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SYNTHESIS OF NOVEL PYRAZOLINE DERIVATIVES CONTAINING IMIDAZO [1, 2-a] PYRIDINES MOIETY VIA LEWIS BASE CATALYST AND THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT

The series of 3-(3-aryl-4, 5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl)imidazo [1, 2-*a*]pyridines **(2a–l)** have been synthesized with better yield within few minutes by using of triethylamine as a catalyst by the condensation of 1-aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1, 2-*a*] pyridin-3-yl]prop-2-ene-1-ones **(1a–l)** with hydrazine hydrate. A considerable increase in the reaction rate has been observed, with better yields. Some of these compounds showed potential antimicrobial activity.

Key words : Chalcones, Triethylamine, Pyrazolines, Antimicrobial activity.

INTRODUCTION

Amongst nitrogen containing five membered heterocycles, pyrazolines have proved to be the most useful frame work for biological activities. Pyrazolines have been reported to show a broad spectrum of biological activities including antinociceptive[1], anti-inflammatory[2], antiamoebic[3], antidepressant[4] and anti-tubercular[5] activities. This stable fragment in bioactive moieties prompted us to synthesize new compounds having better biological activities. The most straightforward protocol for the synthesis of 3-(3-aryl-4, 5-dihydro-1*H*-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl) imidazo [1, 2-*a*] pyridines **2a -l** involves the one-pot condensation of chalcones **(1a–l)** with hydrazine hydrate in the presence of triethylamine catalyst **(Scheme 1)**. The structure of the synthesized compounds has been confirmed on the basis of elemental analysis, ^{1}H NMR, IR and MS spectral data.

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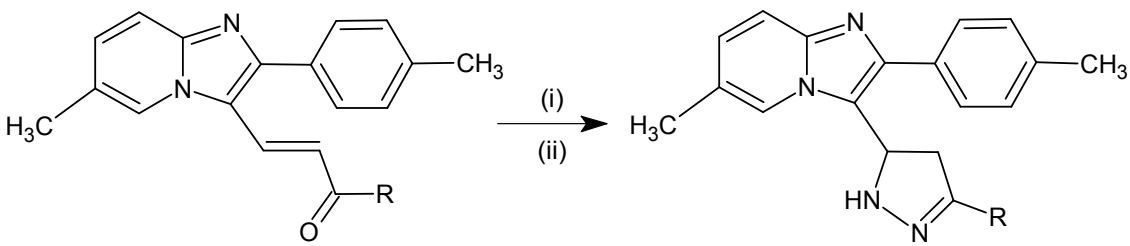
EXPERIMENTAL

Melting points were determined in open capillary and are uncorrected. The purities of the compounds were checked by using TLC (Merck). The IR spectra were recorded on a Simadzu FTIR -8400 instrument in KBr pellets with well defined peaks (cm^{-1}). ^1H NMR spectra were recorded on a Bruker Spectrometer 200 MHz using TMS as an internal standard, chemical shift in δ ppm. Mass spectra were recorded on a Jeol D-300 Spectrometer. The entire synthesized compounds gave satisfactory elemental analysis were carried out on a Carlo Erba 1108 analyzer.

General procedure for the preparation of 3-(3-aryl-4, 5-dihydro-1H-pyrazol-5-yl)-6-methyl-2-(4-methylphenyl) imidazo [1, 2-a]pyridines

In a mixture of 1-aryl-3-[6-methyl-2-(4-methylphenyl) imidazo [1, 2-a] pyridin-3-yl]prop-2-ene-1-one (0.01 mol), hydrazine hydrate 1.0g (0.02 mol) and methanol 25.0 mL, triethylamine was added as a catalyst and stirred for 10 min at 40ºC. The reaction mass cooled at 10-15ºC for 1 hr. The product was filtered and dried it. The crude product was recrystallized from ethanol.



(1a-l) **(2a-l)**

R = Aryl

Scheme 1

(i) $NH_2NH_2H_2O$, (ii) TEA

Other compounds **(2a-l)** were prepared similarly. The physical data of novel synthesized compounds are recorded in Table 1.

The spectral data for compound 3-[3-(4-methoxyphenyl)4, 5-dihydro-1H-pyrazol-5-yl]-6-methyl-2-(4-methylphenyl)imidazo[1, 2-a]pyridine are as follows –

Table 1 : The physical data of all synthesized compound 2a-l.

Compd.	R	mp (°C)	Yield (%)	Nitrogen (%) Calcd. (Found)
2a	4-OCH_3-C_6H_4-	204	72	14.14 (14.12)
2b	4-Cl-C_6H_4-	194	75	13.98 (13.90)
2c	C_6H_5-	92	65	15.30 (15.25)
2d	2, 4-$(Cl)_2$-C_6H_3-	196	72	12.87 (12.96)
2e	4-NO_2-C_6H_4-	>200	65	17.03 (17.08)
2f	4-CH_3-C_6H_4-	147	68	14.73 (14.68)
2g	4-OH-3-OCH_3-C_6H_3-	242	71	13.59 (13.50)
2h	4-Br-C_6H_4-	180	62	12.58 (12.52)
2i	2-OH-C_6H_4-	202	70	14.65 (14.62)
2j	4-OH-C_6H_4-	208	75	14.65 (14.60)
2k	4-NH_2-C_6H_4-	>186	78	16.94 (16.90)
2l	2-C_4H_3S-	228	76	15.05 (15.10)

IR (KBr) cm^{-1} : 2956 (C-H, asym str.), 2854 (C-H, sym str.), 1454 (C-H, def), 1517 (C=C, str.), 3016 (aromatic C-H, str.), 1568 (imidazo C=N, str.), 3301 (pyrazoline N-H, str.).

^1H NMR ($CDCl_3$) δ ppm : 2.27 (s, 3H, CH_3 of imidazo ring), 2.39 (s, 3H, CH_3 of phenyl ring), 3.34-3.40 (d, 2H, CH_2 of pyrazoline), 3.85 (s, 3H, -OCH_3), 5.58-5.77 (double doublet, 1H, CH of pyrazoline), 6.93-6.97 and 7.64-7.68 (two doublets, 4H, J = 8.6Hz, aryl proton of p-methoxy ring), 7.24-7.27 and 7.50-7.54 (two doublets, 4H, J = 8.4Hz, aryl proton of p-methyl ring).

MS m/z value : 396, 247, 222, 206, 174, 145 and 131.

Antimicrobial activity

The anti microbial activity was observed using the cup-plate agar diffusion method[6] by measuring the zone of inhibition in millimeter. All the compounds were screened *in vitro* for their antimicrobial activity against variety of bacterial strain such as *S. aureus*, *B. subtilis*, *P. aeruginosa*, *E. coli* and fungi *A. niger* using dimethyl sulphoxide solvent at 40 µg concentration. Standard drugs like amoxicillin, benzyl penicillin, ciprofloxacin, erythromycin and griseofulvin were used for comparison purpose.

The antimicrobial screening data of all synthesized compounds are recorded in Table 2.

Table 2 : Antimicrobial screening data of compounds (2a-l)

Compd.	*S. aureus*	*B. subtilis*	*E. coli*	*P. Aeruginosa*	*A. niger*
2a	12	12	20	8	13
2b	21	18	17	9	16
2c	12	16	19	15	18
2d	18	19	11	17	18
2e	10	9	12	18	14
2f	18	13	15	17	12
2g	15	8	20	12	12
2h	21	16	17	21	20
2i	12	10	9	6	16
2j	16	14	17	17	14
2k	14	20	21	14	21
2l	22	15	19	17	14
Amoxicillin	24	22	21	18	0
Benzyl penicillin	24	20	21	22	0
Ciprofloxacin	17	17	23	20	0
Erythromycin	18	24	19	21	0
Griseofulvin	0	0	0	0	24

RESULTS AND DISCUSSION

It was interesting to note that the reaction occurred immediately after the addition of the hydrazine hydrate to the solution of chalcone in presence of triethylamine catalyst This work demonstrates a very simple and efficient method for the synthesis of a well functionalized pyrazoline derivatives of biological importance with excellent yields. Also, the results of antimicrobial activity have proved importance of these synthesized novel compounds.

Antimicrobial activity

The screening data indicated that among pyrazolines tested compounds **2b**, **2l** and **2h** showed greater degree of antibacterial activity against *S. aureus*. However, the compounds **2k** showed greater degree of antibacterial activity against *B. subtilis*, the compounds **2a**, **2g** and **2k** showed greater degree of antibacterial activity against *E. coli* and **2h** greater degree of antibacterial activity against *P. aeruginosa*. 2h and 2k showed greater degree of antifungal activity against *A. niger*.

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