

Synthesis, characterization and screening of Some Schiff bases as potential antimicrobial agents

Shipra Baluja^{a*} and Sumitra Chanda^b

Department of Chemistry^a, Department of Bioscience^b, Saurashtra University,
Rajkot 360 005, India

*Email: shipra_baluja@rediffmail.com

Abstract

Schiff bases derived from 4-aminoantipyrene were prepared, and IR and NMR spectral analysis characterized their structure. The Schiff bases produced were (1) 4-[1-aza-2- (2-chlorophenyl) vinyl]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one [SBS11] (2) 4-[1-aza-2- (2-hydroxyphenyl) vinyl]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one [SBS2] (3) 4-[1-aza-4-phenylbuta-1, 3-dienyl] 2,3-dimethyl-1-phenyl-3-pyrazolin-5-one [SBS3] (4) 4-[(4-Hydroxy-3-methoxy-benzylidene)-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one [SBS4], (5) 4-(Benzylidene-amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one [SBS5], (6) 4-[(Furan-3-ylmethylene)-amino]-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-one[SBS6], (7) 4-[4-Methoxy-benzylidene-amino]-1,5-dimethyl-1-2-phenyl-1,2-dihydro-pyrazol -3-one [SBS7]. The antibacterial activity was studied against *S. subfava* NCIM 2178, *B. megaterium* ATCC 9885, *P. pseudoalcaligenes* ATCC 17440, *P. vulgaris* NCTC 8313, *C. freundii* ATCC 10787 and *E. aerogenes* ATCC 13048. The antibacterial activity was done using Agar Ditch method. The antibacterial activity was evaluated in two polar solvents DMSO and DMF. A differential effect of the compounds extracted in a particular solvent (DMSO/DMF) inhibited different bacteria to a different level. It supports the earlier conclusion that antibacterial activity is dependent on molecular structure of the compound, solvent used and the bacterial strain under consideration. However, from the present results, it appears that cinnamaldehyde as side chain with 4-aminoantipyrene as central ligand and DMF as a solvent to be best in inhibiting the studied bacterial strains.

33

34 **Keywords:** Schiff bases, 4-aminoantipyrene, antibacterial activity, DMSO,
35 DMF, drug designing

36

37 **Introduction**

38 The molecular manipulation of promising lead compounds is still a major line
39 of approach to new drugs. Molecular manipulations involves the efforts to
40 combine the separate groups of similar activity into one compounds, thus
41 making structural changes into the compound leading to changes in the
42 biological activity. Schiff bases is known to have fungicidal and bactericidal
43 activity (1,2). The importance of Schiff bases is because of its versatile
44 nature. They are important, in part, due to their application as dyes, liquid
45 crystals and powerful corrosion inhibitors. They have good complexing ability
46 (3). The Schiff bases have been reported to demonstrate a wide range of
47 pharmacological activities which include antibacterial, antifungal, anti-HIV,
48 antitumor, anti-inflammatory, antipyretic, etc. (4-8). Schiff bases have been
49 synthesized from various compounds, the main aim being in search of new
50 lead molecules . Shetye et al. (9) have reported the synthesis of Schiff bases
51 derived from 3-phenyl salicylaldehyde and studied their solution and biological
52 properties. Saghatforoush et al. (10) have prepared tetradentate Schiff bases
53 derived from aminothioether pyridine and salicylaldehyde derivatives and
54 studied their metal complexes. Amanullah et al. (11) synthesized some novel
55 Schiff bases and studied their cyto toxic, antibacterial activity and physico-
56 chemical properties while Khare and Mishra (12) prepared Schiff bases by
57 using 2-amino pyridine, 2-furfuraldehyde. Sahu et al. (13) synthesized Schiff
58 bases from 2-hydroxy-naphthaldehyde with 2-amino-benzothiazole and
59 marked its fungi toxicity. Fioravanti et al. (14) observed antibacterial and
60 antifungal activity in few Schiff bases derived from *N*-heteroaryl benzylamines.
61 Singh et al. (15) synthesized Schiff bases from 4-amino-*N*-carbamimidoyl
62 benzene sulfonamide and studied their antimicrobial activity.

63 Considering the above, the aim of present work was to synthesize
64 some Schiff bases from 4-aminoantipyrene with different side chains and to
65 evaluate their potency as anti bacterial agents.

66

67 Experimental

68 The following Schiff bases have been synthesized:

- 69 (1) 4-[1-aza-2- (2-chlorophenyl) vinyl]-2,3-dimethyl-1-phenyl-3-pyrazolin-5-
70 one [SBS1]
71 (2) 4-[1-aza-2- (2-hydroxyphenyl) vinyl]-2,3-dimethyl-1-phenyl-3-pyrazolin-
72 5- one [SBS2]
73 (3) 4-[1-aza-4-phenylbuta-1, 3-dienyl] 2,3-dimethyl-1-phenyl-3-pyrazolin-5-
74 one [SBS3]
75 (4) 4-[(4-Hydroxy-3-methoxy-benzylidene)-1,5-dimethyl-2-phenyl-1,2-dihydro-
76 pyrazol-3-one [SBS4]
77 (5) 4-(Benzylidene-amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one
78 [SBS5]
79 (6) 4-[(Furan-3-ylmethylene)-amino]-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol
80 - one [SBS6]
81 (7) 4-[4-Methoxy-benzylidene-amino]-1,5-dimethyl-1-2-phenyl-1,2-dihydro-
82 pyrazol-3-one [SBS7]

83

84 Synthesis of Schiff bases

85 The compounds were synthesized from 4-amino antipyrene as described
86 earlier (16,17). The structure of the synthesized Schiff bases is as given
87 below:

88

4 – aminoantipyrene

89

90

91

92

93

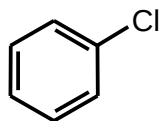
94

95

96

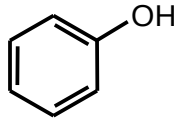
97

98 SBS1: R

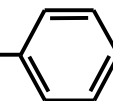


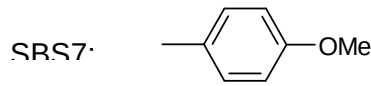
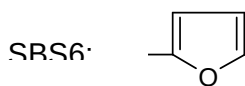
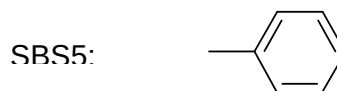
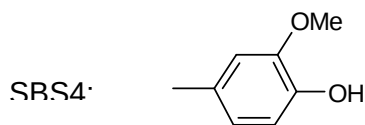
3

SBS2: R



SBS3: R-CH=CH-





Antibacterial activity

The *in vitro* antibacterial screening effects of the investigated compounds were tested against some clinically important bacteria viz. *S. subfava* NCIM 2178, *B. megaterium* ATCC 9885, *P. pseudoalcaligenes* ATCC 17440, *P. vulgaris* NCTC 8313, *C. freundii* ATCC 10787 and *E. aerogenes* ATCC 13048, 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 °C. 0.2 ml of the activated strain was inoculated in Mueller Hinton Agar. Mueller Hinton Agar kept at 45°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°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, where pure solvent was inoculated into the well. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activities of the synthetic compounds.

Results and Conclusions

In all 7 compounds were synthesized and IR and NMR spectral data analysis confirmed their molecular structure. Their data are given below:

129 **SBS1:** ^1H NMR (δ ppm):- 2.50 (3H, C-CH₃), 3.18-3.19 (3H, N-CH₃), 7.26-7.50
 130 (9H, Ar-H), 8.19-8.22 (1H, -N=CH).
 131 IR (KBr, cm⁻¹): NH₂ (str.): 3375, -NH₂(bend): 1649, C=O : 1649, -C=N:-
 132 1589.

133 **SBS2:** ^1H NMR (δ ppm):- 2.42 (3H, C-CH₃), 3.16 (3H, N-CH₃), 6.67-7.52
 134 (9H+1H, Ar-H+-N=CH), 9.63 (1H, -OH
 135 IR (KBr, cm⁻¹): -OH (str.): 3412, -OH(bend): 1381, C=O : 1655, -C=N:-
 136 1593.

137 **SBS3:** ^1H NMR (δ ppm):- 2.45 (3H, C-CH₃), 3.14 (3H, N-CH₃), 7.04-7.25 (2H,
 138 Cinnamyl, H_a + =CH), 7.26-7.52 10H +1H, Ar-H + - N=CH), 9.56-9.58
 139 (1H, Cinnamyl, H_b).
 140 IR (KBr, cm⁻¹): NH₂ (str.): 3307, -NH₂(bend): 1587, C=O : 1655, -C=N:-
 141 1593.

142 **SBS4:** ^1H NMR (δ ppm): 2.46 (3H, -CH₃), 3.10(3H, N-CH₃), 6.91-7.31 (8H, Ar-
 143 H),9.6(1H, N=CH).
 144 IR (KBr, cm⁻¹): - OH (str.): 3412,-OCH₃: 2852, C=O (str.): 1640,-C=N:
 145 1581, - OH (bend.): 1381,-C-H (def) asym: 1377.

146 **SBS5:** ^1H NMR (δ ppm): 2.49 (3H,-CH₃), 3.15 (3H,-OCH₃), 7.39-7.66 (10H, Ar-
 147 H), 9.76 (1H, N=CH).
 148 IR (KBr, cm⁻¹): N-CH₃ (str.): 3160, C=O (str.): 1644, -C=N: 1595,
 149 C=C: 1580,-C-H (def)asym: 1414,-C-H(def)sym :1362.

150 **SBS6:** ^1H NMR (δ ppm): 2.47 (3H,-CH₃), 3.45 (3H, N-CH₃), 6.46-6.56: (8H, Ar-
 151 H), 7.45: (1H, N=CH).
 152 IR (KBr, cm⁻¹): -C-H (str.) asy: 2923,-C-H (str) sym: 2854, C=O (str.):
 153 1649, - N=C (str):1593.

154 **SBS7:** ^1H NMR (δ ppm): 2.46 (3H,-CH₃), 3.10 (3H, N-CH₃)3.65 (3H, N-
 155 CH₃)6.44-7.69 (9H, Ar-H), 9.66 (1H, N=CH).
 156 IR (KBr, cm⁻¹): -O-CH₃:2832, N-CH₃: 3049, N=C: 1647, C=C (Ar.):
 157 1593.

158 The molecular formula, molecular weight, melting point, % yield and R_f values
 159 along with the solvent systems of 7 Schiff bases are given in table 1.

160

Table 1: Analytical and physical data of the investigated compounds

Compound Code	Molecular Formula	Molecular Weight (gm/Mol)	M.P °C	% Yield	R _f Value (Acetone: Benzene)
SBS1	C ₁₈ H ₁₆ N ₃ OCl	325.5	193	62.84	0.62
SBS2	C ₁₈ H ₁₇ N ₃ O ₂	307	197	58.63	0.64
SBS3	C ₂₀ H ₁₉ N ₃ O	317	98	52.03	0.61
SBS4	C ₁₅ H ₁₅ NO ₃	257.28	138	58	0.61
SBS5	C ₁₆ H ₁₇ NO ₂	255.31	142	61	0.50
SBS6	C ₁₈ H ₁₅ NO ₂	277.32	108	58	0.53
SBS7	C ₁₈ H ₁₇ N ₃ O ₅ S	387.41	<300	63	0.48

The antibacterial activity of seven synthetic compounds derived from 4-amino antipyrine in DMSO and DMF against *B. megaterium* and *S. subfava* are shown in Fig.1. Maximum antibacterial activity was shown by SBS3 in both the solvents. The synthesized compounds SBS4, SBS5 and SBS6 showed antibacterial activity only in the solvent DMSO while all other compounds showed negligible activity in either of the solvent. JP16 did not show any activity in either of the polar solvent. The differential response of the synthesized compounds is because of the difference in their structure. All the seven compounds have 4-amino antipyrine as their central ligand and the side chains are different. In SBS1 it is chlorobenzaldehyde, in SBS2 it is hydroxy benzaldehyde, in SBS3 it is cinnamaldehyde, in SBS4 it is vanillin, in SBS5 it is benzaldehyde, in SBS6 it is furfuraldehyde and in SBS7 it is p-anisaldehyde.

The antibacterial activity against the Gram negative bacteria *C. freundii* and *P. vulgaris* in both polar solvents DMSO and DMF are shown in Fig. 2.

179 Here an entirely different trend was observed. Only few compounds i.e.
180 SBS1, SBS2 and SBS3 in DMF showed antibacterial activity against *C.*
181 *freundii* while in *P. vulgaris*, the compounds extracted in DMSO showed
182 antibacterial activity. All the seven compounds extracted in DMSO did not
183 inhibit *C. freundii* while the same compounds in DMF did not inhibit *P.*
184 *vulgaris*. In *C. freundii*, maximum activity was shown by SBS3 followed by
185 SBS2 and SBS1; while in *P. vulgaris*, maximum was shown by SBS1-SBS3,
186 followed by SBS4 and SBS5 and minimum activity was shown by SBS6 and
187 SBS7. This again firmly proves and confirms our earlier conclusion that there
188 is a direct and strong relation between structures of the compound, solvent in
189 which it is extracted and the bacterial strain against which it is being studied.

190 The antibacterial activity against *P. pseudoalkaligenes* and *E.*
191 *aerogenes* are shown in Fig. 3. All the seven compounds synthesized from 4-
192 aminoantipyrene extracted in DMSO could not inhibit the growth of either of
193 these two Gram negative bacteria. The compound extracted in DMF inhibited
194 both these bacteria but a differential effect was envisaged. All the compounds
195 extracted in DMF could inhibit *P. pseudoalkaligenes* but each compound had a
196 different level of inhibition. Maximum inhibitory activity was shown by SBS4
197 and SBS5 followed by SBS3, SBS6 and SBS7 respectively. Minimum activity
198 was by SBS1 and SBS2. In *E. aerogenes*, only SBS3 showed some inhibition
199 while all the other compounds showed no activity. This once again proves the
200 earlier conclusion that antibacterial activity is dependent on molecular
201 structure of the compound, solvent used and the bacterial strain under
202 consideration. Such screening of various organic compounds and identifying
203 active agents is the need of the hour; because successful prediction of lead
204 molecule and drug like properties at the onset of drug discovery will pay off
205 later in drug development. In the present work, cinnamaldehyde as side chain
206 with 4-aminoantipyrene as central ligand and DMF as a solvent appear to be
207 best in inhibiting the studied bacterial strains.

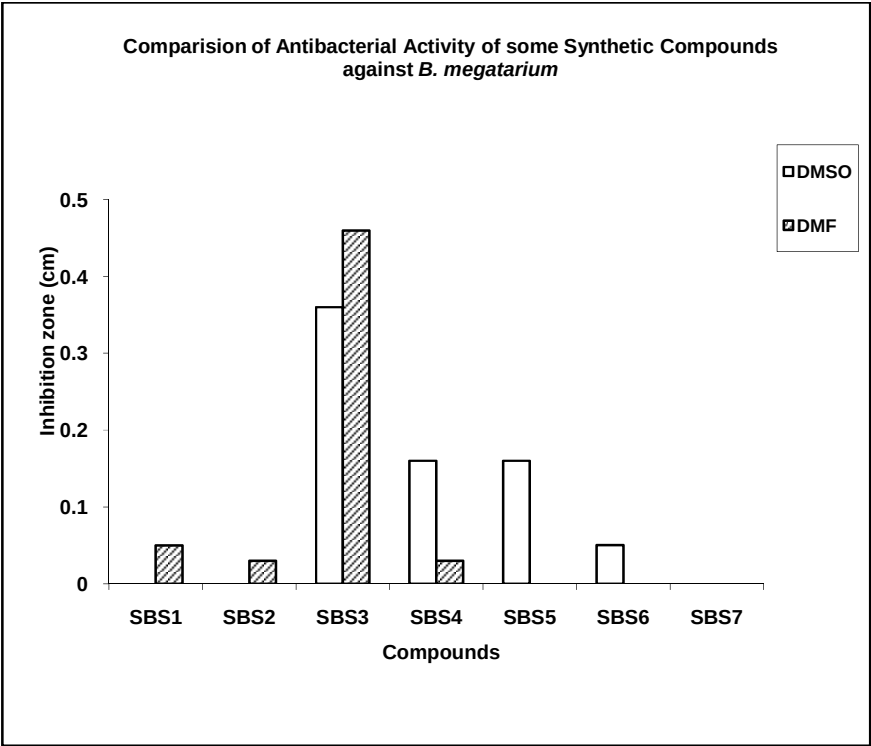
208

209 **References**

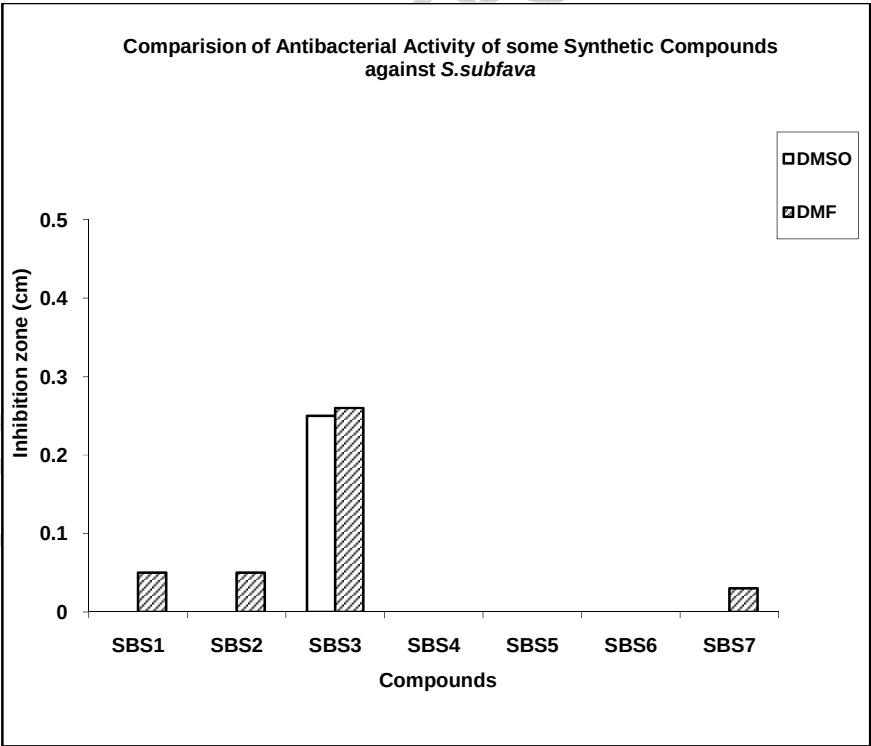
- 210 (1) V. V. Mulwad, J. M. Shirodkar, Ind. J. Hetrocyclic Chem., **11**, 199 (2002).
211 (2) N. O. Shaker, F. H. Abd El-Salam, B. M. El-Sadek, E. M. Kandeel, S. A.

- 212 Baker, J. Am. Sci., **7**, 427 (2011).
213 (3) P. Venkatesh, Asian J. Pharma. Health. Sci., **1**, 8-11 (2011).
214 (4) P. G. More, R. B. Bhalvankar, S. C. Pattar, J. Ind. Chem. Soc., **78**, 474
215 (2001).
216 (5) M. R. Manrao, R. K. Sethi, R. C. Sharma, P. S. Kalsi, J. Ind. Chem. Soc.,
217 **73**, 695 (1996).
218 (6) S. K. Shridhar, S. N. Pandey, E. De Clercq, Boll. Chim. Farma Ceut.,
219 **140**, 302 (2001).
220 (7) Y. Dong-Dong, J. Y. Yan, L. V. Shan, Chin. J. Chem., **19**, 1136 (2001).
221 (8) P. Vicini, A. Geronikaki, M. Incerti, B. Busonera, G. Poni, C. A. Cabras,
222 P. La Colla, Bioorg. Med. Chem., **11**, 4785 (2003).
223 (9) S. S. Shetye, M. S. Mayadeo, N. B. Hexameshwar, Asian J. Chem., **11**,
224 1379 (1999).
225 (10) L. A. Saghatforoush, F. Chalabian, A. Aminkhani, G. Karimnezhad,
226 S. Ershad, Eur. J. Med. Chem., **44**, 4490 (2009).
227 (11) M. Amanullah, S. K. Sadozai, W. Rehman, Z. Hassan, A. Rauf, M. Iqbal,
228 Afr. J. Biotech., **10**, 209 (2011).
229 (12) M. Khare, A. P. Mishra, J. Ind. Chem. Soc., **72**, 231 (2000).
230 (13) K. Sahu, R. K. Behera, R. C. Pathak, A. Nayak, G. B. Behera, Ind. J.
231 Chem., **28B**, 75 (1989).
232 (14) R. Fioravanti, M. Biava, G. C. Porretta, C. Landolfi, N. Simonetti, A. Villa,
233 E. Conte, A. Porta-Puglia, Eur. J. Med. Chem., **30**, 123 (1995).
234 (15) U. K. Singh, S. N. Pandeya, A. Singh, B. K. Srivastava, M. Pandey, Int.
235 J. Pharma. Sci. Drug Res., **2**, 151 (2010).
236 (16) R. Nair, A. Shah, S. baluja, S. V. Chanda, Med. Chem. Res., **11**, 463
237 (2002).
238 (17) Y. Vagasiya, R. Nair, M. Soni, S. Baluja, S. Chanda, J. Serb. Chem.
239 Soc., **69**, 991 (2004).

246 Fig: 1



247



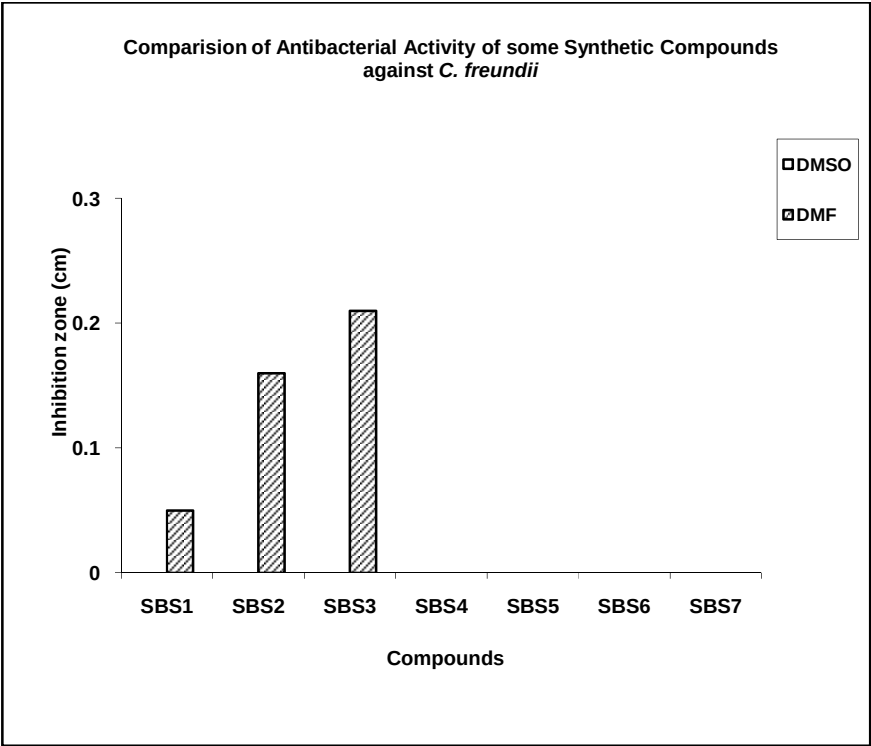
248

249

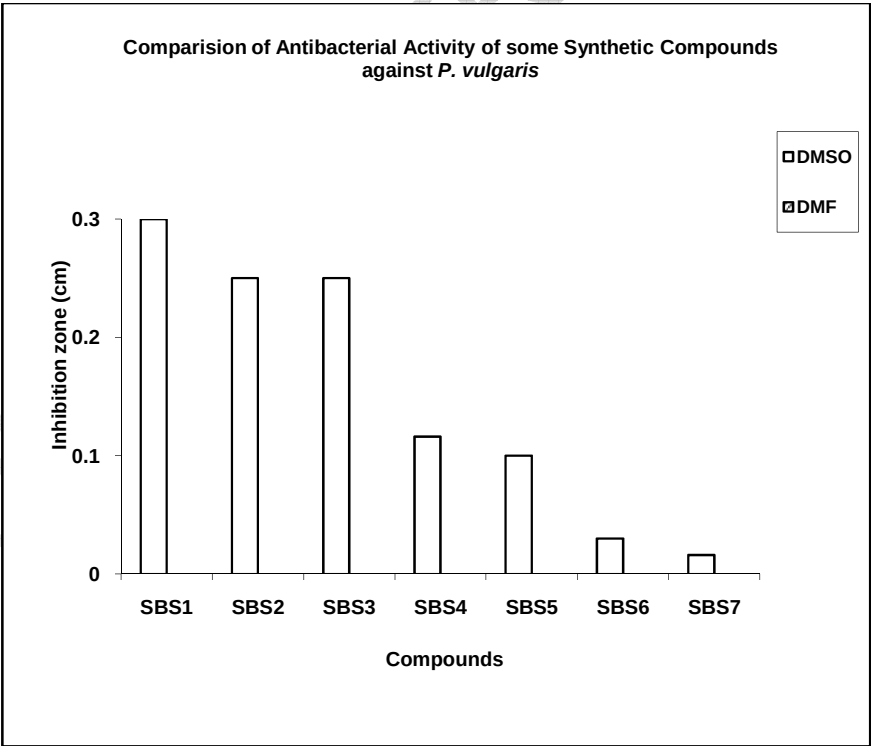
250

251

252 Fig: 2



253



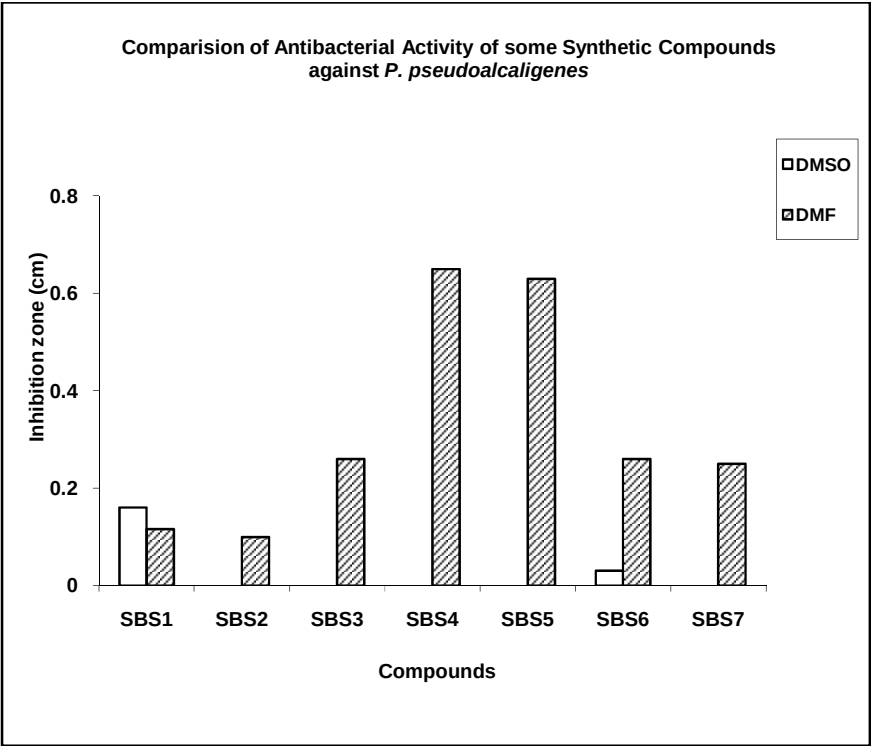
254

255

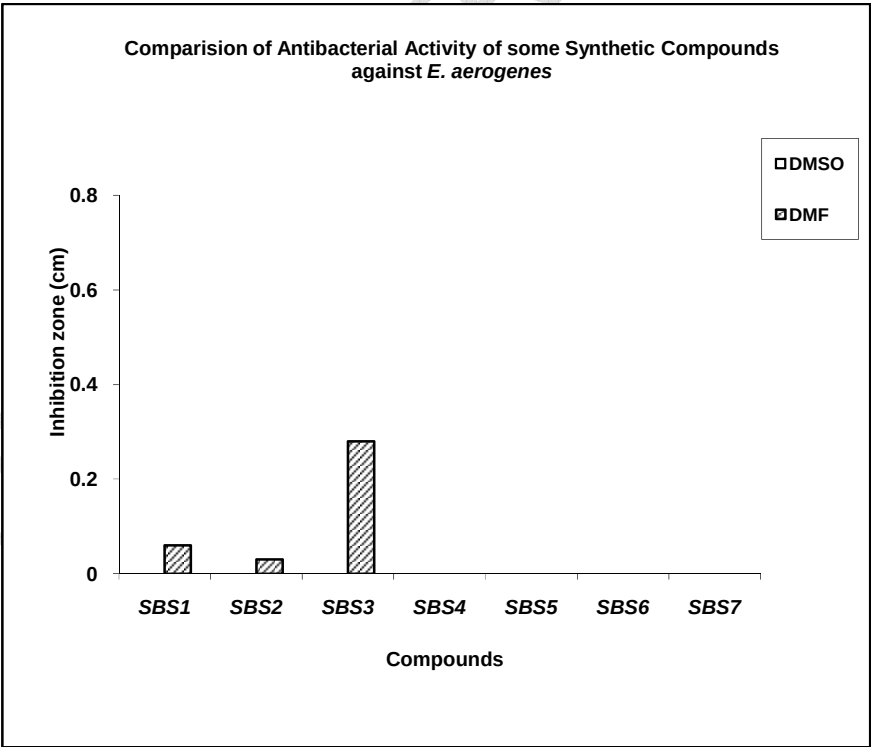
256

257

258 Fig: 3



259



260

261

262