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Synthesis, Characterization and Antimicrobial Evaluation of Some Novel Bis-Schiff Bases

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ABSTRACT

We wish to report here with synthesis of bis-schiff bases via condensation of hydrazone of 2-hydroxy acetophenone with different substituted acetophenone in presence of $SnCl_2$ as a catalyst just by grinding to accomplish the bis-schiff base with moderate to good yields. All the synthesized Schiff bases were analyzed by spectral analysis IR, ^1H NMR and Mass spectrometry. All these bis-Schiff bases were screened for antimicrobial activity by using Agar Disc Diffusion method.

Key words: Bis-schiff bases, Aryl ketones, Spectral Analysis, Antimicrobial Study.

INTRODUCTION

Schiff bases are the compounds which contain –C=N group. These compounds are also known as imines or azomethines but most commonly they are known as Schiff bases to honour Hugo Schiff [1], who reported synthesis of this compound. A lot of work has been done on this class of compound due to their diversified biological activity and multiapplicability. Several medicinal chemists reported a wide range of biological activity of Schiff bases such as Anticancer[2,3] antibacterial[4-10], antifungal, antiviral[11-14], anticonvulsant[15]**,** anti-inflammatory[16-18**]**, analgesic[19], antitubercular[20],antioxidant[21], anthelminthic[22], anticancer[23]. A large number of Schiff base complexes are capable of catalysing variety of reactions. These are stable over a range of temperature, and are less sensitive to moisture. In recent years, there have been numerous reports of their use as homogeneous and heterogeneous catalyst. Schiff bases and their metal complexes are widely being used as catalysts in various biological processes [24].The Schiff bases containing 2,4-dichloro-5-fluorophenyl moieties are effective inhibitors of bacterial growth [25].Therefore it is decided to synthesize some novel bis-schiff bases having halogen moieties in their structures., we adopted grinding technique for the synthesis of some novel Bis-Schiff bases by condensing hydrazone of 2-hydroxy acetophenone[26] and various aromatic and heterocyclic aldehydes in presence of Stanous Chloride as a catalyst to furnish the required product in good yield.These novel bis-schiff bases werescreened for antimicrobial activity by using Agar Disc Diffusion method[27].

EXPERIMENTAL SECTION

All the regents were purchased from Merck and Loba chemicals and used as such. All the melting points determined in an open capillary and are uncorrected. TLC analyses were carried out on glass plates (6 cm) using silica gel and the plates were analyzed by keeping in iodine chamber. The IR spectra were recorded on KBr disc on Shimadzu FT-IR 8300 spectrometer and absorption was expressed in cm^{-1}. The ^1H NMR spectra were recorded on $CDCl_3$ /

DMSO-d_6 on a Brucker instrument at 400 MHz and 300 MHz using tetramethylsilane as the internal standard. Chemical shifts have been expressed in ppm.

The mass spectra were recorded on VG 7070 mass spectrometer using ionization energy of 70 ev.

General Procedure for synthesis of hydrazone

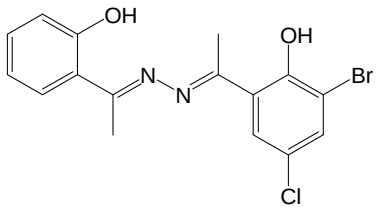
To a mixture of o-hydroxyacetophenone (0.01 mol) and hydrazine hydrate (0.02 mol) in DMSO a catalytic amount of $SnCl_2{\cdot}2H_2O$ was added. The reaction mixture was stirred for few minutes. The completion of reaction was monitored by TLC. The reaction mixture was poured into crushed ice .The solid product obtained was filtered and purified by recrystallisation.

General procedure for the synthesis of bis-Schiff bases:

A mixture of hydrazone**1** and various substituted aromatic substituted ketones**2a-h** was reacted in presence of catalytic amount of $SnCl_2{\cdot}2H_2O$ by grinding technique. The consumption of reactants was observed within a couple of minute monitored by TLC. The expected product was obtained by washing with ice cold water. The separated yellow colored solid product was filtered and recrystallized by using ethanol producing good yield of the product.

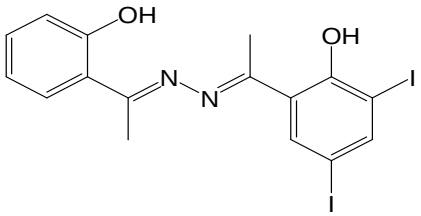
Characterization data bis-Schiff bases

2-Bromo-4-chloro-6-{1-[1-(2-hydroxyphenyl) ethyl] hydrazonoethyl} phenol **(3a)**



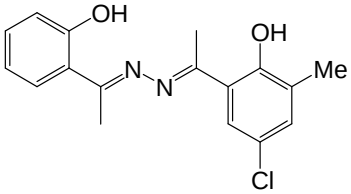
Molecular Formula: $C_{16}H_{14}N_2O_2BrCl$
Molecular Weight: 381.659
IR (ν max cm^{-1}): 3411.1,3070.9,1600.3,1554.3, 1444.4,1362.4,1241.2,749.3.
^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.3 (s,3H),2.4(s,3H),7.1-8.0(m,6H), 12.6 (s, 1H,) 13 (s, 1H).
MS (m/z): 382

2, 4-Diiodo-6-{1-[1-(2-hydroxyphenyl) ethyl] hydrazonoethyl} phenol **(3b)**



Molecular Formula: $C_{16}H_{14}N_2O_2I_2$
Molecular Weight: 520.182
IR (ν max cm^{-1}): 3049, 1599, 1422,1360,1300,1241,750.
^{1}HNMR (400MHz, DMSO-d_6, δ ppm): 2.50(s, 3H), 2.51 (S,3H), 6.90-7.90 (m, 6H), 12.7(S,1H),13.0(S,1H)
MS (m/z): 521.19

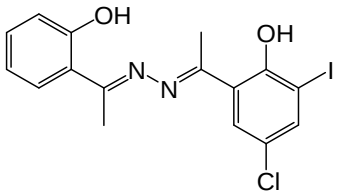
4- Chloro-2- methyl -6-{1-[1-(2-hydroxyphenyl) ethyl] hydrazonoethyl} phenol **(3c)**



Molecular Formula: $C_{17}H_{17}N_2O_2Cl$
Molecular Weight: 316.79

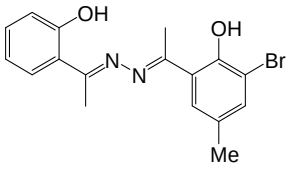
IR (ν max cm^{-1}): 3412 ,1603, 1362,1246,745.
^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.3(S,3H),2.50 (s, 3H), 2.54 (s, 3H), 6.95 -7.90(,6H), 12.84 (s, 1H) , 13 (s, 1H)
MS (m/z): 316.1

4- Chloro-2-iodo -6-{1-[1-(2-hydroxyphenyl) ethyl] hydrazonoethyl} phenol **(3d)**



Molecular Formula: $C_{16}H_{14}N_2O_2ICl$
Molecular Weight: 428.659
IR (ν max cm^{-1}): 3409,1602, 1556, 1243,752.
^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.5 (S, 3H),2.6(S,3H), 6.8-8.2(m,6H), 12.93 (S, 1H),13(S,1H)
MS (m/z): 429.2

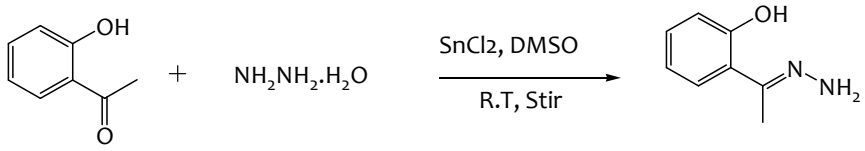
2- Bromo -4- Methyl -6-{1-[1-(2-hydroxyphenyl) ethyl] hydrazonoethyl} phenol **(3e)**



Molecular Formula: $C_{17}H_{17}N_2O_2Br$
Molecular Weight: 361
IR (ν max cm^{-1}):3412,1600,1360,1244,740
^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.25(S,3H),2.5(S,3H),2.6 (s, 3H), 6.90-8.1 (m, 6H), 12.93 (s, 1H),13.1(S1H)
MS (m/z): 361.4

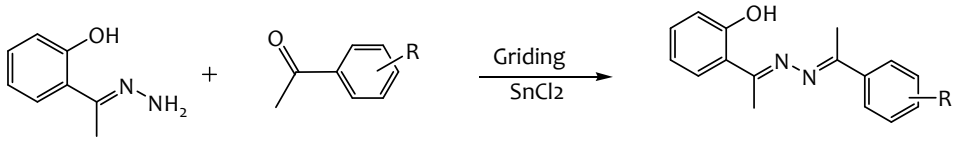
RESULTS AND DISCUSSION

2-Hydroxy acetophenonehydrazone was synthesized by known method by refluxing 2-hydroxy acetophenone with hydrazine hydrate at room temperature in presence of catalyst $SnCl_2$and DMSO solvent. The product was recrystallized by ethanol.



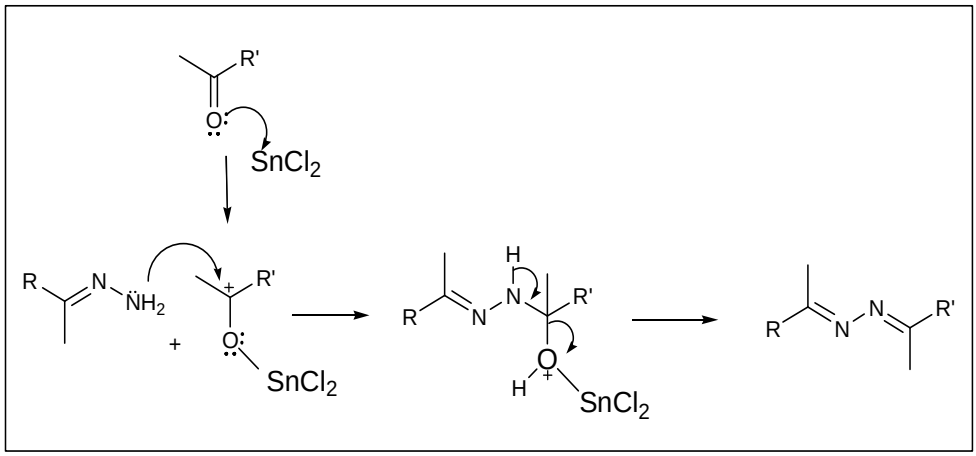
Scheme 1. Synthesis of 2-Hydroxy acetophenone hydrazone

Bis –Schiff Bases were Synthesized by grinding hydrazone with aromatic substituted ketones for 5-7 minutes in presence of catalyst $SnCl_2$.



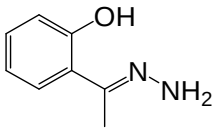
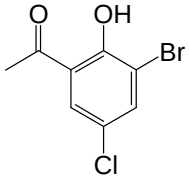
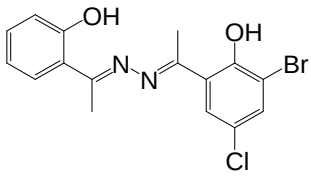
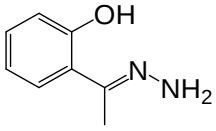
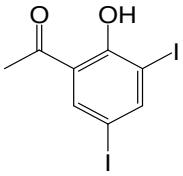
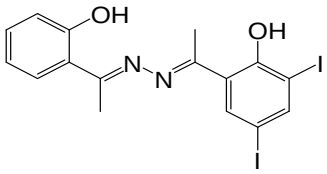
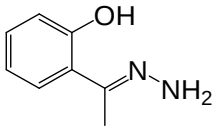
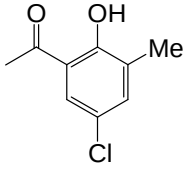
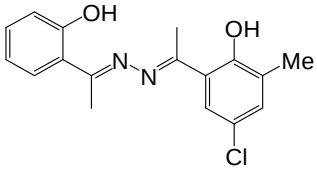
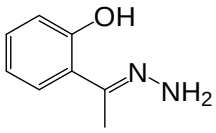
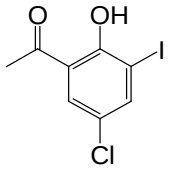
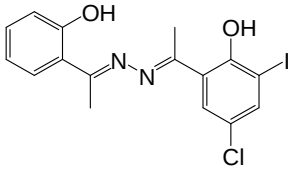
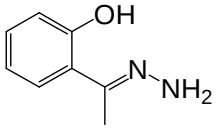
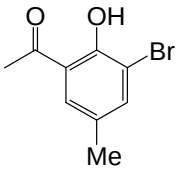
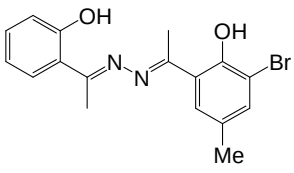
Scheme 2.Synthesis of Bis -Schiff Base

Plausible mechanism



The applicability of the reaction is checked by reaction of hydrazones with various aromatic ketones . We did not observe any remarkable difference in the reaction time for various ketones (mentioned in Table 1).

Table 1.List of bis-Schiff bases (3a-e)

Entry	Hydrazone	Ketone	bis-schiff base	Yield	M.P.
1	 **1**	 **2a**	 **3a**	**68**	**182-183**
2	 **1**	 **2b**	 **3b**	**70**	**155-156**
3	 1	 **2c**	 **3c**	**75**	**201-202-203**
4	 1	 **2d**	 **3d**	**72**	**165-166**
5	 **1**	 **2e**	 **3e**	**75**	**135-136**

Antibacterial activity

The antibacterial activity was carried out by the agar well diffusion method using nutrient agar (NA) plates . NA media had been prepared and plated with bacterial cultures 10^{-6} CFU/mL using seeded agar technique. A cork borer (6 mm diameter) was used to punch wells in solidified medium, which was filled with 100 µL of selected compounds dissolved with DMSO (1 mg/mL). The efficacy of compounds against bacteria was compared with the broad spectrum antibiotic penicillin (1 mg/mL, positive control) and DMSO as negative control. The plates were incubated at 37 °C for 24 h in incubator and the diameter of the zone of inhibition was measured in mm.

Table-1 Antibacterial activity of synthesized compounds

Sr. No.	*Compound*	*Escherichia coli*	*Salmonella typhimurium*	*Staphylococcus aureus*	*Bacillus subtilis*
1	*(3a)*	*-ve*	*-ve*	*14*	*-ve*
2	*(3b)*	*-ve*	*-ve*	*11*	*-ve*
3	*(3c)*	*-ve*	*-ve*	*14*	*-ve*
4	*(3d)*	*-ve*	*-ve*	*16*	*-ve*
5	*(3e)*	*-ve*	*-ve*	*16*	*-ve*
6	*DMSO*	*-ve*	*-ve*	*-ve*	*-ve*
7	*Penicilin*	*14*	*20*	*36*	*28*

Legends: -ve: No Antibacterial activity;
Zone of inhibition: -- mm

The results obtained are summarized in Table-1. It is observed that, the selected compounds showed promising antibacterial activity towards *S. aureus*, while rest of the bacterial strains were found to be resistant to selected compounds at used concentration (1 mg/ml). The maximum activity was shown by 3d and 3e (16 mm), while the minimum activity was observed in 3b (11 mm). The antibiotic, penicillin showed significant inhibition to all bacterial strain i.e. *S. aureus*, *E. coli*, *S. typhimurium*and *B. subtilis* 36, 14, 20 and 28 mm respectively.

Antifungal activity:

The antifungal activity was carried out by the agar well diffusion method [39]. PDA media was prepared and poured in sterilized Petri dishes and kept for 45 min to be solidified, inoculums containing 10^{-6} CFU/mL of fungal spore were spread on the solid agar media. Wells were made in the potato dextrose agar plate using cork borer (6 mm). Then 100 µL of compounds were dissolved with DMSO (1 mg/mL) and placed in the wells and kept in the refrigerator at 4 °C for 30 min for uniform diffusion of the substances then incubated at 30 °C for 24 h. The diameter of the zone of inhibition was measured in millimeter (mm).

Table-2 Antifungal activity of synthesized compounds

Sr. No.	*Compound*	*Aspergillus Niger*	*Penicilliumchrysogenum*	*Fusariummoniliforme*	*AspergillusFlavus*
1	*(3a)*	*-ve*	*-ve*	*-ve*	*-ve*
2	*(3b)*	*-ve*	*RG*	*-ve*	*RG*
3	*(3c)*	*RG*	*RG*	*-ve*	*RG*
4	*(3d)*	*-ve*	*RG*	*-ve*	*RG*
5	*(3e)*	*RG*	*RG*	*-ve*	*RG*
6	*DMSO*	*+ve*	*+ve*	*+ve*	*+ve*
7	*Griseofulvin*	*-ve*	*-ve*	*-ve*	*-ve*

Legends:
+ve: Growth (Antifungal activity absent);
-ve: No growth (More than 90 % reduction in growth Antifungal activity present);
RG: Reduced growth (More than 50 % and less than 90 % reduction in growth observed)

The antifungal activity of selected compounds is shown in Table 2. The results obtained indicate that, all compounds showed moderate to excellent inhibition to fungal strain. However, compound 3a has excellent inhibition to all fungal strains. While compound 3b and 3d inhibit *A. niger*, *F. monoliforme* significantly. *A. niger* is not much susceptible to evaluated compounds in fact it is moderately inhibited by them. Griseofulvin used as standard has excellent results by inhibiting all tested fungal strain.

CONCLUSION

In Continuation, we have developed an environmentally benign green protocol for the synthesis of Schiff bases. The promising features of the presented methodology are Shorter reaction time, Simple work up procedures, good yield

of the product and above all the presented protocol follows the principle of green chemistry. As it was predicted some of the novel bis-schiff bases shows anti-bacterial and anti-fungal activity.

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