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Synthesis, Characterization and Pharmacological Evaluation of Some Novel Schiff Bases Containing 1H-pyrazolo[3,4-b]pyridine Moity

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Abstract: In the present study, a series of novel Schiff bases of 1H-Pyrazolo[3,4-b]pyridine-3-amine were synthesized by condensation with different aromatic aldehydes. The synthesised compounds were screened for their *in vitro* antimicrobial activity. The structure of synthesised compounds 3(a-k) have been established on the basis of their spectral (IR and ^{1}H NMR) and elemental analysis data. The purity of the synthesised compounds was confirmed by TLC.
Key words: Pyrazolopyridine, Schiff base, antimicrobial activity, IR, ^{1}H NMR.

INTRODUCTION

The pyrazolo[3,4-*b*]pyridine system has shown many interesting biological and pharmacological properties, such as antitubercular activity[1,2], activity against gram positive and negative bacteria[3]. Interest in the synthesis of condensed pyrazoles has recently revived because of the wide variety of their biological properties[4-6]. Although the pyrazolo[3,4-b]pyridine ring system has proved to be an interesting class in heterocyclic chemistry, it has received little attention in the literature. Some of its derivatives are important as anticancer agents with low toxicity[7,8], as anti-inflammatories[9],as blood platelet aggregation inhibitors[9],as bone metabolism improvers[10] as adenosine antagonists[11,12] and as controlling herbicides[13]. They also show antifungal and antiparasitic activities[14,15].

There is always need for the safer antibacterial agents and research efforts are going on for developing safer antibacterial agents. Schiff base approach is one of the most promising amongst these[16]. In recent years, there has been an increasing interest in the design and development of Schiff base derivatives. Schiff base are associated with antibacterial, antifungal and

antitubercular activities and have diverse biological activities[17]. Besides, several Schiff bases have been reported to possess remarkable antibacterial[18], anti - fungal[19], anticancer[20], anti HIV[21], anti-inflammatory[22], antiparasitic[23,24] and diuretic[25] activities.

Therefore, it was envisaged that Schiff bases would also exhibit significant antimicrobial activity; we hereby report the antimicrobial activity of Schiff bases of 1H-pyrazolo[3,4-b]pyridine-3-amine.

MATERIALS AND METHODS

Experimental

Melting points were determined in open capillary tubes in a Thomas Hoover melting point apparatus and are uncorrected. The purity of the compounds was confirmed by thin layer chromatography using silica gel glass plates and solvent system of Ethylacetate:Hexane (3:7) ml. The spots were developed in iodine chamber and visualized under ultraviolet lamp. Infrared (IR) and ^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded for the compounds in SHIMADZU FTIR 8400 Spectrophotometer and BRUKER Spectrometer (300 MHz) respectively. Chemical shifts are reported in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. Elemental analysis (N) was undertaken with Perkin Elmer 2400 instrument and the measured values agreed within 0.4% with the calculated.

In the present work a novel series of various substituted Schiff bases were synthesized through condensation reaction. Reactions of 1H-pyrazolo[3,4-b]pyridine-3-amine with different aromatic aldehydes have been carried out in absolute ethanol in the presence of glacial acetic acid, and a variety of Schiff base derivatives have been isolated according to the synthetic scheme-1. The method used for the preparation and isolation of the compounds gave materials of good purity as evidenced by their spectral analyses and thin layer chromatography.

A solution of 2-chloro-3-cyno pyridine (1) (0.01 mol) in hot methanol (15.0 ml) is prepared in a three-necked round-bottom flask fitted with a stirrer at room temperature, drop wise added hydrazine hydrate (2.5 eq.) over a period of 5 minutes, stirr the reaction mass for 30 min at room temperature and reflux for 4.0 hrs in water bath. After completion of the reaction cool the reaction mass at room temperature give product 1H-pyrazolo[3,4-b]pyridine(2). Mixture of 1H-Pyrazolo[3,4-b]pyridine-3-amine (0.01 mol) and aromatic aldehydes (0.01 mol) was taken in ethanol (25.0 ml) and added catalytic amount of gla. acetic acid. The reaction mixture was refluxed for 8.0-10 hrs. on waterbath. The product was isolated and crystallized from absolute ethanol give Schiff base(3). Physical data of all synthesized compounds are recorded in Table-1.

Table 1: Physical Constants of N-((z)Benzylidine)-1H-pyrazolo[3,4-b]pyridine-3-amine

Compound	R	M.P. ^oC	Yield %	% of Nitrogen	
				Calcd.	Found
3a	2-OH	192	90	23.52	23.50
3b	3-NO_2	205	70	26.21	26.20
3c	4-OH	288	70	23.52	23.54
3d	4-N.N(CH_3)2	254	85	26.40	26.41
3e	4-OH-3-OCH_3	230	80	20.88	20.85
3f	4-Cl	208	85	21.83	21.84
3g	4-NO_2	300	75	26.21	26.23
3h	H	195	80	25.21	25.20
3i	4-OCH_3	180	95	22.21	22.19
3j	2-Cl	150	92	21.83	21.84
3k	4-F	178	71	23.32	23.35

z = Different functional groups (R)

RESULTS AND DISCUSSION

Biological activity

Minimum inhibitory concentration (MIC) of all the synthesized compounds was determined against four different strains, viz two Gram positive bacteria (*S. aureus & S. pyogenes* and two Gram negative bacteria (*E. coli & P. aeruginosa*) compared with standard drugs gentamycin, ampicillin, chloramphenicol, ciprofloxacin, & norfloxacin by broth dilution method.[26] Antifungal activities against *C. albicans*, *A. niger* and *A. clavatus* organisms were compared with standard drugs nystatin and greseofulvin by same method.

Antibacterial activity

From screening results, substituted schiff base **3f** (R = -4-Cl) possesses very good activity against E. coli compared with ampicillin while **3d** (R = -4-N,N(CH_3)$_2$) and **3i** (R= -4-OCH_3) against S.aureus and S.pyogenus, **3c** (R= -4-OH) and **3g** (R= -4-NO_2) against E-coli, **3k** (R= -4-F) against S.aureus and E-coli possesses moderate activity compared with ampicillin. The remaining schiff bases possess poor to very poor activity against all four bacterial species.

Antifungal activity

Antifungal screening data showed that substituted schiff bases **3f** (R = -4-Cl) against C. albicans show highly promising activity compare with standard drug while **3d** (R = -4-N,N(CH_3)$_2$, and **3h** (R = H) against C. albicans, **3k** (R = -4-F) against A.niger while **3i** (R = -4-OCH_3) against A.niger and A.clavatus shows very good activity compare with standard drug. The remaining compounds exhibited only moderate to poor activity.

Table 2:Biological Evaluation of N-((z)Benzylidine)-1H-pyrazolo[3,4-b] pyridine-3-amine

Sr. No.	Comp.	Antibacterial Activity				Antifungal activity		
		Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
		Gram +*ve* Bacteria		Gram –*ve* Bacteria				
		S.aureus	S.pyogenus	E.coli	P.aeruginosa	C.albicans	A.niger	A.clavatus
1	3a	250	250	200	1000	500	1000	1000
2	3b	1000	500	250	250	500	1000	1000
3	3c	200	200	100	200	500	500	500
4	3d	100	100	1000	250	250	500	500
5	3e	200	200	250	500	1000	500	500
6	3f	250	250	62.5	100	200	500	500
7	3g	500	1000	100	200	500	>1000	>1000
8	3h	200	200	200	250	250	500	500
9	3i	100	100	1000	500	1000	250	250
10	3j	1000	250	500	1000	500	>1000	>1000
11	3k	100	250	100	250	500	250	1000

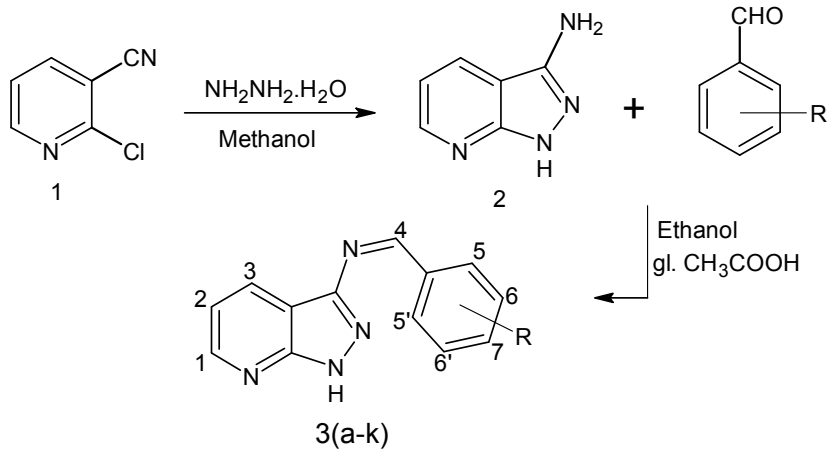
MINIMAL INHIBITION CONCENTRATION

Standard Drugs	E.coli	P.aeruginosa	S.aureus	S.pyogenus
	(microgramme/ml)			
Gentamycin	0.05	1	0.25	0.5
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50
Ciprofloxacin	25	25	50	50
Norfloxacin	10	10	10	10

MINIMAL FUNGICIDAL CONCENTRATION

Standard Drugs	C.Albicans	A.Niger	A.Clavatus
	(microgramme/ml)		
Nystatin	100	100	100
Greseofulvin	500	100	100

z = Different functional groups (R)



R= H, 4-Cl, 2-OH, 4-OH, 4-NO_2, 3-NO_2, 4-OCH_3, 2-Cl, 4-F, 4-$N(CH_3)_2$ etc.

Scheme-1

2-((E)-(1H-pyrazolo[3,4-b]pyridin-3-ylimino)methyl)phenol (3a)

IR: (KBr) m (cm^{-1}): 3414 (NH), 3122 (OH), 2942, 2875 (C-H), 1666 (-N=CH-), 1284 (C-N), 1224 (C-O-C); ^1H NMR ($CDCl_3$) : 13.01 (s, 1H, NH), 11.39 (s, 1H, Ar-OH), 8.71 (s, 1H, H4), 7.48-7.35 (m, 3H, H1,H3,H5'), 7.05-6.95 (m, 4H, H2,H6,H6',H7); Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.54; H, 04.23; N, 23.52; Found: C, 65.57; H, 04.20; N, 23.50.

(E)-N-(3-nitrobenzylidene)-1H-pyrazolo[3,4-b]pyridin-3-amine (3b)

IR: (KBr) m (cm^{-1}): 3425 (NH), 2932, 2861 (C-H), 1656 (-N=CH-), 1281 (C-N), 1219 (C-O-C); ^1H NMR ($CDCl_3$) : 12.92 (s, 1H, NH), 8.69 (s, 1H, H4), 8.59-8.54 (m, 2H, H1,H5'), 7.42-7.30 (m, 3H, H2,H3,H7), 7.02-6.98 (m, 2H, H5,H6); Anal. Calcd. for $C_{13}H_9N_5O_2$: C, 58.43; H, 03.39; N, 26.21; Found: C, 58.40; H, 03.38; N, 26.20.

4-((E)-(1H-pyrazolo[3,4-b]pyridin-3-ylimino)methyl)phenol (3c)

IR: (KBr) m (cm^{-1}): 3409 (NH), 3130 (OH), 2960, 2870 (C-H), 1660 (-N=CH-), 1279 (C-N), 1219 (C-O-C); ^1H NMR ($CDCl_3$) : 13.00 (s, 1H, NH), 11.20 (s, 1H, Ar-OH), 8.70 (s, 1H, H4) 7.45-7.31 (m, 3H, H1,H3,H5'), 7.00-6.94 (m, 4H, H2,H5,H6,H6'); Anal. Calcd. for $C_{13}H_{10}N_4O$: C, 65.54; H, 04.23; N, 23.52; Found: C, 65.57; H, 04.20; N, 23.50.

(E)-N-(3-(dimethylamino)benzylidene)-1H-pyrazolo[3,4-b]pyridin-3-amine (3d)

IR: (KBr) m (cm^{-1}): 3419 (NH), 2965, 2873 (C-H), 1648 (-N=CH-), 1280 (C-N), 1222 (C-O-C); ^1H NMR ($CDCl_3$) : 12.80 (s, 1H, NH), 8.59 (s, 1H, H4), 8.48-8.42 (m, 2H, H1,H3), 7.43-7.38 (m, 3H, H2,H5,H5'), 7.05-6.97 (m, 2H, H6,H6'), 2.78 (s, 6H, -CH_3); Anal. Calcd. for $C_{15}H_{15}N_5$: C, 67.90; H, 05.70; N, 26.40; Found: C, 67,88; H, 05.72; N, 26.41.

4-((E)-(1H-pyrazolo[3,4-b]pyridin-3-ylimino)methyl)-2-methoxyphenol (3e)

IR: (KBr) m (cm^{-1}): 3425 (NH), 3130 (OH), 2950, 2871 (C-H), 1664 (-N=CH-), 1280 (C-N), 1221 (C-O-C); ^1H NMR ($CDCl_3$) : 13.20 (s, 1H, NH), 10.87 (s, 1H, Ar-OH), 8.78 (s, 1H, H4), 8.59-8.56 (m, 1H, H1), 7.52-7.49 (m, 3H, H2,H5,H5'), 7.38-7.34 (m, 2H, H3,H6); Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 04.51; N, 20.88; Found: C, 62.71; H, 04.50; N, 20.85.

(E)-N-(4-chlorobenzylidene)-1H-pyrazolo[3,4-b]pyridin-3-amine (3f)

IR: (KBr) m (cm^{-1}): 3411 (NH), 2961, 2874 (C-H), 1661 (-N=CH-), 1268 (C-N), 1222 (C-O-C); ^1H NMR ($CDCl_3$) : 13.11 (s, 1H, NH), 8.73 (s, 1H, H4) 8.51-8.47 (m, 1H, H1), 7.68-7.64 (m, 3H, H3,H5,H5'), 7.31-6.27 (m, 3H, H2,H6,H6'); Anal. Calcd. for $C_{13}H_9ClN_4$: C, 60.83; H, 03.53; N, 21.83; Found: C, 60.84; H, 03.50; N, 21.84.

(E)-N-(4-nitrobenzylidene)-1H-pyrazolo[3,4-b]pyridin-3-amine (3g)

IR: (KBr) m (cm^{-1}): 3422 (NH), 2931, 2861 (C-H), 1652 (-N=CH-), 1284 (C-N), 1217 (C-O-C); ^1H NMR ($CDCl_3$) : 13.94 (s, 1H, NH), 8.70 (s, 1H, H4), 8.55-8.51 (m, 3H, H1,H6,H6'), 7.68-7.63 (m, 3H, H3,H5,H5'), 7.38-7.34 (m, 1H, H2); Anal. Calcd. for $C_{13}H_9N_5O_2$: C, 58.43; H, 03.39; N, 26.21; Found: C, 58.42; H, 03.36; N, 26.23.

(E)-N-benzylidene-1H-pyrazolo[3,4-b]pyridin-3-amine (3h)

IR: (KBr) m (cm^{-1}): 3432 (NH), 2928, 2859 (C-H), 1653 (-N=CH-), 1277 (C-N), 1219 (C-O-C); ^1H NMR ($CDCl_3$) : 13.01 (s, 1H, NH), 8.71 (s, 1H, H4), 8.58-8.53 (m, 1H, H1), 7.37-7.34 (m, 3H, H3,H5,H5'),

7.30-7.24 (m, 4H, H2,H6,H6',H7); Anal. Calcd. for $C_{13}H_{10}N_4$: C, 70.26; H, 04.54; N, 25.21; Found: C, 70.22; H, 04.52; N, 25.20.

(E)-N-(4-methoxybenzylidene)-1H-pyrazolo[3,4-b]pyridin-3-amine (3i)

IR: (KBr) m (cm^{-1}): 3411 (NH), 2964, 2874 (C-H), 1663 (-N=CH-), 1282 (C-N), 1221 (C-O-C); ^1H NMR ($CDCl_3$) : 13.18 (s, 1H, NH), 8.73 (s, 1H, H4), 8.50-8.47 (m, 1H, H1), 7.46-7.40 (m, 3H, H2,H5,H5'), 735-7.31 (m, 3H, H3,H6,H6'), 3.52 (s, 3H, OCH3; Anal. Calcd. for $C_{14}H_{12}N_4O$: C, 66.65; H, 04.79; N, 22.21; Found: C, 66.67; H, 04.77; N, 22.19.

(E)-N-(2-chlorobenzylidene)-1H-pyrazolo[3,4-b]pyridin-3-amine (3j)

IR: (KBr) m (cm^{-1}): 3412 (NH), 2967, 2876 (C-H), 1669 (-N=CH-), 1272 (C-N), 1220 (C-O-C); ^1H NMR ($CDCl_3$) : 13.21 (s, 1H, NH), 8.75 (s, 1H, H4), 8.58-8.54 (m, 1H, H1), 7.74-7.70 (m, 2H, H3,H6), 7.28-6.22 (m, 4H, H2,H5',H6',H7); Anal. Calcd. for $C_{13}H_9ClN_4$: C, 60.83; H, 03.53; N, 21.83; Found: C, 60.80; H, 03.51; N, 21.84.

(E)-N-(4-fluorobenzylidene)-1H-pyrazolo[3,4-b]pyridin-3-amine (3k)

IR: (KBr) m (cm^{-1}): 3415 (NH), 2960, 2873 (C-H), 1665 (-N=CH-), 1275 (C-N), 1224 (C-O-C); ^1H NMR ($CDCl_3$) : 13.34 (s, 1H, NH), 8.77 (s, 1H, H4), 8.59-8.56 (m, 1H, H1), 7.70-7.66 (m, 3H, H3,H5,H5'), 7.38-6.32 (m, 1H, H2), 7.00-6.97 (t, 2H, H6,H6'); Anal. Calcd. for $C_{13}H_9FN_4$: C, 64.99; H, 03.78; N, 23.32; Found: C, 64.96; H, 03.801; N, 23.35.

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