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Research Article

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

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ABSTRACT

Schiff base derivatives of N-(1Z)-[((mono or di-substituted aryl)-1,3-diphenyl-1H-pyrazol-4-yl) methylene]-4,6-dimethoxy pyrimidine-2-amine were synthesized by the acid catalyzed condensation of (mono- or di- substituted aryl)-1,3-diphenyl- 1H-pyrazole-4-carbaldehyde derivatives with 4,6-dimethoxy-2- amino pyrimidine. 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, 4,6-dimethoxy-2- amino pyrimidine, Antimicrobial studies.

INTRODUCTION

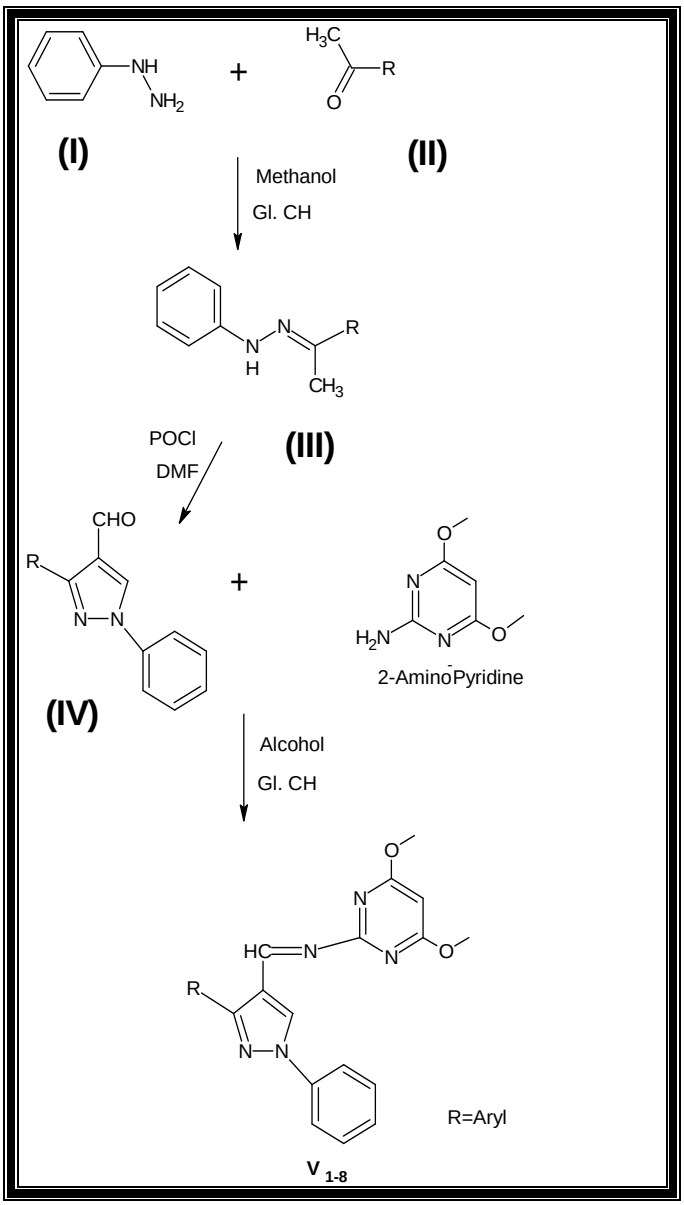
Azomethines (Schiff bases) are the compounds containing characteristic -C=N- group. Several methods have been reported for the preparation of azomethines. Selvam *et. al*[1] have prepared sulfonamide and its derivatives as anti-HIV agents. More *et. al*[2] have marked the biological activity of Schiff bases synthesized from aminothiazoles. Parikh and Vyas[3] has reported some Schiff bases derived from pyrazole derivative. 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[4]. They are well known intermediates for the preparation of azetidinones, thiazolidinones[5], oxadiazolines and many other derivatives. Azomethines exhibit a wide range of pharmacological activities like antimicrobial[6] antiparasitic[7], antiinflammatory[8], anticancer[9,10] *etc*. A large number of substituted pyrazole derivatives are prepared and tested for variety of biological activities like anti HIV[11], antiinflammatory[12], antimicrobial[13], fungicidal[14] *etc*. Pyrimidine derivatives also possess wide therapeutic activities such as antiviral[15], anti HIV[16], anticancer[17], antimicrobial[18].

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*-{(1Z)-[1,3- diphenyl -1*H*- pyrazol -4-yl] methylene}4,6-dimethoxy-pyrimidine-2-amines**(V_{1-8})** were obtained by preparation method (Scheme 1).

SCHEME-I



[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-[(1Z)-(1,3-Diphenyl-1H-pyrazol-4-yl)methylene]-4,6-dimethoxy pyrimidine-2-amine***
A mixture of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde (2.48gm, 0.01M) and 2-amino -4,6-dimethoxy pyrimidine (1.55 gm, 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.- 92 °C, Yield, 88%, ($C_{22}H_{19}N_5O_2$; **Calculated** : C, 68.56; H, 4.97; N, 18.17%; **Found** : C, 68.59; H, 5.02; N, 18.15%).

This similar experimental procedure was followed to prepare other analogs of this series. Their characterization data are given in **Table 1.**

TABLE NO. 1 : Physical data of N-[(1Z)-(1,3-Diphenyl-1H-pyrazol-4-yl)methylene]-4,6-dimethoxypyrimidine-2-amine ($V_{1\text{-}8}$)

Compd. No.	R	Molecular Formula	F.W.	%Yield	M.P.ºC	% of C	% of H	% of N
						Found (Calcu.)	Found (Calcu.)	Found (Calcu.)
V_1	C_6H_5	$C_{22}H_{19}N_5O_2$	385.41	88	92	68.59/68.56	5.02/4.97	18.15/18.17
V_2	4-CH_3-C_6H4	$C_{23}H_{21}N_5O_2$	399.44	84	90	69.29/69.16	5.33/5.30	17.49/17.53
V_3	4-OCH_3-C_6H_4	$C_{23}H_{21}N_5O_3$	415.44	86	98	66.56/66.49	4.93/5.09	16.88/16.86
V_4	4-Cl-C_6H_4	$C_{22}H_{18}N_5O_2Cl$	419.86	84	95	62.98/62.93	4.26/4.32	16.71/16.68
V_5	4-Br-C_6H_4	$C_{22}H_{18}N_5O_2Br$	464.31	87	84	56.98/56.91	3.87/3.91	15.16/15.08
V_6	4-NO_2-C_6H_4	$C_{22}H_{18}N_6O_4$	430.41	82	109	61.33/61.39	4.27/4.22	19.56/19.53
V_7	3-NO_2-C_6H_4	$C_{22}H_{18}N_6O_4$	430.41	82	69	61.43/61.39	4.26/4.22	19.51/19.53
V_8	2,4-di-Cl-C_6H_3	$C_{22}H_{17}N_5O_2Cl_2$	454.30	85	112	58.18/58.16	3.79/3.77	15.39/15.42

(1) Formula Weights (F.W.) are calculated with atomic weights given in Merck Index (15th ed.-2013)
(2) Melting points are measured in open capillaries and are uncorrected

BIOLOGICAL EVALUATION
Antimicrobial activity of N-[(1Z)-(1,3-Diphenyl-1H-pyrazol-4-yl) methylene] -4,6-dimethoxy pyrimidine-2-amine and its derivatives
Antimicrobial activity study of the synthesized compounds was carried out by using broth dilution method.

STANDARD DRUGS

Table. 2 MINIMAL BACTERICIDAL CONCENTRATION (MICROGRAM / ML)

ORGANISM→ DRUGS ↓	*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. 3 MINIMAL FUNGICIDAL CONCENTRATION (MICROGRAM / ML)

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

ANTIBACTERIAL ACTIVITY

Table- 4 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	500	>1000	>1000	500
V_2	4-CH_3-C_6H4	500	250	>1000	500
V_3	4-OCH_3-C_6H_4	250	250	500	500
V_4	4-Cl-C_6H_4	250	250	500	250
V_5	4-Br-C_6H_4	250	100	500	250
V_6	4-NO_2-C_6H_4	500	250	500	250
V_7	3-NO_2-C_6H_4	500	500	500	500
V_8	2,4-Cl-C_6H_3	100	250	250	100

Table-5 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	500	500	500
V_2	4-CH_3-C_6H4	250	250	500
V_3	4-OCH_3-C_6H_4	250	500	250
V_4	4-Cl-C_6H_4	>1000	>1000	500
V_5	4-Br-C_6H_4	>1000	500	500
V_6	4-NO_2-C_6H_4	500	>1000	>1000
V_7	3-NO_2-C_6H_4	500	500	>1000
V_8	2,4-Cl-C_6H_3	>1000	>1000	>1000

RESULTS AND DISCUSSION

The synthesis of *N*-{(1Z)-[(1,3-diphenyl-1*H*-pyrazol-4-yl) methylene]-4,6—dimethoxy-pyrimidin-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 4,6-dimethoxy-pyrimidine-2-amine, as described in the general procedure.

Spectral study of N-{[3(4-methylphenyl)-1-phenyl-1H-pyrazol-4-yl]-methylene}-4,6-dimethoxy-pyrimidin-2-amine (V_2)

IR (KBr) cm $^{-1}$: 1569.8 (C=N stretching of Schiff base); 3121.4 (Ar C-H stretching); 1504.7 (Ar C=C stretching); 1598.4 (C=N str. of pyrazole ring); 1220.0 (C-N stretching); 1520 (C=N str. of pyrimidine ring); 1192.8 (C-N str. of pyrimidine ring)

^{1}H-NMR ($CDCl_3$) δ (ppm): 9.1629 (1H, s, -CH=N-); 8.5113 (1H, s, pyrazol ring); 7.068-7.7810 (5H+4H, m, phenyl ring of pyrazole moiety); 5.8119 (1H, S, pyrimidine ring proton); 3.7727 (6H, S, methoxy group of pyrimidine ring); 2.2951 (3H, S, aromatic methyl group).

Mass Spectra (*m/z*) : 400.14 $[MH]^+$, 347.10, 297.09, 245.11, 182.0, 145.0

(1) IR spectrum showed absorption band at 1569.8 cm^{-1} indicated the stretching vibation of-CH=N- (Schiff-base) confirming the condensation of reactants. The pyrimidine ring breathing appeared at 1520 cm^{-1} and 1192.8 cm^{-1} . The pyrazole moiety also appears around 1598.4 cm^{-1} (C=N str.) and 1220.1 cm^{-1} (C-N str.) as intense bands. The other peaks of IR spectra prove the structure of Schiff base derivatives.

(2) ^{1}H NMR spectrum displayed signals for the presence of one proton (CH=N-) at 9.1629 ppm (1H, s) which also confirms the condensation of reactants, one proton of pyrazole ring at 8.5113 ppm (1H, s), four protons of one of phenyl ring attached with pyrazole moiety and five proton of another phenyl ring meance total nine protons as at 7.068 ppm - 7.810 ppm (9H, m), one proton of pyrimidine ring at 5.8119 ppm., six protons of two methoxy group of pyrimodine ring as at 3.77 ppm (6H, S).

(3) The base peak of ESI-MS of compound V_2 was found at 400.14. Based upon the combination of M+1 position, nitrogen rule and fragmentation pattern, the molecular formula was found to be $C_{23}H_{21}N_{21}O_2$.

The characterized heterocyclic compounds containing pyrazole ring were subjected for antimicrobial screening with gram +ve; gram –ve bacteria and also fungi using the above mentioned procedure. The result table no. **F** indicates that inplace of C_6H_5 group when 4-OCH_3-C_6H_4 group is present it shows better activity against three organisms. Inplace of 4-Cl-C_6H_4 when 4-Br-C_6H_4 was used it gave better activity against P. Areuginosa organism. Introduction of 4-NO_2 group did not increase activity. Same observation was observed for 3-NO_2-C_6H_4 derivative. When 4-Cl-C_6H_4 and 2,4-di-Cl-C_6H_3 were compared, the latter compound showed better antibacterial activity against three bacterial cultures. Halogen substituted benzene derivatives are uneffective antifungals. On introduction of 4-CH_3 or 4-OCH_3 group, the compound showed a slight higher activity in comparison with unsubstituted benzene derivative. Introduction of NO_2 group did not show any significant difference in antifungal activity.

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

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. These compounds were subjected to antibacterial and antifungal screening. Although the overall, the antimicrobial and antifungal activities were less compared to the standard drugs. Still some structure-activity relationship features for this series gave hopeful indication to get effective antibacterial activity.

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