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Synthesis, spectral studies, antibacterial and antifungal activity of 2" – amino - 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" – amino - 4" - [2 - (4' -chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-aryl nicotinonitriles (**4a-4l**) have 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, ^{1}H-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, Antiallergic[1], Antagonist[2,3], Antifungal[4], Antiepileptic[5], Antibacterial[6], Anticonvulsant[7], Antitubercular[8], Analgesic[9], Insecticidal[10], Antisoriasis[11], Antihypertensive[12] etc. In view of getting to synthesized imidazo [1, 2-a] pyridines derivatives and evaluated for their antibacterial activity and 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. The simple pyridine compounds are prepared by the cyclization of aliphatic raw material. The availability of 3-cyanopyridines, nicotinamide and nicotinic acid make possible their use as synthetic intermediates.

In the past years, considerable evidence has been accumulated to demonstrate the efficiency of cyanopyridines. To further assess the potential of such class of compounds, cyanopyridine derivatives of 2" – amino - 4" - [2 - (4' -chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-6"-aryl nicotinonitryles have been prepared, by the cyclocondensation of 2-(4'-chlorophenyl)-6-methyl-3-(1"-aryl- 2"-propene-1"-one-3-yl) -imidazo [1,2-a] pyridines in presence of malononitrile and ammonium acetate.

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

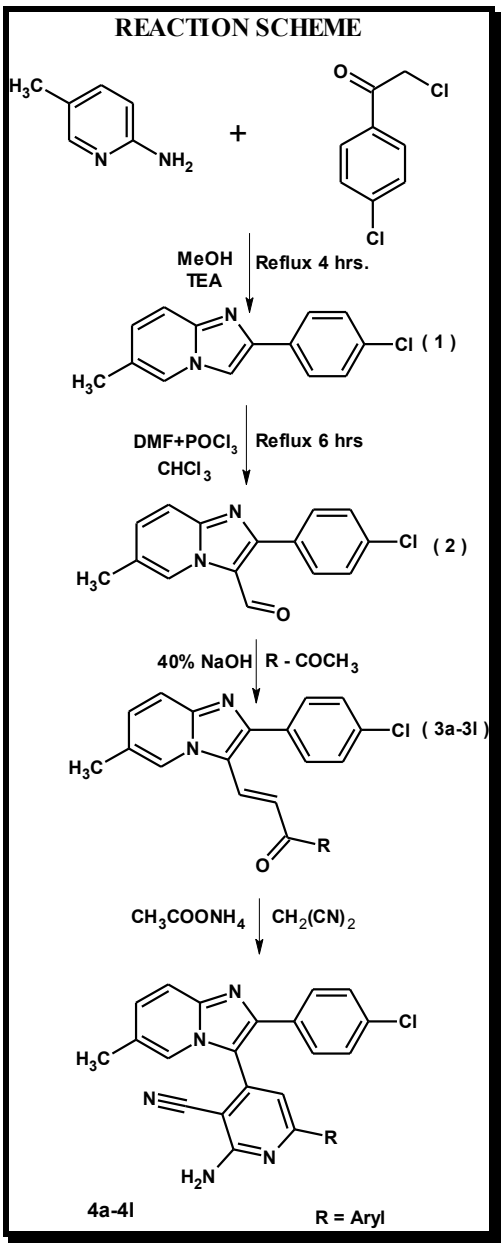
REACTION SCHEME
MeOH
TEA
Reflux 4 hrs.
(1)
DMF+POCl3
CHCl3
Reflux 6 hrs
(2)
40% NaOH
R - COCH3
(3a-3l)
CH3COONH4
CH2(CN)2
4a-4l
R = Aryl

Table: I

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

Compound Id	Ar	Molecular Formula	M.P. ^{0}C	Antimicrobial Activity				Antifungal Activity	% of Nitrogen	
				B. Mega	*S.aureus*	*E.Coil*	*S. typhi*	*A. niger*	Calcd.	Found.
4a	C_6H_5-	$C_{26}H_{18}ClN_5$	210	16	14	13	15	17	16.07	16.05
4b	3-Cl-C_6H_4-	$C_{26}H_{17}Cl_2N_5$	180	18	16	15	14	14	14.89	14.87
4c	4-Cl-C_6H_4-	$C_{26}H_{17}Cl_2N_5$	195	19	21	17	19	19	14.89	14.86
4d	2-4-$(Cl)_2$-C_6H_3-	$C_{26}H_{16}Cl_3N_5$	160	22	19	16	17	22	13.87	13.85
4e	4 -F-C_6H_4-	$C_{26}H_{17}ClFN_5$	205	21	17	21	24	21	15.43	15.41
4f	4-Br-C_6H_4-	$C_{26}H_{17}BrClN_5$	165	19	16	19	23	18	13.60	13.59
4g	4 -OH-C_6H_4-	$C_{26}H_{18}ClN_5O$	190	18	17	23	19	18	15.50	15.48
4h	4-NH_2-C_6H_4-	$C_{26}H_{19}ClN_6$	150	16	22	17	24	22	18.64	18.62
4i	4-CH_3-C_6H_4-	$C_{27}H_{20}ClN_5$	159	15	17	17	19	16	15.57	15.56
4j	4-OCH_3-C_6H_4-	$C_{27}H_{20}ClN_5O$	169	22	16	16	17	19	15.03	15.01
4k	3-NO_2-C_6H_4-	$C_{26}H_{17}ClN_6O_2$	177	16	24	24	17	12	17.48	17.45
4l	4-NO_2-C_6H_4-	$C_{26}H_{17}ClN_6O_2$	185	13	17	17	15	13	17.48	17.46

2. EXPERIMENTAL SECTION

All the melting point was measured by open glass capillary method and are uncorrected. IR absorption spectra (νmax in cm^{-1}) were recorded on a Shimadzu IR -435 spectrophotometer using KBr pellet method, ^{1}HNMR spectra on Hitachi, R-1200 (300-mHz) spectrometer using DMSO-d6 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^{o}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^{o}C. ,

Anal. Calcd. For $C_{14}H_{11}ClN_2$: Require; C, 69.28, H, 4.53, N, 11.54 %, Cl,14.63. 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.). ^{1}H-NMR (DMSO-d6, δ ppm); 2.3 (s, 3H, $–CH_3$); 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^{o}C. Start drop wise addition of 165 ml $POCl_3$ within 1.0 hr (exothermicity observed) stir 30 min at 0-5^{o}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^{o}C.

Anal. Calcd. For $C_{15}H_{11}ClN_2O$: 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). ^{1}H-NMR (DMSO-d6, δ ppm); 2.4 (s, 3H $–CH_3$); 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] pyridine-3-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 seprated was filterated and crystallized from ethanol, Yield 56 %, m. p. 170^{o}C.

Anal. Calcd. For $C_{24}H_{19}ClN_2O$: 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.). ^{1}H-NMR (DMSO-d6, δ ppm); 2.43-2.44 (s, 6H, $–CH_3$); 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 publications.

[E] Synthesis of 2"–amino - 4"-[2 -(4'–chlorophenyl) – 6 - methyl imidazo [1, 2– a] pyridine –3–yl]- 6"-(4"'-methylphenyl) nicotinonitriles (4i)

A mixture of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"' -methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine. (3.40 g, 0.01 mol), malononitrile (0.66 g, 0.01 mol) and ammonium acetate (2.31 g, 0.03 mol) in DMF (30 ml) was refluxed for 8 hrs. The content was

poured in to crushed ice. The solid was obtained filtered, washed with water and crystallized from dioxane. Yield 58%, m.p. 159 ^{o}C.

Anal. Calcd. For $C_{27}H_{20}ClN_5$: Required : C, 72.07; H, 4.48; N, 15.57 %; found : C, 72.07; H, 4.48; N, 15.56 %; IR (KBr, cm^{-1}): 2941 (C-H str, Sym,) ; 1384 (C-H def, sym.); 1456 (C-H def, asym.); 3052 (C-H Str. Aromatic); 796 (C- H, Str, o.p.p def.); 1490 (C=C str.) ; 1186 (C-N str.); 2941 (C-H Str.); 1598 (C=N);703(C-Cl). ^{1}H-NMR ($CDCl_3$, δ ppm); 2.22-2.26 (s, 3H $-CH_3$); 6.9-8.0 (m, 12H, Ar-H); 4.2 (s, Ar-NH_2). m/z: 51,66, 119, 209, 242, 304, 435, 449.

Similarly other 2" – amino - 4" - [2 - (4' -chlorophenyl)-6-methyl imidazo [1,2-a] pyridine 3-yl]-6"-aryl nicotinonitriles were synthesized. The physical data are recorded in Table No. I.

3. ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY

2"-amino-4"-[2-(4'-Chlorophenyl)-6 - methyl imidazo [1, 2–a] pyridine – 3- yl]- 6"-aryl nicotinonitrile products were evaluated in vitro for their antimicrobial activities against *Bacillus megaterium, Salmonella taphimurium, staphylo coccus aureus, Escherichia coli* and *Aspergilus niger* using DMF as solvent at 50 µg / ml. concentration by cup-plate method[13]. After 24 hrs of incubation at 37^{o}C, The zones of inhibition were measured in mm. The activity was compared with the known 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. The comparable antibacterial and antifungal activity is represented in Table-II.

Table: II

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

Compound	***B.maga***	***S.aureus***	***E.Coli***	***S.typhi***	***A.niger***
(4a – 4l)	4c,4f,4h	4c,4f,4j,4k	4c,4h,4i,4j	4d,4f,4j,4k	4d,4e,4l.
Activity of standard drugs.					
Compound	***B.maga***	***S.aureus***	***E.Coli***	***S.typhi***	***A.niger***
1.Ampicillin	22	19	19	22	---
2.chlorampenicol	22	23	22	25	---
3.norfloxacin	22	22	24	23	---
4.gresiofulvin	---	---	---	---	22

4. CONCLUSION

2" – amino - 4" - [2 - (4' -chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]-6"- aryl-nicotinonitriles (**4a-4l**) have been synthesized. The compounds **4c**, **4d**, **4f**, **4j**, **4k**, 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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