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Schiff bases - Synthesis, Characterization and Antibacterial activity

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ABSTRACT

Six Schiff bases viz. (1) 4-[1-aza-2- (2-chlorophenyl) vinyl]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one [SS1] (2) 4-[1-aza-2- (2-hydroxyphenyl) vinyl]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one [SS2] (3) 4-[1-aza-4-phenylbuta-1, 3-dienyl] 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one [SS3] (4) 4-[2-aza-2- (2-chlorophenyl) vinyl] benzene sulfonamide [SS4] (5) 4-[2-aza-2- (2-hydroxyphenyl) vinyl] benzene sulfonamide [SS5] (6) [1-aza-4-phenylbuta-1, 3-dienyl] benzene sulfonamide [SS6] synthesized from sulphanilamide and 4- aminoantipyrene were characterized by IR and NMR spectral analysis. The antibacterial activity was studied against P. *pseudoalcaligenes ATCC 17440, P. vulgaris NCTC 8313, C. freundii ATCC 10787, E. aerogenes ATCC 13048, S. subfava NCIM 2178 and B. megaterium ATCC 9885.* The antibacterial activity was evaluated using Agar Ditch method. Two polar solvents were used viz Dimethyl formamide (DMF) and Dimethyl sulfoxide (DMSO). A differential effect of the compounds was found in the bacterial strains investigated and the solvents used, again suggesting that the antibacterial activity is dependent on the molecular structure of the compound, solvent used and the bacterial strains under consideration. In the present work, sulphanilamide as the central ligand and solvent DMF appears to be the best in inhibiting the studied clinically important bacterial strains.

Keywords: antibacterial activity, Schiff bases, polar solvents, drug designing

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INTRODUCTION

The discovery and development of antibiotics are among the most powerful and successful achievements of modern science and technology for the control of infectious diseases. However, the increasing antimicrobial resistance emergence and its dissemination among bacterial strains reduced the efficiency of treatment success of large amount of drugs. Previously all drugs were derived from natural substances especially from higher plants. However, many new chemotherapeutic agents are synthetically derived, based on rational drug design. In fact, drug design is an integrated developing discipline, which deals with development of new drugs on rational basis. The mankind is faced with ever-increasing health threats from "exotic" and opportunistic infections, multi-drug resistant pathogens and cancers. In order to combat these important health problems, discovery of new medicinal agents with novel modes of activity is imperative.

Schiff bases have wide range of applications in medicine and synthetic chemistry. They are of biological, pharmaceutical and of analytical interest. They have been synthesized from an array of compounds giving a diverse range of structurally different compounds. For eg. they have been synthesized from thiosemicarbazide and mercapto-1,2,4-triazoles, amino acids, amino thiazoles, 3-phenyl salicyaldehyde, 2-azetidinones, etc.[1-5] These Schiff bases are reported to have pharmaceutical importance; they show analgesic, anti-inflammatory, antipyretic activity, antifungal and antibacterial activity [6-9].

Considering the above, in the present work, some Schiff bases have been synthesized from sulphanilamide and 4-amino antipyrene and their antibacterial activity has been investigated against a few medically important bacteria.

MATERIALS AND METHODS

All chemicals used in this investigation were reagent grade and were purified when necessary. The IR spectra (KBr pellets) of Schiff bases were scanned on IR (FTIR-8400) over the frequency range from 4000 – 400 cm^{-1}. NMR spectra were scanned on Bruker Spectometer by using deuterated DMSO as a solvent. The melting points of the compounds were determined with a Gallenkamp point apparatus.

Synthesis of Schiff bases

The compounds were synthesized from sulfonamide and 4-aminoantipyrene as described earlier [10]. The structure of the synthesized Schiff bases is as given below:

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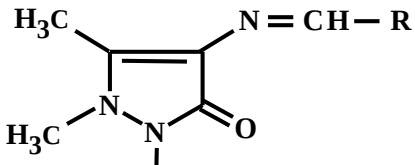
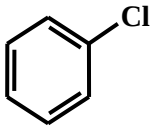
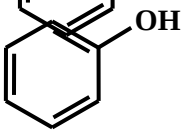
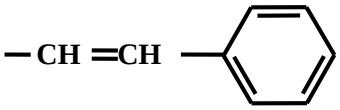
[1] 4 - aminoantipyrene

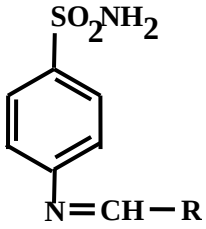


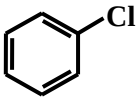
SS1: R = 

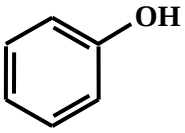
SS2: R = 

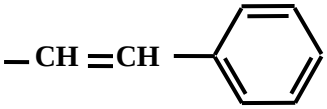
SS3: R = 

[2] Sulphanilamide



SS4: R 

SS5: R = 

SS6: R = 

Antibacterial testing

The *in vitro* antibacterial screening effects of the investigated compounds were tested against two Gram positive and four Gram negative bacteria viz. *S. subfava NCIM 2178 and B. megaterium ATCC 9885; P. pseudoalcaligenes ATCC 17440, P. vulgaris NCTC 8313, C. freundii ATCC 10787 and E. aerogenes ATCC 13048* respectively, by the well diffusion method using Mueller Hinton Agar No.2 as the nutrient medium. Stock solutions (10 mg/ml) were prepared by dissolving the compound in DMSO or DMF. The bacterial strains were activated by inoculating a loop full of test strain in 25ml of N-broth and the same was incubated for 24h in an incubator at 37 ^{o} C. 0.2 ml of the activated strain was inoculated in Mueller Hinton Agar. Mueller Hinton Agar kept at 45^{o}C was then poured in the Petri dishes and allowed to solidify. After solidification of the media, 0.85 cm ditch was made in the plates using a sterile cork borer and these were completely filled with the test solution. The plates were incubated for 24 h at 37^{o}C. The mean value obtained for the three wells was used to calculate the zone of growth inhibition of each sample. The controls were maintained for each bacterial strain and each solvent. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activities of the synthetic compounds.

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RESULTS AND CONCLUSIONS

The structural information of organic molecules could be obtained from their IR spectra. IR spectroscopy is an excellent method for the qualitative analysis because except for optical isomers, the spectrum of a compound is unique. It is most useful for the identification, purity and gross structural details. Information about structure of a molecule is obtained from its absorption. The atomic and electronic configuration of a molecule is responsible for the position of absorption bands. NMR spectroscopy is useful for qualitative chemical analysis and consists of measuring the energy that is required to change a spinning nucleus from a stable orientation to a less stable orientation in the magnetic field. Some nuclei spin about their axes. Different spinning nuclei possess different frequencies in the magnetic field and absorb radiations of different frequencies to change their orientations. The frequencies at which absorption occurs can be used for qualitative analysis. The decrease in intensity of incident radiation owing to absorption during a particular transition can be used for qualitative analysis.

In all, 6 compounds were synthesized and IR, NMR spectral data and CHN analysis confirmed their molecular structure. The IR, NMR and CHN analysis data are given below:

SS1: ^{1}H NMR (δ ppm):- 2.50 (3H, C-CH_3), 3.18-3.19 (3H, N-CH_3), 7.26-7.50 (9H, Ar-H), 8.19-8.22 (1H, -N=CH).
IR (KBr, cm-1): NH_2 (str.): 3375, -NH_2(bend): 1649, C=O : 1649, -C=N-: 1589.
Anal. Calcd: C : 66.36, H: 5.22, N: 12.90, Found : C : 66.42, H: 5.25, N: 12.93.

SS2: ^{1}H NMR (δ ppm):- 2.42 (3H, C-CH_3), 3.16 (3H, N-CH_3), 6.67-7.52 (9H+1H, Ar-H+ -N=CH), 9.63 (1H, -OH).
IR (KBr, cm-1): -OH (str.): 3412, -OH(bend): 1381, C=O : 1655, -C=N-: 1593.
Anal. Calcd: C : 70.36, H: 5.54, N: 13.68, Found : C : 70.40, H: 5.59, N: 13.73.

SS3: ^{1}H NMR (δ ppm):- 2.45 (3H, C-CH_3), 3.14 (3H, N-CH_3), 7.04-7.25 (2H, Cinnamyl, H_a + =CH), 7.26-7.52 10H +1H, Ar-H + - N=CH), 9.56-958 (1H, Cinnamyl, H_b).
IR (KBr, cm-1): NH_2 (str.): 3307, -NH_2(bend): 1587, C=O : 1655, -C=N-: 1593.
Anal. Calcd: C : 75.71, H: 5.99, N: 13.25, Found : C : 75.75, H: 6.05, N:13.30.

SS4: ^{1}H NMR (δ ppm):- 6.36-8.88 (8H + 1H, Ar-H + N=CH), 10.46 (2H, -NH_2).
IR (KBr, cm-1): NH_2 (str.): 3296, -NH_2(bend): 1582, S=O : 1340, -C=N-:1618, C-Cl: 723.
Anal. Calcd: C : 52.97, H: 3.74, N: 9.51, S: 10.87, Found : C : 53.02, H: 3.80, N: 9.53, S: 10.93.

SS5: ^{1}H NMR (δ ppm):- 6.32-8.71 (8H + 1H, Ar-H + N=CH), 9.98 (2H, -NH_2), 10.90 (2H, -OH).
IR (KBr, cm-1): -OH(str): 3462, -OH(bend): 1410, NH_2 (str.): 3344, -H_2(bend): 1616, S=O : 1369, -C=N-: 1572.

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Anal. Calcd: C : 56.52, H: 4.35, N: 10.14, S: 11.59, Found : C : 56.55, H: 4.39, N: 10.16, S: 11.63.

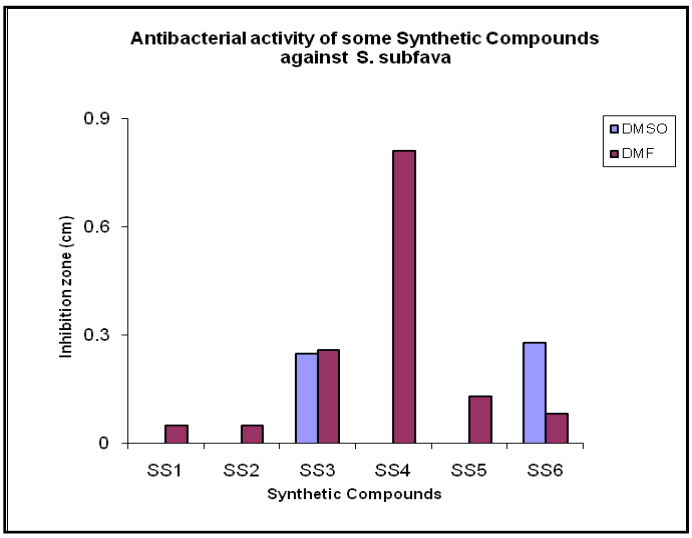
SS6: ^{1}H NMR (δ ppm):- 6.33-8.30 (11H + 1H, Ar-H + N=CH), 9.69-9.72 (2H, -NH_2).
IR (KBr, cm-1): -NH_2 (str.): 3308, -NH_2(bend): 1600, S=O : 1333, -C=N-: 1624, vinyl proton: 915,
Anal. Calcd: C : 62.94, H: 5.59, N: 9.79, S: 11.19, Found : C : 62.95, H: 5.65, N: 9.80, S: 11.

The molecular formula, molecular weight, M.P., % yield and R_f values of 6 Schiff bases are given in table 1.

Table 1: Compound code, Molecular formula, Molecular weight, Melting point, percentage yield and R_f values.

COMPOUND CODE	MOLECULAR FORMULA	MOLECULAR WEIGHT (gm)	M. P. °C	% YIELD	Rf*
S1	$C_{18}H_{16}N_3OCl$	325.5	193	62.84	0.62
SS2	$C_{18}H_{17}N_3O_2$	307	197	58.63	0.64
SS3	$C_{20}H_{19}N_3O$	317	98	52.03	0.61
SS4	$C_{13}H_{11}N_2O_2SCl$	294.5	190	67.9	0.62
SS5	$C_{13}H_{12}N_2O_3S$	276	234	61.4	0.61
SS6	$C_{15}H_{14}N_2O_2S$	286	220	59.8	0.59

* Acetone : Benzene



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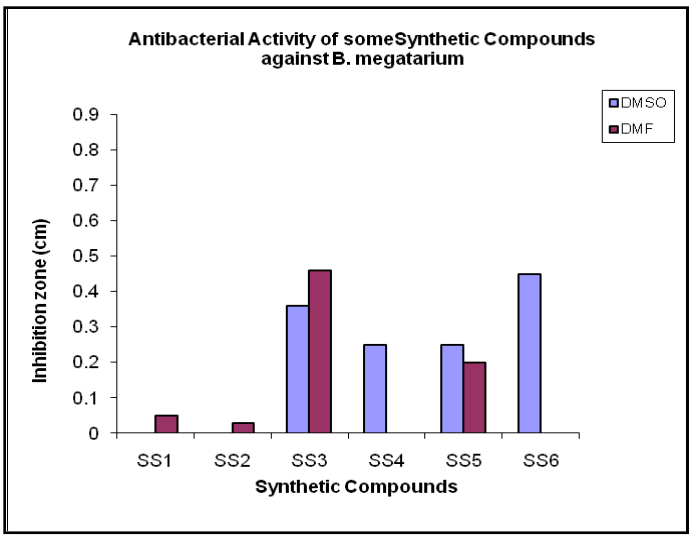

Fig: 1: Antibacterial activity of some compounds against *S. subfava* and *B. magatarium*

The antibacterial activity of all the six synthetic compounds on Gram positive bacteria *S. subfava* and *B. megatarium* are shown in Fig. 1. The antibacterial activity was more when the compounds were extracted in DMSO than in DMF; except SS4 in *S.subfava*. In *S. subfava*, only two compounds i.e. SS3 and SS6 in DMSO showed inhibitory activity while all the six compounds in DMF showed antibacterial activity though a different level of inhibition was envisaged. Maximum activity was shown by SS4 followed by SS3. All the others showed slight inhibitory activity. An entirely different trend was observed with Gram positive bacteria

B. megatarium. Maximum number of compounds in DMSO showed inhibitory activity; maximum activity was shown by SS6 followed by SS3, SS4 and SS5 respectively. No activity was shown by SS1 and SS2. The same compounds in DMF could not evolve same response against this bacteria. SS3 showed considerable inhibition followed by SS5; while other compounds showed negligible activity. This discrepancy in the activity is because of difference in their structure. In these Schiff bases, two central ligands are used i.e. SS1-SS3 has 4-amino antipyrene as central ligand while SS4-SS6 the central ligand is sulphanilamide. The attached side chains are also different in all the compounds. In SS1 it is chloro benzaldehyde, in SS2 it is hydroxy benzaldehyde and in SS3 it is cinnamaldehyde. Again from SS4 to SS6, the side chains are as above. From these results, it appears that sulphanilamide as a central moiety and cinnamaldehyde as side chain is good enough to inhibit these two Gram positive bacteria.

The *in vitro* antibacterial activity against *P. vulgaris* and *P. pseudoalkaligenes* in DMF and DMSO are shown in Fig.2. Here also a differential effect of the compounds (in a particular solvent) was envisaged. All the six compounds in DMSO could inhibit *P. vulgaris* but the same compounds in DMF were unable to inhibit this pathogenic bacteria. All the compounds in DMSO produced almost same level of inhibition. On the other hand, the same six compounds produced an entirely different trend when *P. pseudoalkaligenes* is considered. The solvent DMF proved to be much better than DMSO against these bacteria. Only two compounds i.e.

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SS1 and SS6 in DMSO could evoke some inhibitory activity while all the compounds in DMF inhibited this bacteria though to a different level. Maximum inhibition was by SS5 followed by SS3 and SS6. Minimum activity was with SS2. Here again it can be concluded that the central ligand and the attached side chain plays an important role in producing inhibitory activity. It appears that sulphanilamide is better than 4-aminoantipyrene as a central ligand. Our earlier work also showed similar results (Nair et al. 2002). Though, nothing can be said about the solvent.

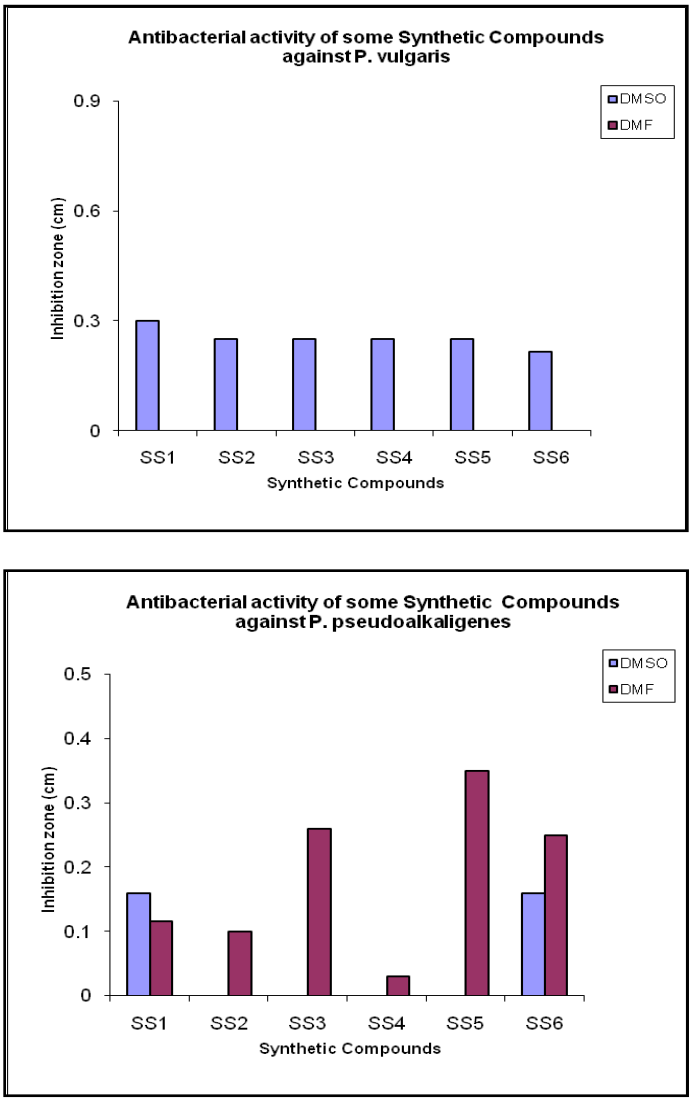

Fig: 2: Antibacterial activity of some compounds against *P.vulgaris* and *P.pseudoalkaligenes*

Figure 3 shows the inhibitory zones produced by six synthetic compounds against *C. freundii* and *E. aerogenes* in DMF and DMSO. Both these bacteria were inhibited by the synthetic compounds when they were extracted in DMF while only two compounds inhibited one of the bacteria i.e. *E. aerogenes*. In *C. freundii* maximum inhibitory activity was with SS3 followed by SS2 and SS6. The other three compounds showed slightly less activity. In *E.*

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aerogenes a clear distinct maximum inhibition was shown by SS4 – SS6 followed by SS3. SS1 and SS2 showed slight inhibitory activity.

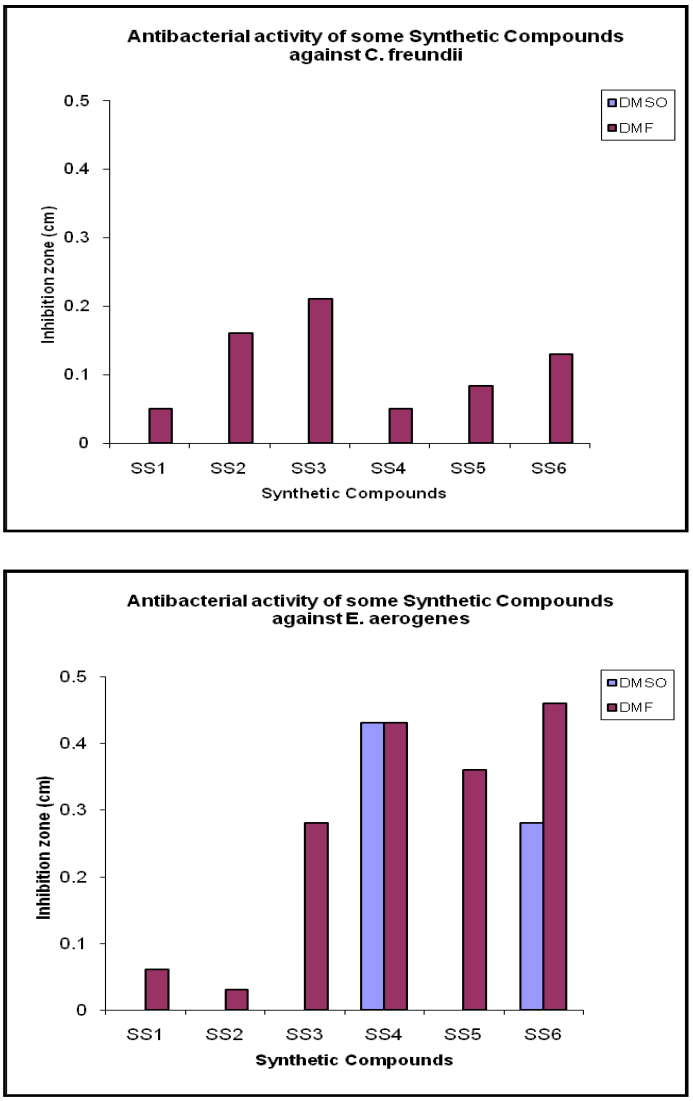

Fig: 3: Antibacterial activity of some compounds against *C.freundi* and *E.aerogenes*

From the present work, it can be concluded; that it cannot be assumed that one solvent is better than the other. It is dependent on the molecular structure of the compound, the solvent used and the particular bacterial strain under consideration considered. Amongst the solvents used, DMF appears to be better than DMSO. This is in agreement with our earlier work [11-13] that polar solvents may be beneficial in our attempt to search lead molecules for drug designing. Such screening of various organic compounds and identifying active agents is the need of the hour; because successful prediction of lead molecule and drug like properties at the onset of drug discovery will pay off later in drug development.

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