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Synthesis and biological screening 2-[(4'-chlorophenyl)-6-methylimidazo [1, 2 - a] pyridin - 3 - yl] methylene - 1" - aryl -2" phenyl-5"-oxo-imidazolines

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ABSTRACT

2-[(4'-chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-yl]methylene-1"-aryl-2"-phenyl-5"-oxo-imidazolines. (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}HNMR, Mass spectral data, elemental analysis and thin layer chromatography.

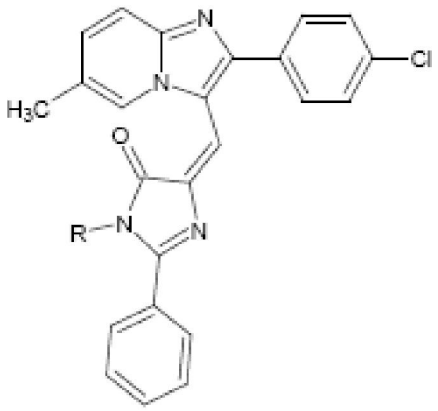
KEYWORDS

5-Oxo imidazolines;
(Heterocyclic chemistry).

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 anti bacterial and anti fungal activity. Imidazo (1,2a) Pyridinesderivaties posses antifungal[1, 2, 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 activitiy. 2-[(4'-chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-yl]methylene-1"-aryl-2"-phenyl-5"-oxo-imidazolines have been synthesised by the condensation of 4"-{[2-(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl] methylene}-2"-phenyl- 5"-oxazolone with aromatic amines.

The products (4a-4l) were assigned the IR ^{1}HNMR, Mass spectral data, elemental analysis and TLC. The physical data and antimicrobial activities are represented in TABLE - 1.



(4a-4l) R=Aryl

ANTIMICROBIAL ACTIVITY

2-[(4'-chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-yl]methylene-1"-aryl-2"-phenyl-5"-oxo-

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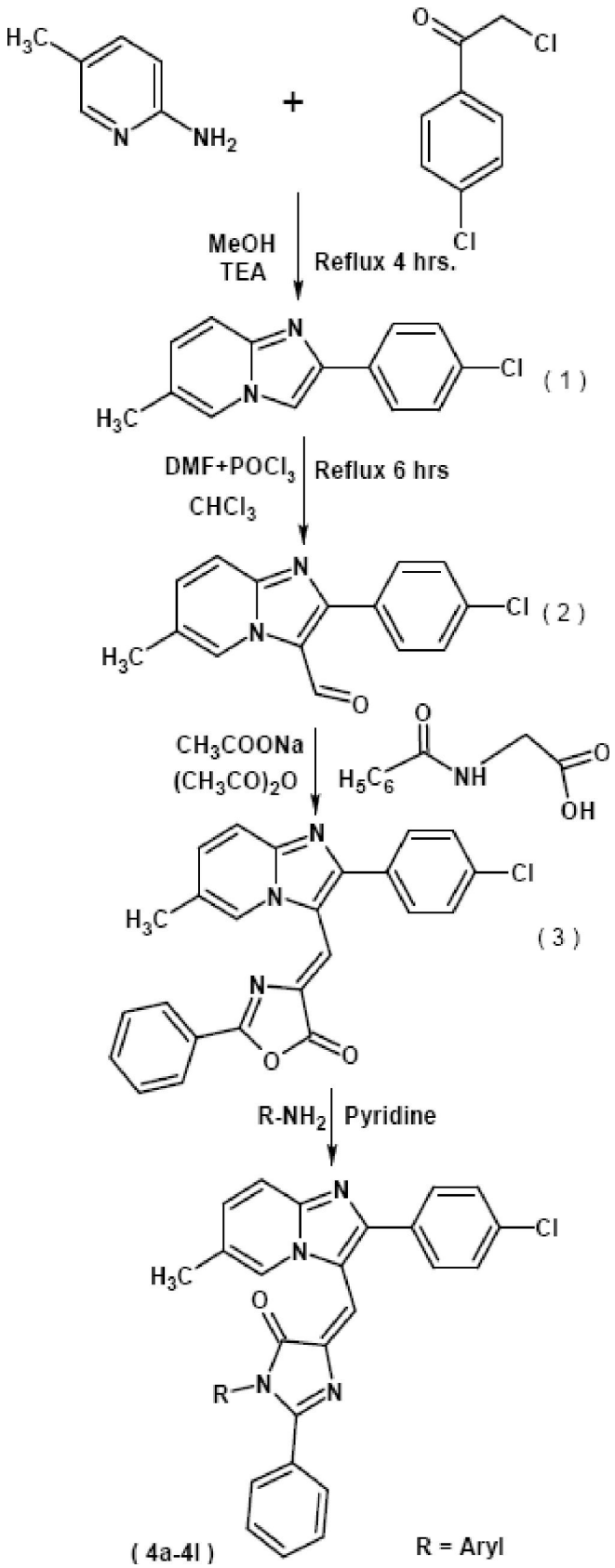
Reaction scheme



imidazolines. Products were evaluated in vitro for their antimicrobial activities against *Gram +ve bacteria like Bascillus megaterium, Bacillus Subtillus, Staphylo Coccus aureus, Bacillus Cereus. Gram –ve bacteria like Escherichia coli, Antrobactor Arogens, Salmonella Taphimurium, Pscudonomus valgaries. Fungi As per gillus niger, As per gillus awamori* using DMF as solvent at 50 µg / ml. concentration by cup-plate method[16]. After 24 hrs of incubation at 37 °C, The zones of inhibition were measured in mm. The activity was compared with known standard drugs, viz, ampicillin, chloramphenicol, norfloxacin, gresiofulvin at same concentration.

All the synthesized compounds (1), (2), (3i), (4a-4l), showed moderate to good and remarkable activities with compare to known standard drugs at the same concentration, which is represented in TABLE-1. The Compareble antimicrobial activity are represented in TABLE-2

EXPERIMENTAL SECTION

All the melting point were measured by open glass capillary method and are uncorrected. IR absorption spectra (Vmax 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 stadrard (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 tharmopocket and condensor. 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 tri ethyl amine at room temperature till P^H 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.p200 °C.,

Anal. Calcd. For $C_{14}H_{11}ClN_2$ Require : C, 69.28,

TABLE 1 : The physical data and antimicrobial activities of compounds (1), (2), (3i), (4a-4l), [Zone of inhibition in mm]

Comp	R	Moleculer Formula	M.P ^{0}C	Antibacterial Activity							Antifungl Activity		% of Nitroge	
				B. mega	B.Sub Tilics	S.au-reus	B. Ce reus	E. Coil	A. rogens	S. typhi	P. Val garis	A. niger	A. awamori	Caled	Found
1	---	$C_{14}H_{11}ClN_2$	200	16	20	19	18	18	18	18	21	15	19	11.54	11.50
2	---	$C_{15}H_{11}ClN_2O$	180	13	23	15	20	20	19	20	23	18	20	10.35	10.33
3i	---	$C_{24}H_{16}ClN_3O_2$	143	15	22	16	21	19	23	16	27	20	22	10.16	10.12
4a	C_6H_5-	$C_{30}H_{21}ClN_4O$	155	14	18	16	16	17	17	16	21	18	16	11.46	11.44
4b	3-Cl-C_6H_4-	$C_{30}H_{20}Cl_2N_4O$	195	21	20	20	18	19	19	22	18	16	21	10.70	10.68
4c	4-Cl-C_6H_4-	$C_{30}H_{20}Cl_2N_4O$	173	16	17	15	15	18	18	18	19	21	19	10.70	10.68
4d	2-4-$(Cl)_2$-C_6H_3-	$C_{30}H_{19}Cl_3N_4O$	180	18	21	14	17	22	19	24	20	19	17	10.04	10.02
4e	4 -F-C_6H_4-	$C_{30}H_{20}ClFN_4O$	165	22	20	19	17	21	22	18	19	18	15	11.05	11.03
4f	4-Br-C_6H_4-	$C_{30}H_{20}BrClN_4O$	190	14	17	20	19	18	20	15	21	20	19	9.87	9.85
4g	4 -OH-C_6H_4-	$C_{30}H_{21}ClN_4O_2$	168	15	18	19	16	20	21	16	18	18	21	11.10	11.08
4h	4-NH_2-C_6H_4-	$C_{30}H_{22}ClN_5O$	166	14	15	22	20	21	19	20	17	19	16	13.90	13.89
4i	4-CH_3-C_6H_4-	$C_{31}H_{23}ClN_4O$	163	16	18	14	17	20	18	17	20	18	15	11.14	11.11
4j	4-OCH_3-C_6H_4-	$C_{31}H_{23}ClN_4O_2$	200	21	20	20	19	18	19	21	19	22	14	10.80	10.79
4k	3-NO_2-C_6H_4-	$C_{30}H_{20}ClN_5O_3$	182	18	19	15	17	17	20	16	21	15	18	13.12	13.10
4l	4-NO_2-C_6H_4-	$C_{30}H_{20}ClN_5O_3$	198	15	17	17	19	15	18	16	17	12	19	13.12	13.10

TABLE 2 : Compounds showing comparable antimicrobial activity with known standerd drugs.

Compounds	B.mega	B.Sub tilis	S.aureus	B.Cerus	E.Coli	A.aro gens	S.typhi	P.Valgaries	A.niger	A. awa mori
(4a – 4l)	4b,4e, 4j	4b,4c, 4e,4j	4b,4e,4f, 4h,4j	4f, 4g, 4j, 4l	4b,4d,4e, 4h,4i	4e, 4f, 4g, 4k	4b,4d, 4h,4j	4d, 4f, 4j, 4k	4e,4f, 4j	4f, 4g, 4l
Activity of standard drugs.										
drugs	**B.mega**	**B.Sub tilis**	**S.aureus**	**B.Cerus**	**E.Coli**	**A.aro gens**	**S.typhi**	**P.Valgaries**	**A.niger**	**A. awa mori**
1.Ampicillin	22	21	19	18	19	20	22	23	---	--
2.Chlorampenicol	22	23	23	20	22	21	25	22	---	--
3.Norfloxacin	22	22	22	21	24	23	23	24	---	--
4.Greseofulvin	---	--	---	-	---	--	---	--	22	23

H, 4.53, N, 11.54 %,Cl,14.63 ; Found: C, 69.26, H, 4.52, N, 11.50, Cl, 14.60 %.) IR (KBr) : 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}HNMR (DMSO-d6);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, tharmopocket and condensor 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 distilation. Cool reaction mass at room temperature and poured in 2.0 lit ice cold water. Below room temperature P^H adjust neutral by coustic solution. Filter and crystal-lized 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, Cl, 13.10 % ; Found: C, 66.54, H, 4.08, N, 10.33, Cl, 13.09 %.) IR (KBr) : 2900 (C-H

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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}HNMR (DMSO-d6);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 4"-{[2-(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl] methylene}-2"-phenyl- 5"-oxazolone

A mixture of benzoylaminoacetic acid (6.0 gm,0.029 mol),acetic anhydride(4.27 gm,0.032 mol),sodium acetate(2.62 gm,0.032 mol) and 6–methyl– 2 - (4' - chlorolphenyl)imidazo [1,2-a] pyridine - 3 - carboxaldehyde (4.36 gm,0.032 mol) was heated on a waterbath for 4 hrs. Resulting mass poured into ice cold water,filtered and crystallized from DMF. Yield 66%, m.p.143 ^oC.

[D] Synthesis of 2-[(4'-chlorophenyl) - 6 - methylimidazo [1,2-a] pyridin-3-yl] methylene-1"-(phenyl)-2"-phenyl-5"-oxo- imidazoline(4a)

A mixture of phenyl amine (3.0 g, 0.01 mol) and 4"-{[2-(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl] methylene}-2"-phenyl- 5"-oxazolone (4.26 g, 0.01 mol) in dry pyridine (30 ml) was refluxed for 10 hrs in oil bath. Resulting mass was poured into crushed ice and neutralised with HCl, filtered and crystallized from dioxane. Yield 65%, mp. 155ºC.

($C_{30}H_{21}ClN_4O$; Required : C, 73.69; H, 4.33; N, 11.46%; found : C, 73.67; H, 4.30; N, 11.44%)IR (KBr) : 2860 (C-H str., Sym,) ; 1370 (C-H def., sym.) ; 1442 (C-H def., asym.); 3057 (C-H Str., Aromatic);1462 (C=C str.) ; 1128(C-N str.);1680 (C=O): 1627 (C=N);786(C-Cl) ^{1}HNMR ($CDCl_3$);2.32 (s, 3H $-CH_3$);6.9-8.1 (m, 16H Ar-H);. m/z: 44, 66, 78, 92, 112, 130, 157, 174, 185, 232, 247, 270, 305, 334, 359, 411, 473, 488.

Similarly other 5-oxo-imidazolines (4a-4l) have been prepared. The physical constants are recorded in TABLE No 1.

SUMMARY

2-[(4'-chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-yl]methylene-1"-aryl-2"-phenyl-5"-oxo-imidazolines (4a-4l) have been synthesized. Some of the compounds 4b,4d, 4,e, 4f, 4g, 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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