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Synthesis and antimicrobial screening of 2"-amino-4"-[2-(4'-chlorophenyl) -6-methyl imidazo[1, 2-a]pyridine -3-yl]-6"-aryl-4"-H-pyran-3"- carbonitrile

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ABSTRACT

3-Cyano-4,6-disubstituted 4H-pyrans are endowed with a variety of pharmacodynamic activities Looking to the interesting properties of cyanopyrans, it was considered worthwhile to synthesis some new 2"-amino-4"-[2-(4'-chlorophenyl) -6-methyl imidazo [1,2-a] pyridin-3-yl]-6"-aryl- 4"-H-pyran-3"- carbonitrile (**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, Antifungal[1-3], Antiallergic[4], Analgesic[5], Antagonist[6,7], Antitumor[8], CNS active agent[9], Cytotoxic[10], Inhibitors of cell proliferation[11], Gastric acid secretion inhibitor[12], Antimicrobial[13], Hypolipidemic[14], Antipyretic[15] etc. In view of getting to synthesized imidazo[1,2-a] pyridines derivatives and evaluated for their antimicrobial activity.

Heterocyclic compounds such as pyran derivatives continue to be a rich source of innovative chemistry because a number of pharmaceutical, dyestuffs, sweaty-smelling substances, insecticide possess this ring system. Pyran ring system is also present in large number of naturally occurring colored compounds, in vitamin-E, hemorrhagic compounds in cloves, in certain alkaloids and other substances.

Pyran is a doubly unsaturated six member ring system with single oxygen as hetero atom. The two double bonds may be conjugated as α, β or 1,2-pyran or isolated as in α, δ or 1,4-pyran. A degree of stabilization of the pyran nucleus is achieved by substituting phenyl group in the 2 or 4 and preferably also in the 6 position.

Cyanopyrans have been synthesized by the Condensation of 2 - (4' – chlorophenyl) – 6 – methyl–3 [1"-aryl-2"-prop-en-1"-ones-3-yl]imidazo[1,2-a] pyridines with malononitrile. 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.

2. ANTIMICROBIAL ACTIVITY

2"-amino-4"-[2-(4'-chlorophenyl) -6-methyl imidazo [1, 2-a] pyridin-3-yl]-6"-aryl- 4"-H-pyran-3"- carbonitrile (**4a-4l**) products 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 *Aspergilus niger* using DMF as solvent at 50 µg / ml. concentration by cup-plate method[15]. 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

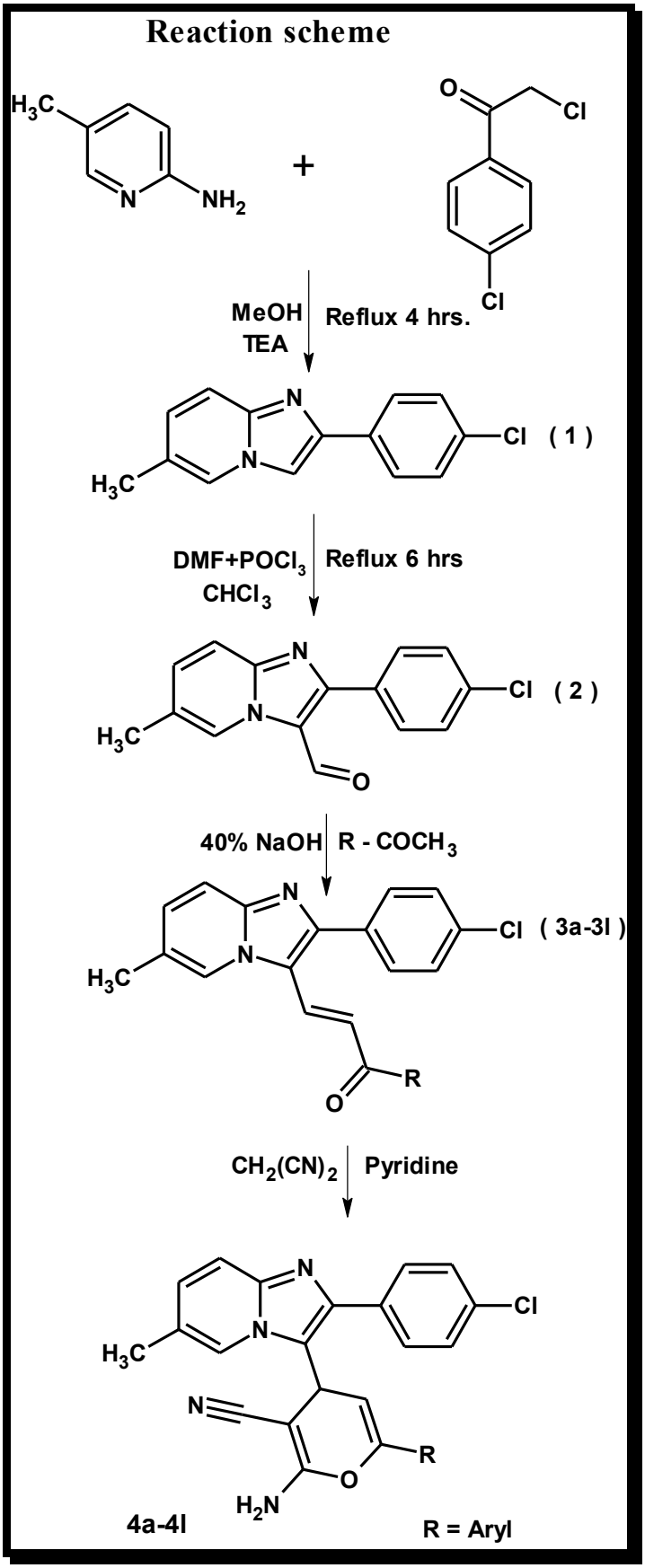

Table: I

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

Comp. Id	R	Molecular Formula	M.P. ^{0}C	Antibacterial Activity				Antifungal Activity	% of Nitrogen	
				B. Mega	*S. aureus*	*E. Coil*	*S. typhi*	*A. niger*	Calcd.	Found
4a	C_6H_5-	$C_{26}H_{19}ClN_4O$	180	15	14	16	16	17	12.77	12.72
4b	3-Cl-C_6H_4-	$C_{26}H_{18}Cl_2N_4O$	165	18	15	16	14	15	11.84	11.81
4c	4-Cl-C_6H_4-	$C_{26}H_{18}Cl_2N_4O$	155	22	23	24	17	15	11.84	11.80
4d	2-4-$(Cl)_2$-C_6H_3-	$C_{26}H_{17}Cl_3N_4O$	195	19	14	16	21	22	11.03	11.01
4e	4-F-C_6H_4-	$C_{26}H_{18}ClFN_4O$	183	18	15	16	16	21	12.26	12.22
4f	4-Br-C_6H_4-	$C_{26}H_{18}BrClN_4O$	200	21	20	15	24	19	10.80	10.80
4g	4 -OH-C_6H_4-	$C_{26}H_{19}ClN_4O_2$	175	13	16	17	14	18	12.32	12.30
4h	4-NH_2-C_6H_4-	$C_{26}H_{20}ClN_5O$	210	21	15	20	19	19	15.43	15.41
4i	4-CH_3-C_6H_4-	$C_{27}H_{21}ClN_4O$	165	19	15	18	16	18	12.37	12.35
4j	4-OCH_3-C_6H_4-	$C_{27}H_{21}ClN_4O_2$	190	18	20	22	24	18	11.95	11.90
4k	3-NO_2-C_6H_4-	$C_{26}H_{18}ClN_5O_3$	166	17	19	17	22	15	14.97	14.91
4l	4-NO_2-C_6H_4-	$C_{26}H_{18}ClN_5O_3$	177	15	17	16	14	21	14.97	14.95

3. 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}H-NMR 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.p200^{o}C.

Anal. Calcd. For $C_{14}H_{11}ClN_2$ 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.). ^{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 165ml $POCl_3$ within 1.0 h (exothermicity observe) 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 6.0h. Remove $CHCl_3$ by vacuum distillation. Cool reaction mass at room temperature and poured in 2.0 lit ice cold water. Below room temperature P^H adjust neutral by caustic solution. Filter and crystallized from methanol. Yield 70%, mp180^{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] 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^{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 publication.

[E] Synthesis of 2"-amino-4"-[2-(4'-chlorophenyl)-6-methylimidazo[1,2-a]pyridine-3-yl]-6"-(4"'-methylphenyl)-4"-H-pyran-3"-carbonitrile(4i)

A mixture of 2-(4'-chlorophenyl)-6-methyl-3-[1"-4"'-methylphenyl)-2"-propene-1"-one-3-yl]-imidazo[1,2-a]pyridine (2.74 gm, 0.01 mol) and malononitrile (0.66gm, 0.01 mol) in pyridine

(20 ml), was heated under reflux for 12 hrs on oil-bath. The reaction mixture was cooled and poured on to crushed ice. The product was neutralized with 20% HCl, where upon a solid separated out, which was filtered dried and crystallized from ethanol. Yield 65%, m.p.165^{o}C

Anal. Calcd. For $C_{27}H_{21}ClN_4O$: Required : C, 71.60; H, 4.67; N, 12.37%; found C, 71.58; H, 4.65; N, 12.35%. IR (KBr, cm^{-1}): 28 (C-H str, Sym, ; 1359 (C-H def, sym.); 1444 (C-H def, asym.); 3051 (C-H Str. Aromatic); 799 (C- H, Str, o.p.p def.); 1487 (C=C str.); 1027 (C-N str.); 1228 (C-O-C); 2990-2850 (C-H Str.); 1598 (C=N); 721(C-Cl). ^{1}H-NMR ($CDCl_3$, δ ppm); 2.2-2.3 (s, 3H, $–CH_3$); 6.9-8.1 (m, 7H, Ar-H); m/z: 43, 78, 212, 242, 288, 305, 262, 437, 452.

Similarly, other 2"-amino-4"-[2-(4'-chlorophenyl) -6-methyl imidazo [1,2-a] pyridine-3-yl]-6"-aryl - 4"-H-pyran-3"- carbonitrile (**4a-4l**) were prepared. The physical data are recorded in Table No. I.

Table: II

Compounds showing comparable antimicrobial activity with known standerd 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.					
	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"-(4"'-methylphenyl)-4"-H-pyran-3"-carbonitriles (**4a-4l**) have been synthesized. Some of the compounds **4c, 4d, 4f, 4h** and **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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