.83	16.78	15	14	17	19	**20**
2j	3-NH_2, 2-OH.C_6H_3-	$C_{16}H_{20}ClN_5O$	162	20.98	20.90	**21**	15	19	16	17

3. 3. Synthesis of 1-[5'-(2"-n-butyl-4"-chloro-1"-H-imidazol-5"-yl)-3'-(4"'-methoxy phenyl)-4',5'-dihydro-1'-H-pyrazole-1-yl]-ethanone (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, 0.01 M), glacial acetic acid (0.6 ml, 0.01 M) and Hydrazine hydrate (0.32 ml, 0.01 M) take in RBF. The reaction mixture was refluxed in oil bath for 6 hrs. at 120 °C temperature. After completion of the reaction, the reaction mixture was poured into crushed ice. The products were formed filtered it, dried it. The product was crystallized in 1, 4-dioxane.

Yield: 76%; M.P.: 295 °C; (Required: C: 60.88; H: 6.18: N: 14.95%; $C_{19}H_{23}ClN_4O_2$; Found: C: 60.82; H: 6.13; N: 14.89%).

IR (KBr): 2927 (C-H str. asym); 2862 (C-H str. sym); 1440 (C-H str. Def); 3077 (C-H str. aromatic); 1597 (C=C ring skeletal); 1179 (C-H i.p. def); 751 (C-H- str.o.o.p.def); 1561 (C-N str.); 1511(C=N str.); 3477 (N-H str.); 1440 (N-H bending); 1680 (C=O str.); 851 (C-Cl); 1230 (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$\underline{H}$); 3.3 (S, 3H, -C=O-C$\underline{H_3}$); 3.8 (S, 3H, -OC$\underline{H_3}$); 7.4 (d, 2H, -C$\underline{H_2}$); 7.6 (T, 1H, -C$\underline{H}$); 7.1 (d, 2H, Ar-$\underline{H}$); 8.0 (d, 2H, Ar-$\underline{H}$).

m/z: 375, 343, 338, 317, 276, 267, 217, 190, 184, 157, 107, 98, 77, 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.

3. 4. Synthesis of 5-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-3-(4''-methoxy phenyl)-1-phenyl-4, 5-dihydro-1-H-pyrazole (4i)

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, 0.01 M), Phenyl hydrazine (0.8 ml) and 1, 4-dioxane (15 ml) take in a RBF. The reaction mixture was refluxed in oil bath for 6 hrs. at 120 °C. After completion

of the reaction, the reaction mixture was poured into crushed ice. The products were formed, filtered it, dried it. The product was crystallized in 1, 4-dioxane.

Yield: 77%; M.P.: 116 °C; (Required: C: 67.55; H: 6.16; N: 13.70%; $C_{23}H_{25}ClN_4O$; Found: C: 67.53; H: 6.14; N: 13.68%).

IR (KBr): 2927 (C-H str. asym); 2864 (C-H str. sym); 1438 (C-H str. Def); 3032 (C-H str. aromatic); 1597 (C=C ring skeletal); 1177 (C-H i.p. def); 691 (C-H- str.o.o.p.def); 1561 (C-N str.); 1545 (C=N str.); 3493 (N-H str.); 1438 (N-H bending); 829 (C-Cl); 1231 (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, -OC<u>H</u>$_3$); 3.3 (d, 3H, -C<u>H</u>$_2$-C<u>H</u>); 7.6 (d, 2H, Ar-<u>H</u>); 8.0 (d, 2H, Ar-<u>H</u>); 7.0 (T, 1H, Ar-<u>H</u>); 8.2 (d, 2H, Ar-<u>H</u>); 7.1-7.2 (d, 2H, Ar-<u>H</u>).

m/z: 409, 377, 351, 333, 308, 275, 251, 224, 184, 157, 133, 107, 98, 77, 57, 43, 41, 40, 31.

Similarly, other compounds (4a-4j) were synthesized.

The physical data and antimicrobial activity of (4a-4j) represented in Table 3.

Table 2. The physical data and antimmicrobial activity of compounds (3a-3j). 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*
3a	C_6H_5-	$C_{18}H_{21}ClN_4O$	276	16.25	16.19	15	16	18	19	18
3b	3-OH.C_6H_4-	$C_{18}H_{21}ClN_4O_2$	157	15.53	15.50	17	13	**20**	**22**	14
3c	4-OH.C_6H_4-	$C_{18}H_{21}ClN_4O_2$	291	15.53	15.45	18	14	19	17	**22**
3d	3-NH_2.C_6H_4-	$C_{18}H_{22}ClN_5O$	>300	19.46	19.40	**22**	17	18	19	16
3e	4-Cl.C_6H_4-	$C_{18}H_{20}Cl_2N_4O$	131	14.77	14.71	17	**22**	18	16	19
3f	4-Br.C_6H_4-	$C_{18}H_{20}BrClN_4O$	135	13.22	13.19	19	17	**24**	18	**21**

3g	3-NO_2.C_6H_4-	$C_{18}H_{20}ClN_5O_3$	149	17.96	17.91	16	13	18	15	**20**
3h	4-NO_2.C_6H_4-	$C_{18}H_{20}ClN_5O_3$	128	17.96	17.89	15	14	19	**20**	17
3i	4-OCH_3.C_6H_4-	$C_{19}H_{23}ClN_4O_2$	295	14.95	14.89	18	19	16	16	18
3j	3-NH_2, 2-OH.C_6H_3-	$C_{18}H_{22}ClN_5O_2$	>300	18.63	18.59	**20**	**23**	17	19	**21**

Table 3. The physical data and antimmicrobial activity of compounds (4a-4j). 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*
4a	C_6H_5-	$C_{22}H_{23}ClN_4$	140	14.79	14.71	13	17	14	14	19
4b	3-OH.C_6H_4-	$C_{22}H_{23}ClN_4O$	146	14.19	14.10	15	19	17	10	**21**
4c	4-OH.C_6H_4-	$C_{22}H_{23}ClN_4O$	184	14.19	14.08	16	14	18	11	15
4d	3-NH_2.C_6H_4-	$C_{22}H_{24}ClN_5$	>300	17.78	17.72	14	19	18	12	18
4e	4-Cl.C_6H_4-	$C_{22}H_{22}Cl_2N_4$	135	13.55	13.49	**20**	18	19	**21**	**22**
4f	4-Br.C_6H_4-	$C_{22}H_{22}BrClN_4$	142	12.24	12.19	**23**	**22**	18	17	14
4g	3-NO_2.C_6H_4-	$C_{22}H_{22}ClN_5O_2$	127	16.52	16.49	19	16	17	15	17

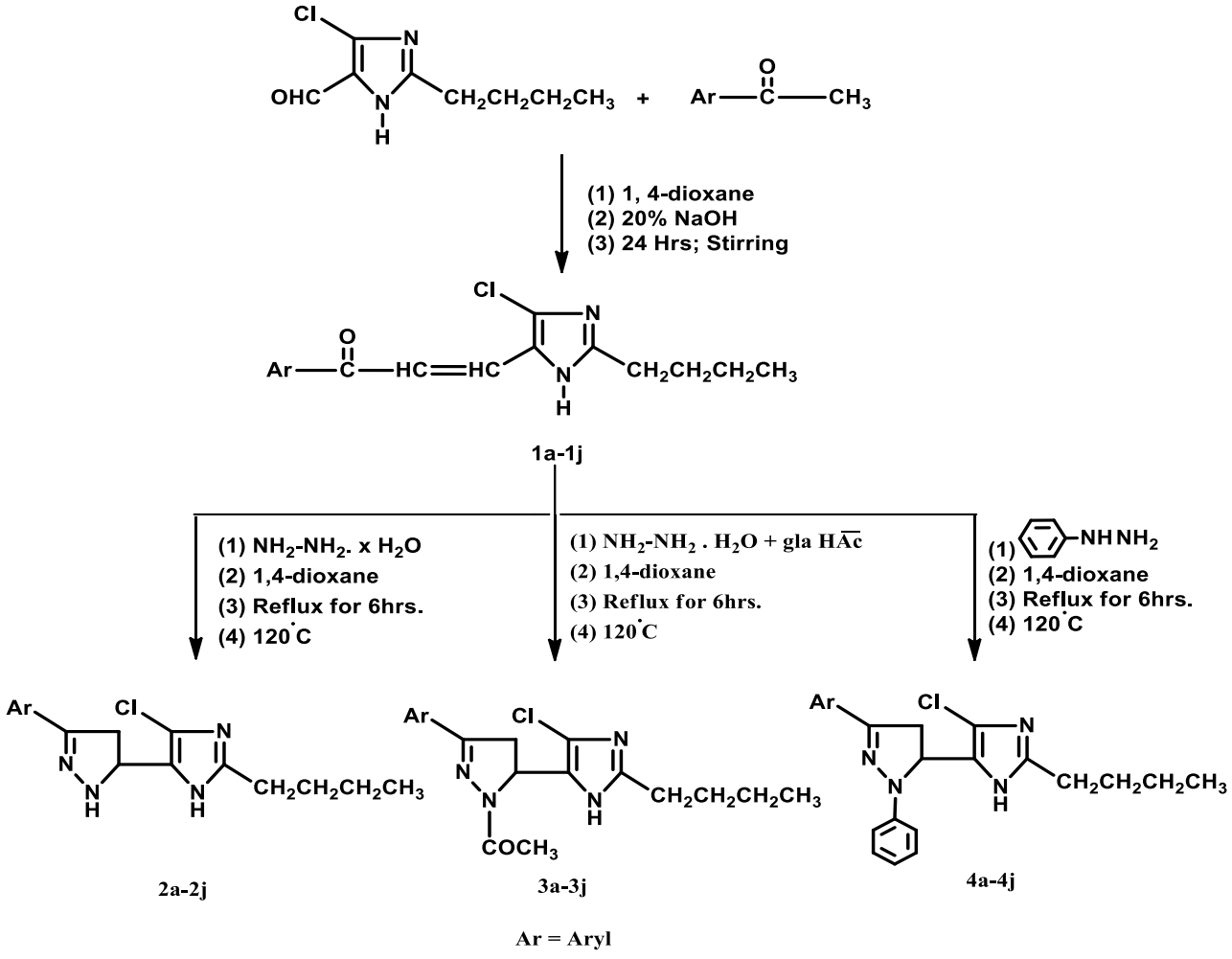
4h	4-NO_2.C_6H_4-	$C_{22}H_{22}ClN_5O_2$	119	16.52	16.45	17	19	**21**	12	**21**
4i	4-OCH_3.C_6H_4-	$C_{23}H_{25}ClN_4O$	116	13.70	13.68	15	**20**	**22**	14	18
4j	3-NH_2, 2-OH.C_6H_3-	$C_{22}H_{24}ClN_5O$	280	17.09	17.10	**21**	19	18	**20**	**20**

Table 4. 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	2e	2c	2e	2b
		2j	2f	2d	2h	2c
		-	-	-	-	2d
		-	-	-	-	2i
	(3a-3j)	3d	3e	3b	3b	3c
		3j	3j	3f	3h	3f
		-	-	-	-	3g
		-	-	-	-	3j
	(4a-4j)	4e	4f	4h	4e	4b
		4f	4i	4i	4j	4e
		4j	-	-	-	4h
		-	-	-	-	4j

Activity of Standard Drugs:						
1	Ampicillin (50 µg/ml)	27	26	25	28	-
2	Chloramphenicol (50 µg/ml)	29	28	27	25	-
3	Norfloxacin (50 µg/ml)	32	30	24	27	-
4	Fluconazole (50 µg/ml)	-	-	-	-	26

4. REACTION SCHEME



Scheme 1

5. CONCLUSIONS

5-(2'-n-butyl-4'-chloro 1'-H-imidazol-5'-yl)-3-aryl-4, 5-dihydro-1-H-pyrazoles. **(2a-2j);** 1-[5'-(2"-n-butyl-4"-chloro-1"-H-imidazol-5"-yl)-3'-Aryl-4',5'-dihydro-1'-H-pyrazol-1-yl]-ethanones. **(3a-3j)** and 5-(2'-n-butyl-4'-chloro-1'-H-imidazol-5'-yl)-3-Aryl-1-phenyl-4,5-dihydro-1-H-pyrazoles. **(4a-4j)** have been synthesized. The compounds 2b, 2c, 2d, 2e, 2f, 2h, 2i, 2j, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3j, 4b, 4e, 4f, 4h, 4i, 4j 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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