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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SCHIFF'S BASE AND ARYL AMINOMETHYL DERIVATIVES.

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ABSTRACT. Schiff's bases are obtained on heating an aldehydes with aromatic amine in presence of glacial acetic acid. These are the compounds containing characteristic –HC=N– group. Aryl amino methyl derivatives of heterocyclic compounds to synthesize by selective reduction of schiff's bases (imine group) with sodiumborohydride in controlled experimental condition.
Schiff's base of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanimines & Aryl amines of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanamines were prepared. Their chemical structures were confirmed by means of IR, NMR, Mass data and by elemental analysis. All of the synthesized compounds were tested for their antibacterial and antifungal activity.

INTRODUCTION

Literature study revealed that schiff's bases derivatives have a wide variety of uses such as antiviral[1], antifungal[2], antiparasitic[3], antibacterial[4], antipyretic[5], anti-inflammatory[6], plant hormone activity[7], and antitubercular[8]. Aryl amines exhibit a wide range of biological activities such as P2X7 receptor antagonists[9], HDM2-p53 protein-protein antagonists[10], MCH1 receptor antagonist[11], NPY5 antagonists[12], dual Atk1/2 inhibitors[13]. This inspired us to synthesize schiff's base of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanimines (1a-l) & Aryl amines of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanamines (2a-l).

The structure of synthesized compounds were assigned based on Elemental analysis, I.R. ^{1}H-NMR and Mass spectral data. The antimicrobial activity was assayed by using the cup-plate agar diffusion method [14] by measuring the zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activities[15] against varieties of bacterial strains such *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli* and Fungi *Aspergillus niger* using Dimethylformamide solvent at 40 µg/ml concentration. Standard drugs like Amoxicillin, Benzyl penicillin, Ciprofloxacin, Erythromycin and Griseofulvin were used for comparison purpose. (Table-1).

RESULTS AND DISCUSSION:

The synthesis of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanimines (1a-l) was prepared by reaction of 2-(4-Methylephenyl)imidazo[1,2-*a*]pyridin-3-carbaldehyde (Type-I) and Amine derivatives in presence of glacial acetic acid & N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanamines (2a-I) have been prepared by

the reduction of N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanimines with sodiumborohydride in methanol at ambient temperature (Scheme-1).

The formulas of the selected compounds were confirmed by the elemental analysis and their structures were determined by IR ,[1] H-NMR , and mass spectral data.

ANTIBACTERIAL ACTIVITY:

It has been observed from the microbiological data that all compounds (1a-l) and (2a-l) were found to be mild to moderately active against Gram positive and Gram negative bacterial strains. How ever the maximum activity was observed in compounds (1d),(1k),(2b),(2d) against *S.aureus*. The significant activity was observed in compounds (1e),(1k),(2j),(2l) against *B.subtilis*. The maximum activity was displayed by the compounds (1i),(1k),(2b),(2k), against *E.coli.* The compounds (1h),(1l),(2a), and (2l) were comparatively more effective against *P. aeruginosa*.

ANTIFUNGAL ACTIVITY:

The antifungal data revealed that compounds were least toxic to the fungal strain. However mild activity was shown by the compounds (1c),(1d),(1j),(2c),(2g),(2h), against A. niger. The antibacterial activity was compared with standard drug viz. Amoxicillin, Benzyl Penicillin, Ciprofloxacin, Erythromycin and antifungal activity was compared with standard drug viz. Griseofulvin.

EXPERIMENTAL SECTION:

Melting points were taken in open capillary tubes are uncorrected. IR spectra (cm^{-1}) were recorded on Shimadzu-435-IR Spectrophotometer and, ^{1}H-NMR spectra on Bruker spectrometer(300MHz) using TMS as an internal standard, chemical shift in δ ppm.

General procedure for the preparation of 2-(4-Methylephenyl)imidazo[1,2-*a*]pyridin-3-carbaldehyde (Type-I):

Align 2.0 lit 4/N RBF equipped with over head stirrer with condenser on water bath. Charged 84 ml DMF and 1.0 lit $CHCl_3$ into RBF. It was cooled at 0 - 5 ^oC temperature. Slowly added 165 ml $POCl_3$ within 1.0 h. During addition the exothermicity was controlled. Temperature raised at 10-15 ^oC and stirred for 30 minutes. 50g (0.225 mol) of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine was added slowly, temp. raises, refluxed for 6 hrs. $CHCl_3$ was removed by vacuum distillation and reaction mass cooled at room temperature, poured into 2.0 lit ice cold water. Neutral pH adjusted bellow room temperature with the help of mild coustic solution. The solid mass was collected by filtration, washed with water, dried and crystallized from the methanol. Yield 80%, m.p. 152 ^oC.

General procedure for the preparation of N-Aryl-1-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]methanimines (1a-l):

A mixture of 6-Methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde 2.5g (0.01mol), p-anisidine 1.23g (0.01mol) and catalytic amount of glacial acetic acid in 20 ml methanol was refluxed for 16 hrs. The contents was cooled and product isolated by filtration and

dryed it. The crude product was recrystallized from methanol. Yield, 75%, m.p. 178 ^{o}C, Elemental Analysis Calculated for $C_{23}H_{21}N_3O$; Found : C-77.93%, H-5.66%, N-11.75%; Requires:C-77.72%, H-5.96%, N-11.82%. Similarly, N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanimines have been prepared. The physical data are recorded in table no.1.

N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanimines (1a-l):

Yield 75 %, m.p. 178^{0}C; IR(KBr): ν 2958, 2852,1444,1398 (Alkane, -CH_3), 1585 (Imidazo[1,2-a], C=N str.), 1244 (pyridine, C-N str.); 1608 (schiff base, C=N str.), 3026, 1481, 1107, 1029, 829 (Aromatic), cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.82 (s,3H,-OCH_3) , 2.43 (s,6H,-CH_3), 8.78 (s,1H,-CH=N-Ar), 6.90-7.69 (m,11H, Ar-H) , Mass: m/z = 355 M.F.: C_{23} $H_{21}N_3O$.

General procedure for the preparation of N-Aryl-1-[6-methyl-2-(4-methylphenyl) imidazo[1,2-*a*]pyridin-3-yl]methanamines (2a-I):

3.55g (0.01mol) *N*-(4-Methoxyphenyl)-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanimine was taken in 25 ml methanol and cooled at 5-10 ^{o}C temperature. Sodiumborohydride 0.57g (0.15mol) was added over a period of 30 min. The reaction mixture stirred over night at room temperature. Reaction mass was then poured in ice water and excess of sodiumborohydride was neutralized by adding dil.HCl. The product was extracted with ether and washed with water. Dried over anhydrous Na_2SO_4 and finally the ether was evaporated to give amino methyl derivatives. Yield, 56%, m.p. 165 ^{o}C, Elemental analysis calculated for $C_{23}H_{23}N_3O$; Found : C- 77.98%; H-6.48%; N-11.99%; Requires : C-77.28%, H-6.49%, N-11.76%. Similarly, other *N*-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanamines were prepared. The physical data are recorded in table no.1.

N-Aryl-1-[6-methyl-2-(4-methylphenyl)imidazo[1,2-*a*]pyridin-3-yl]methanamines (2a-I):

Yield 56 %, m.p. 165 ^{0}C; IR(KBr): ν 2942, 2899,1463,1388 (Alkane, -CH_3), 1604 (Imidazo[1,2-a], C=N str.), 1232 (pyridine, C-N str.); 3288 (Amine, N-H str.), 3020, 1520, 1114, 1035, 823 (Aromatic), cm^{-1}; ^{1}H-NMR ($CDCl_3$) : δ 3.64 (s, 3H, -OCH_3) , 2.31 & 2.33 (s, 6H, -CH_3), 4.52 (s, 2H, Ar-N-CH_2-), 5.70 (s, 1H, Ar-NH-) 6.60-7.68 (m,11H, Ar-H) , Mass: m/z = 357 M.F.: $C_{23}H_{23}N_3O$.

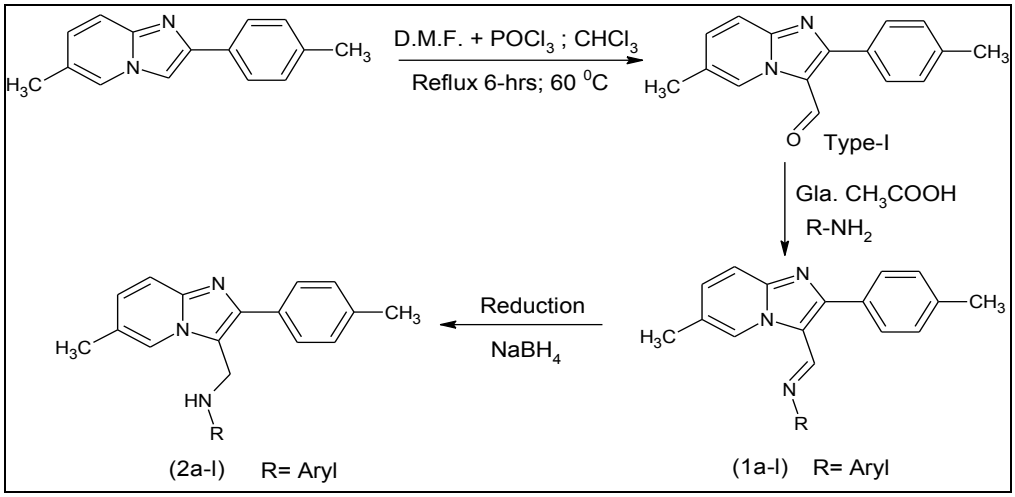
Table-1

Characterization data of the compounds (1a-l) and (2a-l):						
compd no.	R	Molecular formula	Mole. Wt.	M.P. (^{0}C)	Nitrogen %	
					Calcd.	Found
1a	4-OCH_3-C_6H_4-	$C_{23}H_{21}N_3O$	355	178	11.82	11.75
1b	4-OH-C_6H_4-	$C_{22}H_{19}N_3O$	341	186	12.31	12.25
1c	C_6H_5-	$C_{22}H_{19}N_3$	325	222	12.92	12.89
1d	4-Cl-C_6H_4-	$C_{22}H_{18}ClN_3$	359.5	236	11.68	11.75
1e	3-Cl-C_6H_4-	$C_{22}H_{18}ClN_3$	359.5	148	11.68	11.67
1f	2,5-$(Cl)_2$-C_6H_3-	$C_{22}H_{17}Cl_2N_3$	394	108	10.65	10.67
1g	3,4-$(Cl)_2$-C_6H_3-	$C_{22}H_{17}Cl_2N_3$	394	225	10.65	10.59
1h	4-F-C_6H_4-	$C_{22}H_{18}FN_3$	343	184	12.24	12.27
1i	3-NO_2-C_6H_4	$C_{22}H_{18}N_4O_2$	370	166	15.13	15.20
1j	4-NO_2-C_6H_4-	$C_{22}H_{18}N_4O_2$	370	120	15.13	15.10
1k	1-$C_{10}H_7$-	$C_{26}H_{21}N_3$	375	dec.176	11.20	11.19
1l	3-CH_3-C_6H_4	$C_{23}H_{21}N_3$	339	118	12.38	12.41
2a	4-OCH_3-C_6H_4-	$C_{23}H_{23}N_3O$	357	165	11.76	11.99
2b	4-OH-C_6H_4-	$C_{22}H_{21}N_3O$	343	dec.195	12.24	12.22
2c	C_6H_5-	$C_{22}H_{21}N_3$	327	176	12.84	12.80
2d	4-Cl-C_6H_4-	$C_{22}H_{20}ClN_3$	361.5	dec.180	11.61	11.65
2e	3-Cl-C_6H_4-	$C_{22}H_{20}ClN_3$	361.5	178	11.61	11.68
2f	2,5-$(Cl)_2$-C_6H_3-	$C_{22}H_{19}Cl_2N_3$	396	194	10.60	10.56
2g	3,4-$(Cl)_2$-C_6H_3-	$C_{22}H_{19}Cl_2N_3$	396	dec.260	10.60	10.61
2h	4-F-C_6H_4-	$C_{22}H_{20}FN_3$	345	138	12.17	12.15
2i	3-NO_2-C_6H_4	$C_{22}H_{20}N_4O_2$	372	165	15.05	15.03
2j	4-NO_2-C_6H_4-	$C_{22}H_{20}N_4O_2$	372	136	15.05	15.06
2k	1-$C_{10}H_7$-	$C_{26}H_{23}N_3$	377	175	11.14	11.11
2l	3-CH_3-C_6H_4	$C_{23}H_{23}N_3$	341	dec.204	12.41	12.40

Table-2

compd no.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity
	S. aureus	B.subtilis	E.coli	*P.aeruginosa*	A.niger
1a	13	18	16	11	10
1b	16	19	17	12	13
1c	11	13	16	17	21
1d	20	10	15	11	17
1e	10	20	12	8	15
1f	14	17	13	19	14
1g	11	15	9	18	11
1h	12	16	11	21	16
1i	11	12	18	13	15
1j	15	19	15	12	17
1k	18	20	21	10	8
1l	7	11	18	19	10
2a	13	17	11	19	9
2b	20	17	18	15	12

2c	16	14	12	8	21
2d	20	10	18	12	15
2e	11	18	12	8	15
2f	19	10	9	18	11
2g	10	17	10	17	15
2h	12	17	11	18	16
2i	13	18	17	12	10
2j	15	19	16	11	14
2k	10	17	21	11	8
2l	7	21	15	19	12
Amoxicillin	24	22	21	18	0
Benzyl penicillin	24	20	21	22	0
Ciprofloxacin	17	17	23	20	0
Erythromycin	18	24	19	21	0
Griseofulvin	0	0	0	0	24



Scheme-1

CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds. Which show significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

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