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Synthesis and biological screening of 2-(4′-chlorophenyl)-6-methyl-3-(3″- aryl - 1″-acetyl/phenyl -4″,5-dihydropyrazol-5″-yl)- imidazo[1, 2-a]pyridines

V.V.Bhuva, V.N.Patolia, A.U.Patel, D.M.Purohit*

Shree M. and N. Virani science college, Chemistry Department, Kalawad Road, Rajkot-5,Gujarat, (INDIA)

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ABSTRACT

2-(4′-chlorophenyl)-6-methyl-3-(3″-aryl-1″acetyl-4″,5″-dihydropyrazol-5″-yl)imidazo [1,2-a] pyridines **(4a-4l)**; 2-(4'-chlorophenyl)-6-methyl-3-(3″-aryl-1″-phenyl-4″,5″ dihydropyrazol-5″-yl) imidazo [1, 2-a] pyridines**(5a-5l)** 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.

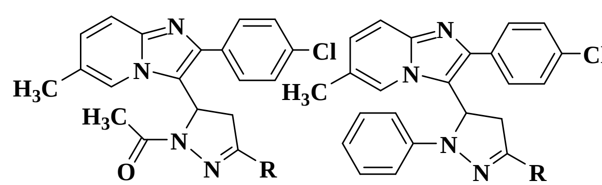
KEYWORDS

Pyrazolines;
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 varieties of biological activities such as, Hypnotic[1], Anthelmintic[2], Antiulcer[3,4], Hypnoselective and anxioselective activities[5]. Amyloidformation inhibitors[6], Antiinflammatory, analgesic, antipyretic[7,8] etc.In view of getting to synthesized imidazo [1,2-a] pyridines derivatives and evaluated for their antimicrobial activitiy.

The chemistry of pyrazoline was reviewed by Jarobe in 1967. 2-Pyrazoline consist a unique class of five member nitrogen heterocycle. During the past year considerable evidance has been accumulated to demostrate the importance of 2-pyrazoline derivatives pyrazolines have proved to be the most useful frame work for biological activities. The chemistry of pyrazolines, which have been studied extensively for their biodynamic behavior[9] From the literature survey, it was revealed that 2-pyrazolines are better therapeutic agents like, antimicrobial[10],antiinflammatory[11,12], antiallergic[13].



(4a-4l) R= Aryl (5a-5l)

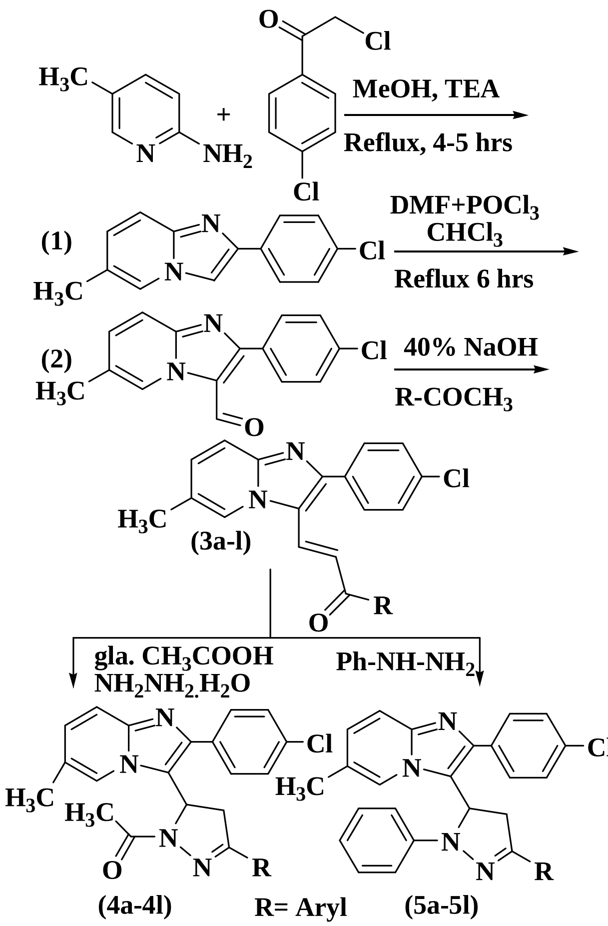
Acetyl pyrazoline have been synthesized by cyclocondensation of 2-(4'-chlorophenyl)-6-methyl-3-[1″-aryl-2″-prop-en-1″-ones-3-yl]-imidazo[1,2-a]pyridines with hydrazine hydrate in glacial acetic acid.

Phenyl pyrazoline have been synthesized by condensation of 2-(4'-chlorophenyl)-6-methyl-3-[1″-aryl-2″-prop-en-1″-ones-3-yl]-imidazo[1,2-a]pyridines with phenyl hydrazine in presence of piperidine as a catalyst.

The products **(4a-4l)** and **(5a-5l)** were assigned the IR ^{1}HNMR, Mass spectral data, elemental analysis and TLC. The physical data and antimicrobial activities are represented in TABLE 1.

Antimicrobial activity

2-(4'-chlorophenyl)-6-methyl-3-(3″-aryl-1″-acetyl-4″,5″-dihydropyrazol-5″-yl)imidazo [1,2-a] py-



SCHEME 1

ridines **(4a-4l)**; 2-(4'-chlorophenyl)-6-methyl-3- (3″-aryl-1″-phenyl-4″,5″–dihydropyrazol-5″-yl)imidazo [1, 2-a] pyridines **(5a-5l)**, 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 50μg/ml. concentration by cup-plate method[14]. After 24 hrs of incubation at 37^{0}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 (1),(2),(3i),(4a-4l),(5a-5l), showed moderate to good and remarkable activities with known standard drugs at the same concentration, which is represented in TABLE 1.

EXPERIMENTAL

All the melting point were 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 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

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 pH adjust 8 to 9. After addition complete heat 60-65^{0}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 and filter it. Yield 86%, m.p200^{0}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, 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.

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^{0}C. Start drop wise addition of 165ml $POCl_3$ within 1.0 h (exothermicity observe) stir 30 min at 0-5^{0}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 pH adjust neutral by coustic solution. Filter and crystallized from methanol. Yield 70%, mp180^{0}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 str, Sym,); 1369 (C-H def, sym.); 1475 (C-H def,

TABLE : 1 The physical data and antimicrobial activities of compounds (1), (2), (3i),(4a-4l), (5a-5l), [Zone of inhibition in mm]

Comp.	R	Moleculer formula	M.P ^{0}C	Antimicrobial Activity				Antifungl activity	% of Nitrogen	
				B.Mega	*S.aureus*	*E.Coil*	*S typhi*	*A.niger*	Caled	Found.
(1)	---	$C_{14}H_{11}ClN_2$	200	16	19	18	18	15	11.54	11.50
(2)	---	$C_{15}H_{11}ClN_2O$	180	13	15	20	20	18	10.35	10.33
(3i)	4-CH_3-C_6H_4-	$C_{24}H_{19}ClN_2O$	170	15	16	19	16	20	7.24	7.22
(4a)	C_6H_5-	$C_{25}H_{21}ClN_4O$	150	16	17	19	15	21	13.06	13.04
(4b)	3-Cl-C_6H_4-	$C_{25}H_{20}Cl_2N_4O$	190	15	16	17	17	18	12.09	12.07
(4c)	4-Cl- C_6H_4-	$C_{25}H_{20}Cl_2N_4O$	155	21	19	20	22	16	12.09	12.07
(4d)	2-4-(Cl) $_2$-C_6H_3*	$C_{25}H_{19}Cl_3N_4O$	180	19	20	16	20	17	11.25	11.23
(4e)	4 -F-C_6H_4-	$C_{25}H_{20}ClFN_4O$	145	11	15	17	17	21	12.54	12.52
(4f)	4-Br-C_6H_4-	$C_{25}H_{20}BrClN_4O$	198	15	19	15	18	15	11.03	11.01
(4g)	4 -OH- C_6H_4-	$C_{25}H_{21}ClN_4O_2$	158	20	21	17	17	22	12.59	12.56
(4h)	4-NH_2-C_6H_4-	$C_{25}H_{22}ClN_5O$	165	15	12	16	23	20	15.78	15.76
(4i)	4-CH_3-C_6H_4-	$C_{26}H_{23}ClN_4O$	203	21	16	17	15	19	12.65	12.63
(4j)	4-OCH_3- C_6H_4-	$C_{26}H_{23}ClN_4O_2$	200	15	20	15	17	16	12.21	12.2
(4k)	3-NO_2-C_6H_4-	$C_{25}H_{20}ClN_5O_3$	167	12	15	19	21	14	14.78	14.76
(4l)	4-NO_2-C_6H_4-	$C_{25}H_{20}ClN_5O_3$	170	15	12	18	17	18	14.78	14.76
(5a)	C_6H_4-	$C_{29}H_{23}ClN_4$	165	21	14	18	13	16	12.10	12.08
(5b)	3-Cl- C_6H_4-	$C_{29}H_{22}Cl_2N_4$	168	10	19	12	18	18	11.26	11.24
(5c)	4-Cl- C_6H_4-	$C_{29}H_{22}Cl_2N_4$	175	15	18	16	16	20	11.26	11.24
(5d)	2-4-$(Cl)_2$ - C_6H_4-	$C_{29}H_{21}Cl_3N_4$	160	18	20	19	18	14	10.53	10.51
(5e)	4-F- C_6H_4-	$C_{29}H_{22}ClFN_4$	175	20	15	18	23	22	11.65	11.64
(5f)	4-Br- C_6H_4-	$C_{29}H_{22}BrClN_4$	160	19	16	16	17	17	10.34	10.32
(5g)	4-OH- C_6H_4-	$C_{29}H_{23}ClN_4O$	163	14	18	19	21	15	11.70	11.68
(5h)	4-NH_2- C_6H_4-	$C_{29}H_{24}ClN_5$	163	13	15	14	16	21	14.65	14.63
(5i)	4-CH_3-C_6H_4-	$C_{30}H_{25}ClN_4$	255	20	14	20	19	14	11.75	11.73
(5j)	4-OCH_3- C_6H_4-	$C_{30}H_{25}ClN_4O$	165	16	17	14	21	18	11.36	11.33
(5k)	3 –NO_2- C_6H_4-	$C_{29}H_{22}ClN_5O_2$	185	19	21	21	16	20	13.79	13.78
(5l)	4-NO_2- C_6H_4-	$C_{29}H_{22}ClN_5O_2$	195	17	15	17	20	17	13.79	13.78

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.

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) + DMF (50 ml). To this add p-methylacetophenone (1.40gm, 0.01mol) and. Stirr the content at room temperature for 24 hrs. in presence of catalytical 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^{0}C.

Anal.Calcd. For $C_{24}H_{19}ClN_2O$ Require : C, 74.51, H, 4.95, N,7.24 ,Cl, 9.16 %; Found: C, 74.50, H, 4.93, N, 7.22 , Cl 9.15 %.) IR(KBr) :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}HNMR (DMSO-d6);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 same journal .

Synthesis of 2-(4′-chlorophenyl)-6-methyl-3-(3″-(4‴-methylphenyl)-1″-acetyl-4″,5″-dihydropyrazol-5″-yl)imidazo [1,2-a] pyridines (4i)

A mixture of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"-methylphenyl)- 2"-prop-en-1"ones-3-yl]-imidazo [1,2-a]pyridine. (3.88 gm, 0.01 mol) and hydrazine hydrate (0.5 gm, 0.01 mol) glacial acetic acid (2 ml) and methanol was refluxed for 10 hrs. The product was isolated and crystallized from ethanol. Yield 65%,m.p.203^{0}C.

Anal. Calcd. For $C_{26}H_{23}ClN_4O$ Require : C, 70.50, H, 5.23, N,12.65,Cl, 8.00 %; Found: C, 70.48, H, 5.20, N, 12.63, Cl 7.99 %.) IR(KBr) :2895 (C-H str, Sym,); 1440, (C-H def, asym.); 1380 (C-H def, asym.); 3650 (C-H Str. Aromatic); 810 (C- H, Str, o.p.p def.); 1580 (C=C str.); 790 (C-Cl) 1210 (C-N str.); 1650. (C=N); 1690 (C=O) ^{1}HNMR (DMSO-d6);2.28-2.52

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

Compound	*B.maga*	*S.aureus*	*E.Coli*	*S.typhi*	*A.niger*
(4a-4l)	4c,4g,4i,4d.	4c,4d,4f,4g,4j.	4a,4c,4k.	4c,4h,4k.	4a,4e,4g,4h.
(5a-5l)	5e,5f,5i,5k	5b,5d,5k	5d,5g,5i,5k.	5e,5j,5g.	5c,5e,5k,5h.
			Activity of standared drugs		
Compound	***B.maga***	***S.aureus***	***E.Coli***	***S.typhi***	***A.niger***
1. Ampicillin	22	19	19	22	-
2. Chlorampenicol	22	23	22	24	-
3. Norfloxacin	22	22	24	23	-
4. Greseofulvin	-	-	-	-	22

(s, 6H –2CH_3);7.02-8.26 (m, 11H Ar-H); 3.00-3.60 (dd 2H -CH_2) 5.70-5.76 (q, 1H -CH). m/z :44, 65, 77, 92, 103, 118, 130, 158, 242, 255, 384, 443.

Similarly other compounds **(4a-4l)** were prepared and their physical data are recorded in TABLE 1.

Synthesis of 2-(4′-chlorophenyl)-6-methyl-3- (3″-(4‴-methylphenyl)-1″-phenyl-4″,5″-dihydropyrazol - 5″-yl imidazo[1, 2-a] pyridines (5i)

A mixture of 2-(4′-chlorophenyl)-6-methyl- 3-[1″-(4‴-methylphenyl)- 2″-prop-en-1″ones-3-yl]-imidazo [1,2-a]pyridine 4.21gms (0.01 mol), and phenyl hydrazine 1.18gms (0.01 mol)add basic catalyst piperidine in 25 ml methanol reflux for 12 hrs. pour reaction mass in ice chilled water. After product filter dry it and recrystllized from ethanol. Yield 54 %, m.p.255^{0}C

Anal. Calcd. For $C_{30}H_{25}ClN_4$ Require : C, 75.54, H, 5.28, N,11.75,Cl, 7.43 %; Found: C, 75.52, H, 5..25, N, 11.73, C, 7.41 %.) IR(KBr) :2995 (C-H str, Sym.,); 1450,(C-H def, asym.); 1385, (C-H def, asym.); 3620 (C-H Str. Aromatic);790 (C- H, Str, o.p.p def.); 1445 (C=C str.); 1200 (C-N str.);1680 (C=N); 750 (C-Cl Str.) ^{1}HNMR (DMSO-d6);2.22-2.58 (s, 6H –2CH_3); 6.85-7.68 (m, 16H Ar-H). 3.17-4.04 (d, 2H -CH_2) 5.80-5.86 (q, 1H -CH). m/z : 44, 66, 75, 111, 154, 253, 268, 308, 378, 380, 399,410,455, 476.

Similarly other compounds **(5a-5l)** were prepared and their physical data are recorded in TABLE 1.

Summary

2-(4′-chlorophenyl)-6-methyl-3-(3″-aryl-1″-acetyl-4″,5″- dihydropyrazol-5″-yl)imidazo [1,2-a] pyridines (4a-4l); 2-(4'-chlorophenyl)-6-methyl-3- (3″-aryl-1″-phenyl-4″,5″-dihydropyrazol-5″-yl) imidazo [1, 2-a] pyridines **(5a-5l)** 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 griseofulvin at same concentration 50μg/ml.

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