**Synthesis, spectral studies,
antibacterial and antifungal activity of
2" – methoxy - 4" -[2 - (4' -chlorophenyl)-6-methyl imidazo [1, 2-a]
pyridin-3-yl]-6"-aryl nicotinonitrile**

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ABSTRACT

Pyridine nucleus plays an important role in medicine, agriculture and industrial chemistry. With a view of biological activities and variety of industrial applications, some new 2" – methoxy - 4" - [2 - (4' -chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-aryl nicotinonitrile(**4a-4l**) has been synthesized. The products have been assayed for their biological activity against Gram +ve, Gram – ve bacteria and fungi. Some of the products showed moderate activity in concentration 50µg/ml. The structures of the products have been elucidated by IR, ¹H-NMR, Mass spectral data, elemental analysis and thin layer chromatography.

1. INTRODUCTION

Imidazo[1,2-a] pyridines are potential bioactive agents due to their wide spectrum of therapeutic importance. A large number of substituted imidazo[1,2-a]pyridine derivatives are prepared and tested for varieties of biological activities such as, antiallergic¹, antagonist^{2,3}, antifunga⁴, antiepileptic⁵, antibacterial⁶, anticonvulsant⁷, antitubercular⁸, analgesic⁹, insecticidal¹⁰, antisoriasis¹¹, antihypertensive¹² etc. In view of getting to synthesized imidazo [1,2-a] pyridine derivatives and evaluated for their antibacterial antifungal activity.

Pyridine, nucleus has been extensively explored for their applications in the field of medicine, agriculture and industrial chemistry. Although many substituted pyridine compounds like other heterocyclic compounds are synthesized with their functional group present from cyclic compounds.

In our continuation work in the chemistry of pyridine nucleus, we have undertaken the synthesis of imidazo[1,2-a]pyridine derivatives such as 2"-methoxy-4"-[2-(4'-Chlorophenyl)-6 - methyl imidazo [1,2-a] pyridine -3-yl]- 6"-aryl nicotinonitrile via chalcone in presence of malononitrile and sodium methoxide.

The products (**4a-4l**) were assigned the IR, ¹H-NMR, Mass spectral data, elemental analysis and TLC. The physical data and antimicrobial activities are represented in Table – I.

2. ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY

2"-methoxy-4"-[2-(4'-Chlorophenyl)-6 - methyl imidazo [1,2-a] pyridine-3-yl]- 6"-aryl nicotinonitriles were evaluated in vitro for their antibacterial activities against Gram +ve and Gram –ve bacteria such as *Bacillus megaterium*, *Salmonella taphimurium*, *staphylo coccus aureus*, *Escherichia coli* and antifungal activity against *Aspergillus niger* using DMF as solvent at 50 µg / ml. concentration by cup-plate method¹⁵. After 24 hrs of incubation at 37°C, the zones of inhibition were measured in mm. The activity was compared with the known standard drugs, viz., ampicillin, chloramphenicol, norfloxacin, gresiofulvin at same concentration.

All the synthesized compounds (**4a-4l**) showed moderate to good and remarkable activities with known standard drugs at the same concentration, which is represented in Table-I.

Reaction scheme

Table: I

The physical data and antimicrobial activities of compounds (**4a-4l**). [Zone of Inhibition in mm]

Compound Id	Ar	Molecular Formula	M.P. °C	Antibacterial Activity				Antifungal Activity <i>A. niger</i>	% of Nitrogen	
				<i>B. Mega</i>	<i>S. aureus</i>	<i>E. Coil</i>	<i>S. typhi</i>		Calcd.	Found
4a	C ₆ H ₅	C ₂₇ H ₁₉ ClN ₄ O	190	16	15	13	19	14	12.43	12.40
4b	3-Cl-C ₆ H ₄	C ₂₇ H ₁₈ Cl ₂ N ₄ O	185	18	19	19	18	19	11.54	11.51
4c	4-Cl-C ₆ H ₄	C ₂₇ H ₁₈ Cl ₂ N ₄ O	170	19	13	15	19	18	11.54	11.52
4d	2,4-Cl ₂ -C ₆ H ₃	C ₂₇ H ₁₇ Cl ₃ N ₄ O	195	14	14	17	23	21	10.78	10.76
4e	4-F-C ₆ H ₄	C ₂₇ H ₁₈ ClFN ₄ O	200	15	22	14	25	18	11.95	11.93
4f	4-Br-C ₆ H ₄	C ₂₇ H ₁₈ BrClN ₄ O	222	18	14	16	17	19	10.57	10.55
4g	4-OH-C ₆ H ₄	C ₂₇ H ₁₉ ClN ₄ O ₂	180	21	17	22	19	18	12.00	12.00
4h	4-NH ₂ -C ₆ H ₄	C ₂₇ H ₂₀ ClN ₅ O	165	20	15	23	23	22	15.03	15.01
4i	4-CH ₃ -C ₆ H ₄	C ₂₈ H ₂₁ ClN ₄ O	159	21	23	21	19	17	12.05	12.02
4j	4-OCH ₃ -C ₆ H ₄	C ₂₈ H ₂₁ ClN ₄ O ₂	160	17	14	17	24	17	11.65	11.61
4k	3-NO ₂ -C ₆ H ₄	C ₂₇ H ₁₈ ClN ₅ O ₃	167	16	17	13	15	14	14.12	14.10
4l	4-NO ₂ -C ₆ H ₄	C ₂₇ H ₁₈ ClN ₅ O ₃	188	14	15	15	16	13	14.12	14.11

3. EXPERIMENTAL SECTION

All the melting point was measured by open glass capillary method and are uncorrected. IR absorption spectra ($\nu_{\max}$ in cm^{-1}) were recorded on a shimadzu IR -435 spectrophotometer using KBr pellet method, ^1H -NMR spectra on Hitachi, R-1200 (300-mHz) spectrometer using DMSO- d_6 method, as internal standard (chemical shift in, δ ppm) and mass spectra on a Joel 300 ev. The compounds were routinely checked by the TLC using silica gel-G.

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl) imidazo[1,2-a]pyridine (1)

Arranged 1.0 lit 4/N RBF equipped with stirrer thermo pocket and condenser. Charge 100ml methanol and 21.3g (0.1 mole) (4-chlorophenyl)acetyl chloride and then charge 11.9g (0.11mole) 2-amino-5- methyl pyridine at room temperature stir till clear solution. Add drops-wise triethyl amine at room temperature till pH adjust 8 to 9. After addition complete heat 60-65°C for 3 to 4 hrs then check TLC. After complies TLC cool reaction mass at room temperature and poured in 1.0 lit water & filter it. Yield 86%, m.p. 200°C.

Anal. Calcd. For $\text{C}_{14}\text{H}_{11}\text{ClN}_2$; Require : C, 69.28, H, 4.53, N, 11.54 %; Found: C, 69.26, H, 4.52, N, 11.50%. IR (KBr, cm^{-1}) : 2958 (C-H str, Sym,); 1466, (C-H def, asym.); 1368 (C-H def, asym.); 3650 (C-H Str. Aromatic); 801 (C- H, Str, o.p.p def.); 1488 (C=C str.); 1350 (C-N str.); 760 (C-Cl Str.); 1648 (C=N Str.) ^1H -NMR (DMSO- d_6 , δ ppm); 2.3 (s, 3H -CH₃); 7.02-7.94 (m, 8H, Ar-H). m/z: 44, 65, 77, 92, 110, 219, 242.

[B] Synthesis of 6 – methyl – 2 - (4'-chlorophenyl) imidazo [1, 2-a] pyridine – 3 - Carboxaldehyde (2)

Arranged 2.0 lit 4/N RBF equipped with stirrer, thermo pocket and condenser in water bath. Charge 84 ml DMF and 1.0 lit CHCl_3 in RBF and cool at 0 - 5°C. Start drop-wise addition of 165ml POCl_3 within 1.0 hr (exothermicity observed). Stir 30 min at 0-5°C. Add 50g of 6-methyl-2-(4-chlorophenyl)imidazo[1,2-a]pyridine slowly temp raise till reflux for 6.0 hrs. Remove CHCl_3 by vacuum distillation. Cool reaction mass at room temperature and poured in 2.0 lit ice cold water. Below room temperature pH adjust neutral by caustic solution. Filter and crystallized from methanol. Yield 70%, m.p.180°C.

Anal. Calcd. For $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}$; Require: C, 66.55, H, 4.10, N, 10.35 %; Found: C, 66.54, H, 4.08, N, 10.33%) IR (KBr, cm^{-1}) : 2900 (C-H str, Sym,), 1369 (C-H def, sym.) ; 1475 (C-H def, asym.); 3650 (C-H Str. Aromatic); 799 (C- H, Str, o.p.p def.) ; 1508 (C=C str.); 1110 (C-N str.); 1715 (C=O); 2820-2750(C-H Str.); 1680 (C=N). ^1H -NMR (DMSO- d_6 , δ ppm); 2.4 (s, 3H -CH₃); 7.2-9.4 (m, 7H Ar-H) ; 10.0 (s, CHO). m/z: 44, 56, 65, 79, 111, 129, 230, 256, 270.

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1''-(4'''methylphenyl)-2''-prop- en-1''ones-3-yl]-imidazo[1,2-a]pyridine (3i)

Dissolve 6-methyl- 2 - (4'-chlorophenyl)imidazo[1,2-a] pyridine3-carboxaldehyde (2.91gm,0.01mol) in a mixture of methanol (50 ml) and DMF (50 ml). To this add p-methyl acetophenone (1.40gm, 0.01mol) and Stir the content at room temperature for 24 hrs in presence of catalytic amount of 40% NaOH. The resulting solution was poured on to crushed ice, thus the solid separated was filtrated and crystallized from ethanol, Yield 56 %, m. p. 170°C.

Anal. Calcd. For $\text{C}_{24}\text{H}_{19}\text{ClN}_2\text{O}$: Require; C, 74.51, H, 4.95, N,7.24% ; Found: C, 74.50, H, 4.93, N, 7.22%. IR (KBr, cm^{-1}): 2860 (C-H str, Sym,); 1470 (C-H def, asym.); 1350 (C-H def, asym.); 3640 (C-H Str. Aromatic); 750 (C- H, Str, o.p.p def.); 1530 (C=C str.); 1350 (C-N str.); 1693 (C=O) 650 (C-Cl Str.). ^1H -NMR (DMSO- d_6 , δ ppm): 2.43-2.44 (s, 6H, -CH₃); 7.22-8.14 (m, 13H, Ar-H); m/z : 44, 65, 91, 119, 292, 242, 267, 386.

Similarly other compounds (3a-3l) were prepared and their physical data are published in our continuous publication.

[D] Synthesis of 2'' –methoxy -4'' -[2 -(4' -chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]-6''-(4'''-methylphenyl) nicotinonitrile (4i)

To a solution of 2-(4'-chlorophenyl)-6-methyl- 3-[1''-(4'''-methylphenyl)- 2''-propene-1''-one-3-yl]-imidazo[1,2-a]pyridine (3.88 gm, 0.01 mol), malononitrile (0.60gm, 0.01 mol) and sodium methoxide in methanol (25ml). The content was heated under reflux with stirring for 12 hrs. The reaction mixture was poured into ice-water and extracted with chloroform. The excess solvent was distilled out and product was crystallized from ethanol. Yield 62%, m.p. 159°C.

Anal. Calcd. For $C_{28}H_{21}ClN_4O$; Required : C, 72.33; H, 4.55; N, 12.05 %; found : C, 71.31; H, 4.53; N, 12.02 %; IR (KBr, cm^{-1}): 2894 (C-H str, Sym,); 1373 (C-H def, sym.); 1440 (C-H def, asym.); 3650 (C-H Str. Aromatic); 799 (C- H, Str, o.p.p def.); 1494 (C=C str.); 1117 (C- N str.); 1209 (C-O-C); 2923-2894 (C-H Str.); 1595 (C=N); 703(C-Cl); 1H -NMR ($CDCl_3$, δ ppm); 2.3-2.4 (s, 3H –CH₃); 7.1-7.6 (m, 7H Ar-H); 4.2 (s, OCH₃). m/z: 43, 112, 132, 205, 224, 242, 268, 374, 464.

Similarly, other 2'' – methoxy - 4'' - [2 - (4' -chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]-6''- aryl nicotinonitriles were prepared. The physical data are recorded in Table No. I.

Table: II

Compounds showing comparable antibacterial and antifungal activity with known standard drugs.

Compound	<i>B.maga</i>	<i>S.aureus</i>	<i>E.Coli</i>	<i>S.typhi</i>	<i>A.niger</i>
(4a – 4l)	4g,4h,4i	4b,4e,6i	4b,4g,4h,4i	4d,4e,4h,4j	4d,4h,
Activity of standard drugs.					
Compound	<i>B.maga</i>	<i>S.aureus</i>	<i>E.Coli</i>	<i>S.typhi</i>	<i>A.niger</i>
1.Ampicillin	22	19	19	22	
2.chloramphenicol	22	23	22	25	
3.norfloxacin	22	22	24	23	
4.greseofulvin					22

4. CONCLUSION

2'' – Methoxy - 4'' - [2 - (4' -chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]-6''- aryl nicotinonitrile (**4a-4l**) have been synthesized. Some of the compounds showed good remarkable antibacterial and antifungal activity with compare to known standard drugs e.g. Ampicillin, chloramphenicol, norfloxacin and gresiofulvin at same concentration 50µg/ml.

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