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Synthesis of 2-(4′-chlorophenyl)-6-methyl- 3-[1′′-aryl-2′′-prop-en-1′′-ones-3-yl] / (3 ′′–aryl - 4′′,5′′-dihydro-1′′-H-pyrazol-5′′-yl)/ (3′′-arylisoxazole-5′′-yl) - imidazo[1,2-a]pyridine

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ABSTRACT

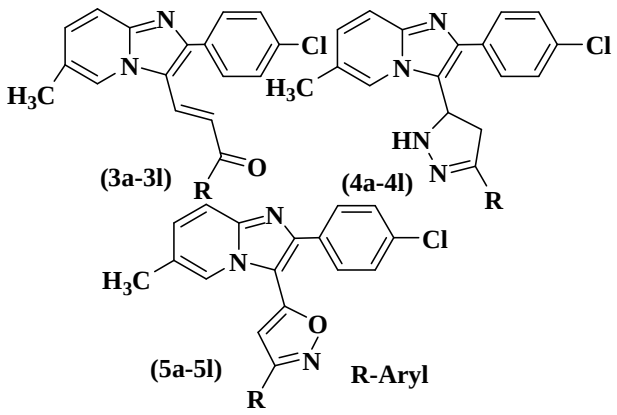
2-(4′-chlorophenyl)-6-methyl-3-[1′′-aryl- 2′′-prop-en-1′′-ones-3-yl)-imidazol [1,2,-a]pyridines. **(3a-31)** ;2-(4'-chlorophenyl)-6-methyl-(3′′-aryl-4′′,5′′-dihydro-1′′-H pyrazol-5′′-yl)imidazo[1,2a]pyridine(4a-41);2-(4'-chlorophenyl) -6-methyl-3-(3′′-arylisoxazole-5′′-yl)-imidazo [1,2-a]pyridine(5a-5l) 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. The structures of the products have been elucidated by IR, ^{1}H NMR, Mass spectral data, elemental analysis and thin layer chromatography.

KEYWORDS

Chalcones;
Pyrazolines;
Isoxazoles

INTRODUCTION

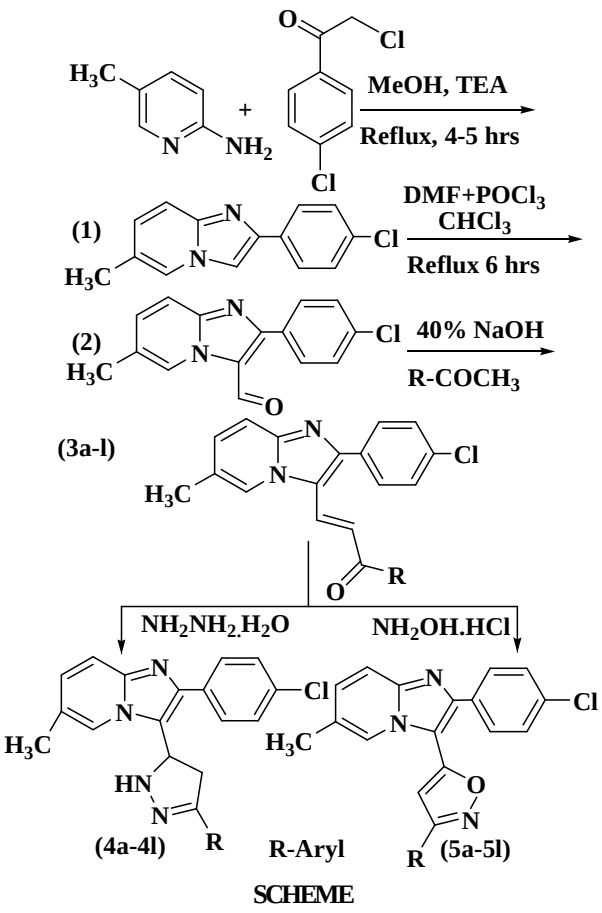
Imidazo[1,2-a]pyridines are potential bioactive agents due to their wide spectrum of therapeutic importance. A large number of substituted imidazo[1,2-a]pyridine derivatives are prepared and tested for varieties of biological activities such as, Hypnotic[1], Anthelmintic[2], Antiulcer[3,4], Hypnoselective 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.



Chalcones have been synthesized by the cyclocondensation of 6-methyl-2-(4′-chlorophenyl) imidazo [1, 2 - a]pyridine-3 -carboxaldehyde with aromatic ketones in presence of alkli.

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. From the literature survey, it was revealed that 2-pyrazolines are better therapeutic agents like, antimicrobial[9], anti-inflammatory[10], anti-allergic[11]. pyrazoles 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.

Isoxazoles are known to exhibit wide spectrum of



SCHEME

biodynamic antiviral[12], insecticidal[13] activities, Isoxazoles have been synthesized by chemoselective Cyclisation of 2-(4′-chlorophenyl)-6-methyl-3 [1′′-aryl-2′′-prop-en-1′′-ones-3-yl]imidazo[1,2-a] pyridines with hydroxyl amine hydrochloride. The products **(3a-3l)**, **(4a-4l)** and **(5a-5l)** were assigned the IR ^{1}H NMR, Mass spectral data, elemental analysis and TLC. The physical data and antimicrobial activities are represented in TABLE 1.

Antimicrobial activity

6-methyl-2-(4′-chlorophenyl) imidazo [1, 2-a]pyridine, 6-methyl-2-(4′′-chlorophenyl) imidazo [1, 2-a]pyridine-3 –carboxaldehyde; 2-(4'-chlorophenyl)-6-methyl-3-(1′′-aryl- 2′′-prop-en-1′′-one-3-yl)-imidazo[1,2-a]pyridine **(3a-3l)**; 2-(4′-chlorophenyl)-6-methyl -3-(3′′-aryl-4′′, 5′′,-dihydro-1′′-H-pyrazol-5′′-yl)-imidazo[1,2-a] pyridine **(4a-4l)**; 2-(4′-chlorophenyl)-6-methyl-3-(3′′-aryl isoxazol-5′′-yl)-imidazo[1,2-a]pyridine **(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)**,**(3a-3l)**,**(4a-4l)**,**(5a-5l)**, showed moderate to good and remarkable activities with known standard drug at the same concentration, which is represented in TABLE 1.

EXPERIMENTAL

All the melting points 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}H NMR 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 21.3 gm (0.1 mole) 1-(4′-chlorophenyl)-2-chloroethenone and than charge 11.9g (0.11mole) 2-amino-5- methyl pyridine at room temperature stir till clear solution. Add drops wise 5.9g (0.055mol) 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, 4.57, N, 11.54 %, Cl, 14.61; Found : C, 69.26, H, 4.56, 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}H NMR (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.

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

Compd.	R	Moleculer formula	M.P ^{0}C	Antibacterial activity				Antifungal activity	% Of Nitrogen	
				B.mega	*S.aureus*	*E.Coil*	*S.typhi*	*A.niger*	Calcd	Found
(1)	-	$C_{14}H_{11}ClN_2$	200	15	18	20	17	14	11.54	11.50
(2)	-	$C_{15}H_{11}ClN_2O$	170	12	16	20	20	19	10.35	10.33
(3a)	C_6H_5-	$C_{23}H_{17}ClN_2O$	101	16	15	18	17	14	7.51	7.49
(3b)	3-Cl- C_6H_4-	$C_{23}H_{16}Cl_2N_2O$	245	15	18	19	14	15	6.88	6.86
(3c)	4-Cl-C_6H_4-	$C_{23}H_{16}Cl_2N_2O$	250	14	16	20	16	18	6.88	6.86
(3d)	2-4-$(Cl)_2$- C_6H_3-	$C_{23}H_{15}Cl_3N_2O$	205	21	19	20	22	15	6.34	6.32
(3e)	4 -F- C_6H_4-	$C_{23}H_{16}ClFN_2O$	126	18	15	17	23	16	7.17	7.15
(3f)	4-Br- C_6H_4-	$C_{23}H_{16}BrClN_2O$	170	12	15	16	18	14	6.20	6.17
(3g)	4 -OH- C_6H_4-	$C_{23}H_{17}ClN_2O_2$	140	15	19	14	16	15	7.20	7.18
(3h)	4-NH_2- C_6H_4-	$C_{23}H_{18}ClN_3O$	190	20	15	18	16	17	10.83	10.82
(3i)	4-CH_3- C_6H_4-	$C_{24}H_{19}ClN_2O$	184	15	12	15	19	20	7.24	7.22
(3j)	4-OCH_3- C_6H_4-	$C_{24}H_{19}ClN_2O_2$	180	22	19	18	21	22	6.95	6.93
(3k)	3-NO_2- C_6H_4-	$C_{23}H_{16}ClN_3O_3$	111	16	20	14	16	20	10.06	10.04
(3l)	4-NO_2- C_6H_4-	$C_{23}H_{16}ClN_3O_3$	250	14	15	17	19	14	10.06	10.04
(4a)	C_6H_5-	$C_{23}H_{19}ClN_4$	160	12	12	20	17	18	14.48	14.45
(4b)	3-Cl-C_6H_4-	$C_{23}H_{18}Cl_2N_4$	155	20	14	18	13	14	13.30	13.27
(4c)	4-Cl-C_6H_4-	$C_{23}H_{18}Cl_2N_4$	145	15	17	14	15	19	13.30	13.27
(4d	2-4-$(Cl)_2$- C_6H_3-	$C_{23}H_{17}Cl_3N_4$	205	20	14	19	23	22	12.29	12.27
(4e)	4 -F- C_6H_4-	$C_{23}H_{18}ClFN_4$	185	21	15	15	16	19	13.84	13.81
(4f)	4-Br- C_6H_4-	$C_{23}H_{18}BrClN_4$	198	13	21	16	19	20	12.03	12.01
(4g)	4 -OH- C_6H_4-	$C_{23}H_{19}ClN_4O$	182	13	17	14	15	16	13.91	13.88
(4h)	4-NH_2- C_6H_4-	$C_{23}H_{20}ClN_5$	210	22	14	20	19	16	17.43	17.40
(4i)	4-CH_3- C_6H_4-	$C_{24}H_{21}ClN_4$	170	15	20	14	16	19	13.98	13.95
(4j)	4-OCH_3- C_6H_4-	$C_{24}H_{21}ClN_4O$	165	17	19	20	22	17	13.44	13.41
(4k)	3-NO_2- C_6H_4-	$C_{23}H_{18}ClN_5O_2$	150	18	19	21	23	15	16.22	16.20
(4l)	4-NO_2- C_6H_4-	$C_{23}H_{18}ClN_5O_2$	190	14	17	17	13	21	16.22	16.20
(5a)	C_6H_5-	$C_{22}H_{16}ClN_3O$	180	13	16	18	20	18	10.89	10.86
(5b)	3-Cl- C_6H_4-	$C_{23}H_{15}Cl_2N_3O$	174	22	20	21	22	20	10.00	9.98
(5c)	4-Cl- C_6H_4-	$C_{23}H_{15}Cl_2N_3O$	168	13	14	16	18	20	10.00	9.98
(5d)	2-4-$(Cl)_2$- C_6H_3-	$C_{23}H_{14}Cl_3N_3O$	165	18	20	16	20	15	9.24	9.22
(5e)	4 -F- C_6H_4-	$C_{23}H_{15}ClFN_3O$	152	16	15	13	12	14	10.41	10.39
(5f)	4-Br- C_6H_4-	$C_{23}H_{15}BrClN_3O$	192	21	12	12	15	16	9.04	9.01
(5g)	4 -OH- C_6H_4-	$C_{23}H_{16}ClN_3O_2$	185	15	15	21	16	20	10.46	10.44
(5h)	4-NH_2- C_6H_4	$C_{23}H_{17}ClN_4O$	180	16	21	17	15	12	13.98	13.95
(5i)	4-CH_3- C_6H_4-	$C_{24}H_{18}ClN_3O$	156	14	16	16	17	19	10.51	10.49
(5j)	4-OCH_3- C_6H_4-	$C_{24}H_{18}ClN_3O_2$	185	20	15	16	20	20	10.10	10.07
(5k)	3-NO_2- C_6H_4-	$C_{23}H_{15}ClN_4O_3$	195	12	21	20	16	15	13.00	12.97
(5l)	4-NO_2- C_6H_4-	$C_{23}H_{15}ClN_4O_3$	190	14	14	16	18	20	13.00	12.97

Synthesis of 6-methyl-2-(4′-chlorolphenyl) 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 (0.225 mole) 6-methyl-2-(4′-chlorophenyl)imidazo [1,2-a]pyridine slowly temp raise up to 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 crystallized from methanol. Yield 80%, mp170^{0}C.

(Anal. Calcd. For $C_{15}H_{11}ClN_2O$ Require : C, 65.55, H, 4.10, N,10.35, Cl, 13.10 %; Found: C, 65.54, 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, 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); 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,

TABLE

Compounds showing comparable antimicrobial activity with known standard drugs

Compounds	*B.maga*	*S.aureus*	*E.Coli*	*S.typhi*	*A.niger*
(3a-3l)	3h,3d,3j.	3b,3d,3g,3j	3b,3c,3d.	3d,3e,3i,3j	3i,3j,3k.
(4a-4l)	4b,4h,4e,4d.	4f,4i,4j.	4a,4d,4h,4j.	4d,4h,4k.	4c,4d,4f,4i,4l.
(5a-5l)	5b,5f,5j.	5b,5h,5k.	5a,5g,5k	5a,5b,5d,5j	5b,5c,5g,5i,5l.
	Activity of standared drugs				
Compound	***B.maga***	***S.aureus***	***E.Coli***	***S.typhi***	***A.niger***
1. Ampicillin(50µg/ml)	22	19	19	22	-
2. Chlorampenicol(50µg/ml)	22	23	22	25	-
3. Norfloxacin(50µg/ml)	22	22	24	23	-
4. Greseofulvin(50µg/ml)	-	-	-	-	22

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 the 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. 184^{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 recorded in TABLE 1.

Synthesis of 2-(4′-chlorophenyl)-6-methyl-3-[3′′-(4′′′-methylphenyl)-4′′,5′′-dihydro 1′′-H-pyrazol-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.(3.82 gm, 0.01 mol) and hydrazine hydrate 1.0gm (0.02mol) in 25 ml methanol was reflux for 12 hrs. The reaction mass stand overnight. After product falls out filter it. recrystllized from ethanol. Yield 72 %, m.p.170^{0}C, (Anal. Calcd. For $C_{24}H_{21}ClN_4$ Require : C, 71.90, H, 5.28, N,13.98,Cl, 8.84 %; Found: C, 71.88, H, 5.26, N, 13.95, Cl 8.83 %.) 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); 3420 (Str. NH) ^{1}H NMR (DMSO-d6);2.21-2.31 (s, 6H –$2CH_3$);7.14-8.09 (m, 12H Ar-H); 3.16-3.52 (dd 2H -CH_2) 5.41-5.51 (q, 1H -CH). m/z :44, 65, 77, 92, 103, 118, 130, 158, 242, 255, 384, 400.

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) isoxazol-5-yl]imidazo[1,2-a]pyridine (5i)

To a solution of 2-(4′-chlorophenyl)-6-methyl- 3-[1′′-(4′′′-methylphenyl)- 2′′-prop-en-1′′ones-3-yl]-imidazo [1,2-a]pyridine (4.27 gm, 0.01 mol) in ethanol (25 ml), anhydrous sodium acetate (0.739gm, 0.01 mol) and hydroxylaminehydrochloride (0.59 gm, 0.01 mol) in acetic acid were added. The reaction mixture was refluxed on oil bath for 7-8 hr. The product was isolated and crystallized from ethanol. Yields 54 %, m.p. 156^{0}C (Anal. Calcd. For $C_{24}H_{18}ClN_3O$ Require : C, 72.0, H, 4.54, N,10.51,Cl, 8.87 o,4.0 %; Found: C, 71.99, H, 4.52, N, 10.49, Cl 8.86 %.) 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);2.26-2.49 (s, 6H –$2CH_3$);7.11-8.32 (m, 12H Ar-H). m/z :44, 66, 75, 111, 154, 253, 268, 308, 378, 380, 399.

Similarly other compounds **(5a-5l)** were prepared

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and their physical data are recorded in TABLE 1. Compounds showing comparable antimicrobial activity with known standerddrugs.

Summary

2-(4'-chlorophenyl)-6-methyl- 3-[1''-aryl- 2''-prop-en-1''-ones-3-yl)-imidazol [1,2,-a]pyridines. **(3a-31)**;2-(4'-chlorophenyl)-6-methyl (3''-aryl-4'',5''-dihydro-1'-H-pyrazol-5''-yl)imidazo[1,2a]pyridine(4a-41);2-(4'-chlorophenyl)-6-methyl-3-(3''-arylisoxazole-5''-yl)-imidazo[1,2-a]pyridine(51-51) 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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