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RESEARCH ARTICLE

A Catalyst Free Synthesis and *In Vitro* Antimicrobial Studies of a Series of Bis-Schiff Bases

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Abstract: A series of bis-Schiff bases (**3a-l**) has been synthesized by condensation of substituted hydrazones (**1a-l**) with 3,5-dibromosalicylaldehyde (**2**) at room temperature within a short period of time under catalytic free conditions. The chemical structures of the synthesized compounds were confirmed on the basis of spectral analysis data. The bis-Schiff base derivatives (**3a-l**) were further screened for their *in vitro* antibacterial activity against plant, human pathogenic bacteria (*Erwinia carotovora*, *Xanthomonas citri*, *Proteus vulgaris*, *Staphylococcus aureus*) and antifungal (*Alternaria* and *Curvularia lunata*) studies. Compounds (**3a-l**) showed promising activities against *S. aureus* and *Proteus vulgaris*.

Keywords: Hydrazones, Dibromosalicylaldehyde, Bis-Schiff bases, Antimicrobial activity

Introduction

Hydrazones have been evolved as an important class in organic synthesis as well as medicinal chemistry[1]. A variety of examples are available in the literature which provide the evidence of fruitful utilities of hydrazone moieties[2] and create the diversion for researchers to explore their studies. Schiff bases or azomethines despite a vast literature continue to be of current interest for their utilities. The formation of Schiff bases via condensation of an amine and an aldehyde is the oldest reaction in chemistry. A broad spectrum of biological activities is associated with Schiff bases such as antibacterial[3], antifungal[4], antioxiant[5], anticonvulsant[6], anti-proliferative[7] and anticancer[8]. Apart from this, Schiff bases are acting

as ligands which co-ordinate to metals through imine nitrogen and another group usually oxygen situated on the original carbonyl compound. The complexes derived from various Schiff bases reported to be synthetically as well as medicinally important scaffolds[9-16].

In continuation to this, various research groups demonstrated the synthesis of bis-Schiff bases[17] and their potencies[18]. Being more specific towards our approach, we synthesized here some novel bis-Schiff base derivatives (**3a-l**) without using any catalytic system and studied their antimicrobial properties.

Experimental

The required chemicals were purchased from S.D. fine chemicals (India). Melting points were determined by an open capillary method and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard either on Brucker 300 MHz or 400 MHz NMR spectrophotometer. The chemical shift values are expressed in part per million (ppm). The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) technique on silica gel plate using petroleum ether and ethyl acetate.

*General procedure for the synthesis of bis-Schiff bases **(3a-l)***

A mixture of substituted hydrazones (**1a-l**, 0.01 mole) and 3,5-dibromosalicylaldehyde (**2**, 0.01 mole) was allowed to react in ethanol at room temperature with shaking. The separated solid was filtered, dried and recrystallized from 95% ethanol to give yellow coloured solid bis-Schiff base derivatives (**3a-l**) in 63-78% yield.

Spectral data of some representative compounds

*2,4-Dibromo-6-{[1-(2-hydroxy-phenyl)-ethylidene]-hydrazonomethyl}-phenol **(3a)***

M.P.: 220 ^{0}C; IR (ν_{max} cm^{-1}): 1612 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.50 (s, 3H, -CH_3), 6.8-7.4 (m, 6H, Ar-H), 8.9 (s, 1H, -CH=N), 10.9 (s, 1H, -OH), 12.1 (s, 1H, -OH). MS (*m/z*): 412.08.

*2,4-Dibromo-6-{[1-(2-hydroxy-3,5-iodo-phenyl)-ethylidene]-hydrazonomethyl}-phenol **(3g)***

M.P.: 272 ^{0}C; IR (ν_{max} cm^{-1}): 3444 (-OH), 2924 (-CH), 1604 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.56 (s, 3H, -CH_3), 6.7-8.03 (m, 4H, Ar-H), 8.86 (s, 1H, -CH=N), 10.8 (s, 1H, -OH), 14.5 (s, 1H, -OH). MS (*m/z*): 663.15.

*2,4-Dibromo-6-{[1-(5-chloro-2-hydroxy-phenyl)-ethylidene]-hydrazonomethyl}-phenol **(3h)***

M.P.: 261 ^{0}C; IR (ν_{max} cm^{-1}): 2924 (-CH), 1608 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.56 (s, 3H, -CH_3), 6.8-7.7 (m, 5H, Ar-H), 8.7 (s, 1H, -CH=N), 10.9 (s, 1H, -OH), 12.1 (s, 1H, -OH). MS (*m/z*): 445.43.

*2,4-Dibromo-6-{[1-(5-methyl,3-iodo-2-hydroxy-phenyl)-ethylidene]-hydrazonomethyl} -phenol **(3i)***

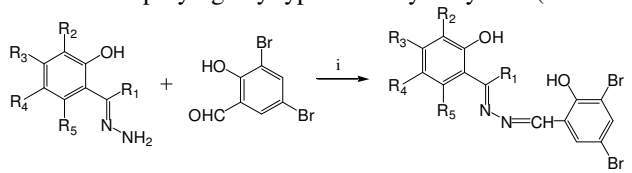
M.P.: 252 ^{0}C; IR (ν_{max} cm^{-1}): 3444 (OH), 2924(-CH), 1608 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.25 (s, 3H, Ar-CH_3), 2.58 (s, 3H, -CH_3), 6.8-7.7 (m, 4H, Ar-H), 8.89 (s, 1H, -CH=N), 10.91 (s, 1H, -OH), 14.1 (s, 1H, -OH). MS (*m/z*): 551.

*2,4-Dibromo-6-{[1-(5-bromo-2-hydroxy-phenyl)-ethylidene]-hydrazonomethyl}-phenol **(3j)***

M.P.: 239 ^{0}C; IR (ν_{max} cm^{-1}): 1610 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.52 (s, 3H, -CH_3), 6.7-6.8 (m, 5H, Ar-H), 8.5 (s, 1H, -CH=N), 10.7 (s, 1H, -OH), 11.9 (s, 1H, -OH). MS (*m/z*): 490.97.

Results and Discussion

The synthesis of a library of bis-Schiff bases (**3a-l**) was achieved by the reaction of dibromosalicylaldehyde (**2**) with various substituted hydrazones (**1a-l**) at room temperature in ethanolic conditions without employing any type of catalytic system (Scheme 1).

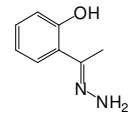
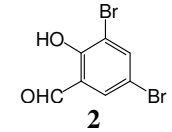
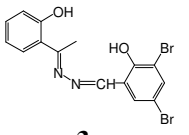
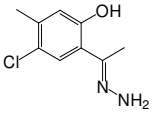
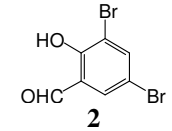
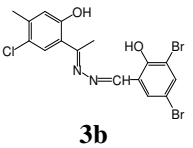
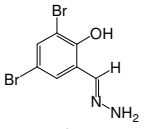
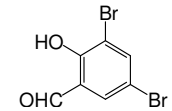
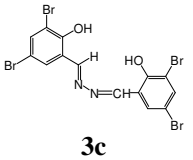
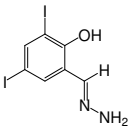
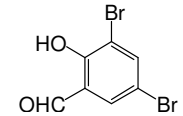
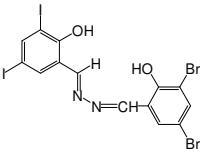


1a-l **2** **3a-l**

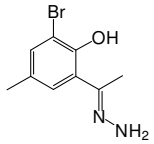
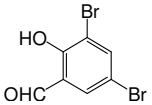
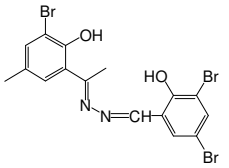
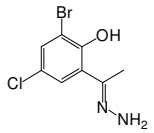
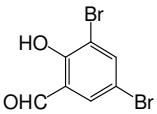
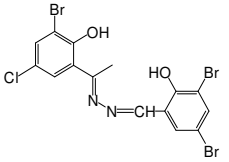
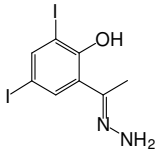
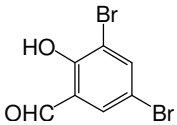
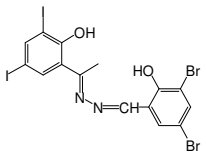
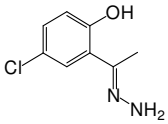
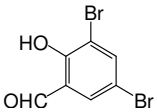
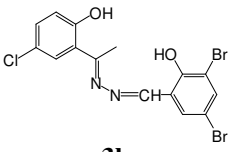
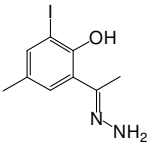
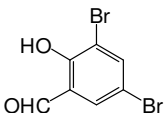
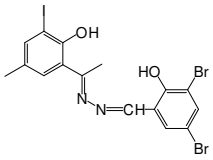
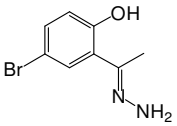
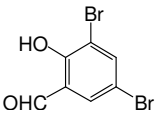
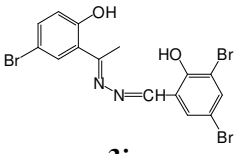
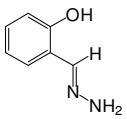
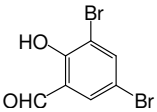
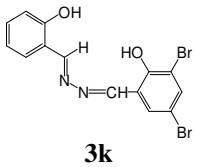
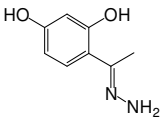
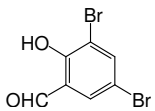
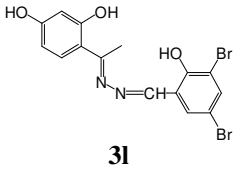
Scheme 1. Reaction conditions i) EtOH, rt, immediately

The hydrazones (**1a-l**) employed, were synthesized in our previous studies[19-20] via reaction of various halo and methyl substituted ortho hydroxy aldehydes and ketones with hydrazine hydrate. The data of the synthesized Schiff bases (Table 1) reflected the smooth applicability of the reaction towards various substituents utilized. The reaction was carried out at room temperature within a couple of minute affording expected bis-Schiff bases (**3a-l**) with high purity (complete consumption of reactants, single spot, TLC) and appreciable yield (63-78%).

Table 1. Synthesis of bis-Schiff bases **(3a-l)**

Entry	Hydrazones (**1a-l**)	DSA2	bis-Schiff bases (**3a-l**)	Yield, %	M.P. ^{0}C
1	 **1a**	 **2**	 **3a**	74	220
2	 **1b**	 **2**	 **3b**	78	263
3	 **1c**	 **2**	 **3c**	72	260
4	 **1d**	 **2**	 **3d**	70	292

Contd…

5	 **1e**	 **2**	 **3e**	68	250
6	 **1f**	 **2**	 **3f**	65	248
7	 **1g**	 **2**	 **3g**	69	272
8	 **1h**	 **2**	 **3h**	71	261
9	 **1i**	 2	 **3i**	67	250
10	 **1j**	 2	 **3j**	75	239
11	 **1k**	 2	 **3k**	78	158
12	 **1l**	 **2**	 **3l**	63	254

DSA- 3, 5-dibromosalicylaldehyde

Biological screening

The *in vitro* antimicrobial activity was performed against 24 h old cultures of four bacteria and two fungi by cup plate method. Compounds **3a-l** were tested for their antimicrobial activity against different plant and human pathogenic bacteria like *Erwinia carotovora*, *Xanthomonas citri*, *Proteus vulgaris*, *Staphylococcus aureus* respectively and antifungal activity against *Alternaria* and *Curvularia lunata* at a concentration of 1000 µg/mL in DMSO using cup plate diffusion method. Nutrient agar and Potato dextrose agars were used to culture the bacteria and fungi respectively. The solutions of Penicillin and Nystatin at concentration of 1000 µg/mL in DMSO were used as standard for comparison of antibacterial and antifungal activity respectively. The results of antimicrobial screening were tabulated in Table 2.

Table 2. Antimicrobial activities of bis-Schiff bases **(3a-l)**

Entry	Ec	Xc	Pv	Sa	Al	Cl
3a	NO	09	08	09	-ve	+ve
	--	(0.90)	(0.66)	(1.10)		
3b	NO	NO	09	14	+ve	-ve
	--	--	(0.75)	(1.75)		
3c	13	10	11	10	-ve	+ve
	(0.92)	(1.00)	(0.91)	(1.25)		
3d	16	NO	14	13	-ve	-ve
	(1.14)	--	(1.16)	(1.62)		
3e	NO	09	08	09	-ve	-ve
	--	(0.90)	(0.66)	(1.10)		
3f	10	NO	11	11	-ve	+ve
	(0.71)	--	(0.91)	(1.37)		
3g	NO	NO	11	14	-ve	-ve
	--	--	(0.91)	(1.75)		
3h	NO	11	12	13	+ve	-ve
	--	(1.10)	(1.00)	(1.62)		
3i	NO	12	11	13	-ve	-ve
	--	(1.20)	(0.91)	(1.62)		
3j	12	11	13	14	-ve	-ve
	(0.85)	(1.10)	(1.08)	(1.75)		
3k	NO	11	14	13	+ve	-ve
	--	(1.10)	(1.16)	(1.62)		
3l	NO	11	11	11	+ve	-ve
	--	(1.10)	(0.91)	(1.37)	+ve	-ve
Penicillin	14	10	12	08	NA	NA
Nystatin	NA	NA	NA	NA	-ve	-ve

Ec- Erwinia carotovora, Xc- Xanthomonas citri, Pv- Proteus vulgaris, Sa- Staphylococcus aureus; Al- Alternaria, Cl- Curvularia lunata and +ve = Growth, -ve = No growth, (-- or NO)- No inhibition, NA- Not Applicable, Activity index= zone of inhibition of compound/ zone of inhibition of standard

Conclusion

In conclusion, we have demonstrated the catalytic free synthesis of a library of bis-Schiff bases (**3a-l**) with diverse functionalities at room temperature within a short period of time, while various reports described the use of hazardous acid catalysts for the synthesis of Schiff bases[9,21]. The synthesized Schiff bases (**3a-l**) exhibited potencies against different strains of

plant and human pathogenic bacteria and fungi. The compound **3d** showed good activity against *Erwinia carotovora*. The compound **3c**, **3h**, **3i**, **3j** and **3l** were observed to possess comparable activity against *Xanthomonas citri*. The compound **3d**, **3f**, **3j** and **3k** showed promising antibacterial activity against *Proteus vulgaris* and *S. aureus* respectively. In addition to this, compounds **3d**, **3e**, **3g**, **3i** and **3j** were also observed to possess potency against the fungi *Alternaria* and *C. lunata* respectively. The antimicrobial screening data of synthesized bis-Schiff bases (**3a-l**) is in agreement to explore the chemistry of such scaffolds with biological aspects.

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