Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(4):1259-1263

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis, spectral and microbial studies of some novel schiff base derivatives of 2-amino pyridine

K. C. Parmar[*], J. J. Vora[#] and S. B. Vasava

[*]Sir P. T. Sarvajanik College of Science, Surat, Veer Narmad south Gujarat University, Gujarat, India
[#]Department of Chemistry, Hemchandrachraya North Gujarat University, Patan, Gujarat, India

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ABSTRACT

Schiff base derivatives of N-(1E)-[((mono or di-substituted aryl)-1,3-diphenyl-1H-pyrazol-4-yl)methylene]-pyridin-2-amine were synthesized by the acid catalyzed condensation of (mono- or di- substituted aryl)-1,3-diphenyl- 1H-pyrazole-4-carbaldehyde derivatives with 2- amino pyridine. Schiff base derivatives were characterized by FT-IR, 1H-NMR, Mass spectral analysis and elemental analysis. All the synthesized compounds have been screened for their antimicrobial activities by using broth dilution method.

Keywords: Schiff base derivatives, 2- amino pyridine, Antimicrobial studies, Synthesis.

INTRODUCTION

Azomethines are generally known as Schiff bases to honour Hugo Schiff, who synthesized such compounds. These are the compounds containing characteristic -C=N- group. Several methods have been reported for the preparation of azomethines. Selvam *et.* **[1]** have prepared sulfonamide and its derivatives as anti-HIV agents. More *et. al***[2]** have marked the biological activity of Schiff bases synthesized from aminothiazoles. Kalpesh S. Parikh **[3]** has reported some Schiff bases derived from pyrazole derivative. Ketan C. Parmar **[4]** has also reported some Schiff bases derived from pyrazole and pyrimidine derivatives. Schiff bases can be synthesized from an aromatic amine and a carbonyl compound by nucleophilic addition forming a hemiaminal, followed by a dehydration to generate an imine**[5]**. They are well known intermediates for the preparation of azetidinones, thiazolidinones**[6]**, oxadiazolines and many other derivatives. Azomethines exhibit a wide range of pharmacological activities like antimicrobial**[7]**, antiparasitic **[8]**, anti-inflammatory **[9]**, anticancer **[10] [11]** *etc.* A large number of substituted pyrazole derivatives are prepared and tested for variety of biological activities like anti HIV**[12]**, anti-inflammatory **[13]**, antimicrobial **[14]**, fungicidal **[15]** *etc*. Pyridine derivatives also possess wide therapeutic activities such as antiviral**[16]**, anti HIV**[17]**, anticancer **[18]**, antimicrobial **[19]**.

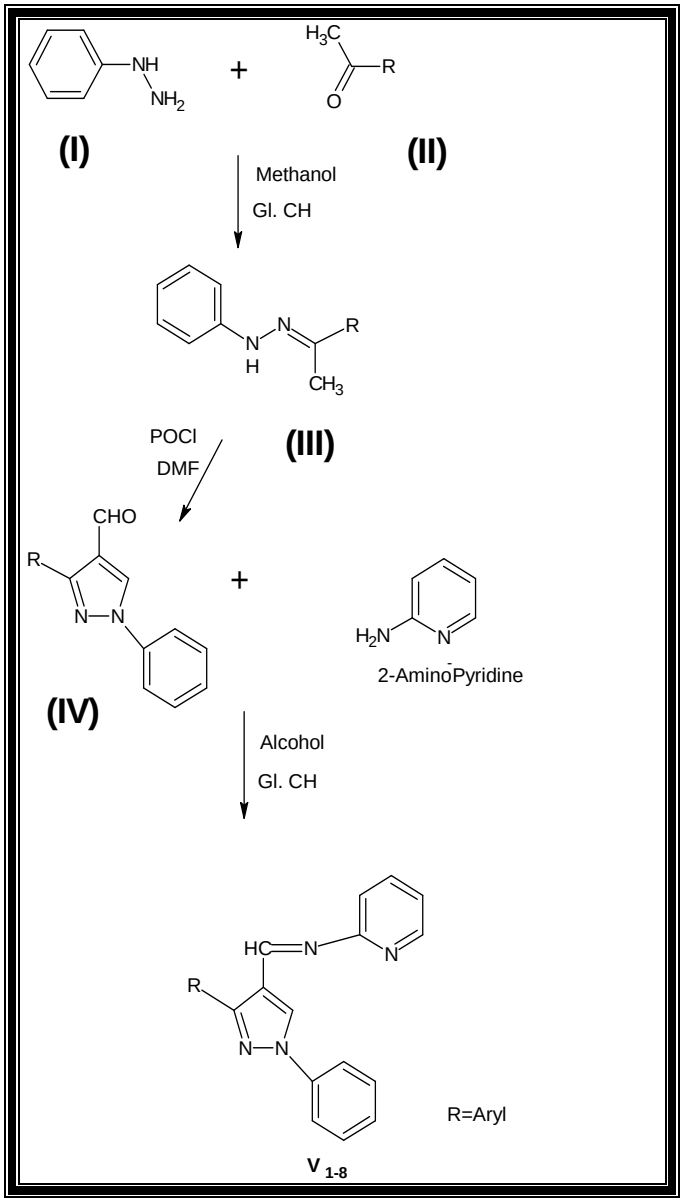
EXPERIMENTAL SECTION

The reagent grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use. The purity of synthesized compounds was checked by thin layer chromatography (TLC) on silica gel plate using ethyl acetate : Cyclo Hexene (7:3). Melting points were determined by open capillary method and are uncorrected. IR spectra are recorded on FT-IR Perkin-Elmer spectrophotometer using KBr disc. ^{1}H-

NMR spectra are recorded in $CDCl_3$ on a Bruker -400 MHz using TMS as internal standard. The chemical shifts are reported as parts per million (ppm) and ESI MS were determined on Discovery Make Thermo Spectrometer.

The compounds *N*-{(1E)-[3-(mono or di-substituted aryl) -1- phenyl -1*H*- pyrazol -4-yl] methylene}-pyridine-2-amines**(V_{1-10})** were obtained by preparation method (Scheme 1).

SCHEME-1



[A] ***Synthesis of N-phenylamino-α-methyl-phenyl azomethine***

A mixture of phenyl hydrazine (1.08gm, 0.01M) and acetophenone (1.20gm, 0.01M) in absolute ethanol was refluxed in waterbath for 4 hrs. in presence of 1ml glacial acetic acid. Product obtained after cooling was crystallized from absolute ethanol. Yield, 1.8gm (90%), M.P: 64^{o}C ($C_{14}H_{14}N_2$; **Calculated** : C, 80.00; H, 6.66; N, 13.37; **Found**: C, 79.92; H, 6.64; N, 13.34%).

This typical experimental procedure was followed to prepare other analogs of this series.

[B] ***Synthesis of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde***

N-Phenylamino-α-methyl-phenyl azomethine (0.84gm, 0.004M) was added in a mixture of Vilsmeier-Haack reagent (prepared by dropwise addition of 1.2ml $POCl_3$ in ice cooled 10ml DMF) and refluxed for 6 hrs. The reaction mixture was poured into crushed ice followed by neutralization using sodium bicarbonate. Crude product was isolated and crystallized from methanol. Yield, 2.16gm (87%), M.P. 125˚C. ($C_{16}H_{12}N_2O$; **Calculated** : C, 77.42; H, 4.84; N, 11.29 %; **Found** : C, 77.39; H, 4.80; N, 11.28 %).

Exactly similar experimental procedure was followed to prepare other analogs of this series

[C] ***Synthesis of N[(1E)-(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-pyridin-2-amine***

A mixture of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (2.48gm, 0.01M) and 2-amino pyridin (0.94gm, 0.01M) was taken in absolute ethanol and few drops of glacial acetic acid were added. Then the mixture was refluxed for 6 h on water bath. The excess solvent was distilled off, then poured into ice cold water; the separated solid was filtered, washed and recrystalized from ethanol. M.P.- 118 °C, Yield, 80%, ($C_{21}H_{16}N_4$; **Calculated** : C, 77.76; H, 4.97; N, 17.27%; **Found** : C, 77.79; H, 5.01; N, 17.22%).

This similar experimental procedure was followed to prepare other analogs of this series. Their characterization data are given in **Table A.**

Table-A Physical data of N-[(1E)-(1,3-diphenyl-1H–pyrazol-4-yl) methylene]-pyridin-2-amine ($V_{1\text{-}8}$)

Compd. No.	R	Molecular Formula	M.W.	%Yield (Final step)	M.P. °C	% of C Found (Calcu.)	% of H Found (Calcu.)	% of N Found (Calcu.)
V_1	C_6H_5	$C_{21}H_{16}N_4$	324.37	80	118	77.79 77.76	5.01 4.97	17.22 17.27
V_2	4-CH_3-C_6H4	$C_{22}H_{18}N_4$	338.40	72	114	78.12 78.08	5.31 5.36	16.58 16.56
V_3	4-OCH_3-C_6H_4	$C_{22}H_{18}N_4O$	354.40	78	128	74.51 74.56	5.16 5.12	15.83 15.81
V_4	4-Cl-C_6H_4	$C_{21}H_{15}N_4Cl$	358.82	75	103	70.31 70.29	4.23 4.21	15.65 15.61
V_5	4-Br-C_6H_4	$C_{21}H_{15}N_4Br$	403.27	84	112	62.55 62.54	3.74 3.75	13.94 13.89
V_6	4-NO_2-C_6H_4	$C_{21}H_{15}N_5O_2$	369.37	85	119	68.25 68.28	4.07 4.09	19.01 18.96
V_7	3-NO_2-C_6H_4	$C_{21}H_{15}N_5O_2$	369.37	84	75	68.31 68.28	4.13 4.09	18.92 18.96
V_8	2,4-di-Cl-C_6H_3	$C_{21}H_{14}N_4Cl_2$	393.26	82	144	64.11 64.14	3.64 3.59	14.27 14.25

Table-B Minimal bactericidal concentration (microgram / ml)

DRUGS ↓ ORGANISM→	*E. coli* MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenus* MTCC 442
GENTAMYCIN	0.05	1	0.25	0.5
CIPROFLOXACIN	25	25	50	50
CHLORAMPHENICOL	50	50	50	50
AMPICILLIN	100	100	250	100

Table-C Minimal fungicidal concentration (microgram / ml)

DRUGS ↓ ORGANISM→	*C.ALBICANS* MTCC 227	*A.NIGER* MTCC 282	*A.CLAVATUS* MTCC 1323
NYSTATIN	100	100	100
GRESEOFULVIN	500	100	100

Table- D Antibacterial activity table

Minimal bactericidal concentration (microgram/ml)					
Compd. No	R	*E. coli MTCC 443*	*P. aeruginosa MTCC 1688*	*S. aureus MTCC 96*	*S. pyogenus MTCC 442*
V_1	C_6H_5	>1000	>1000	>1000	>1000
V_2	4-CH_3-C_6H4	>1000	500	500	500
V_3	4-OCH_3-C_6H_4	500	500	500	250
V_4	4-Cl-C_6H_4	500	250	500	250
V_5	4-Br-C_6H_4	500	250	500	250
V_6	4-NO_2-C_6H_4	>1000	500	500	>1000
V_7	3-NO_2-C_6H_4	500	>1000	500	500
V_8	2,4-Cl-C_6H_3	500	250	500	250

Table-E Antifungal activity table

Minimal fungicidal concentration (microgram / ml)				
Compd. No	R	*C. albicans MTCC 227*	*A. niger MTCC 282*	*A.clavatus MTCC 1323*
V_1	C_6H_5	>1000	>1000	>1000
V_2	4-CH_3-C_6H4	>1000	500	>1000
V_3	4-OCH_3-C_6H_4	500	500	>1000
V_4	4-Cl-C_6H_4	500	500	500
V_5	4-Br-C_6H_4	500	500	500
V_6	4-NO_2-C_6H_4	500	>1000	500
V_7	3-NO_2-C_6H_4	500	250	500
V_8	2,4-Cl-C_6H_3	500	500	500

RESULTS AND DISCUSSION

The synthesis of *N*-{(1*E*)-[((mono- or di- substituted aryl)-1,3-diphenyl-1*H*-pyrazol-4-yl] methylene)pyridin-2-amine(**V_{1-8}**) involved the reaction between appropriate (mono- or di- substituted aryl)-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde(**IV_{1-8}**) and 4-methylpyridine-2-amine, as described in the general procedure.

IR spectrum showed absorption band at 1572.8 cm^{-1} indicated the stretching vibation of-CH=N- (Schiff-base) which confirming the condensation of reactants. The pyridine ring breathing appeared at 1015 cm^{-1} . The pyrazole moiety also appears around 1598.8 cm^{-1} (C=N str.) and 1227.8 cm^{-1} (C-N str.) as intense bands. The other peaks of IR spectra prove the structure of Schiff base derivatives.

^{1}H NMR spectrum displayed signals for the presence of one proton (CH=N-) at 8.4921 ppm (1H, s) which also confirms the condensation of reactants, one proton of pyrazole ring at 8.0850 ppm (1H, s), four protons of pyridine ring and five proton of one of the phenyl ring menace total nine protons as at 6.9657 ppm -7.4997 ppm (9H, m) five protons of another phenyl ring at 7.7491 ppm

The molecular formula of compound (**V_1**) was found to be $C_{21}H_{16}N_4$ on the basis of *m/z* 325.087 $[MH]^{+}$ a base peak was found in mass spectra. The molecular weight is 324.14 (isotopic mass) as per the Nitrogen Rule.

Spectral study of N[(1E)-(1,3-diphenyl-1H-pyrazol-4-yl)methylene]-pyridin-2-amine (V_1)
IR (KBr) cm $^{-1}$: 1572.8 (C=N stretching of Schiff base); 3121.1 (Ar C-H stretching); 1520.3 (Ar C=C stretching); 1598.8 (C=N str. of pyrazole ring); 1224.0 (C-N stretching); 1015 (pyridine ring breathing); 2829.9

^{1}H-NMR ($CDCl_3$) δ (ppm): 8.4921 (1H, s, -CH=N-); 8.0850 (1H, s, pyrazol ring); 6.9657-7.4997 (5H, m, phenyl ring and 4H, m, pyridine ring); 7.7491 (5H, m, phenyl ring).

Mass Spectra (*m/z*) : 325.087 $[MH]^+$, 293, 279, 202, 165

The overall activity results suggest that new synthesized compounds were much less sensitive than the standard drugs.

However an internal comparison is carried out. It was observed that unsubstituted phenyl derivative was almost inactive against all bacteria. Substitution by halogen slightly increase the activity. However disubstitution does not significantly increase antibacterial activity. Substitution of aromatic hydrogen by nitro group does not seem to increase antibacterial activity.

Unsubstituted phenyl derivative is much less efficient as antifungal too. However the substitution of aromatic hydrogen by groups like halogen, nitro raised antifungal activity to a small level. Out of all compounds 3-nitro phenyl derivative showed the most effective antifungal activity amongst all.

Over all, It was observed that halogenations increase the antibacterial activity and nitration in 3 phenyl position increased antifungal activity.

CONCLUSION

In all, eight pyrazoline derivatives were synthesized. These compounds were characterized for their structure elucidation. Various chemical and spectral data supported the structures thought of. Antibacterial and antifungal studies of these compounds indicate that, in general, they possessed lower antimicrobial activity. It may possible to increase the antimicrobial activity by proper molecular manipulation.

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