Available online at http://ajol.info/index.php/ijbcs

Int. J. Biol. Chem. Sci. 4(1): 69-74, February 2010

International Journal of Biological and Chemical Sciences

ISSN 1991-8631

Original Paper

http://indexmedicus.afro.who.int

Structure-activity relationship of Schiff base derivatives of bis(aminophenyl)disulfide and *p*-vanillin as antimicrobial agents

Yasoda NARAIN [1], Sabina JHAUMEER-LAULLOO [1] and Minu Gupta BHOWON [1*]

[1] *Department of Chemistry, Faculty of Science, University of Mauritius Reduit, Mauritius.*
[*] *Corresponding author, E-mail: mbhowon@uom.ac.m*

ABSTRACT

A series of Schiff bases **(1-9)** were assayed for antibacterial (*S. aureus, E. faecalis P. aeruginosa)* and antifungal *(C. albicans and A. niger)* activities using disc diffusion method. Among the compounds tested [bis(*p*-methoxybenzaldimino)phenyldisulfide], **5** showed the most favourable antibacterial and [o,o'-(N,N-dipicolinyldene)diazadiphenyldisulfide], **6** antifungal activities with MICs of 1 mg/mL and 0.025 mg/mL against *S. aureus* and *C. albicans* respectively.

Keywords: Antibacterial activity, antifungal, Schiff bases, disulfide.

INTRODUCTION

The rapid emergence of multidrug resistant organism poses a significant threat to global health. Schiff bases bearing sulphur, aryl or heterocyclic groups having nitrogen are known to possess biological activities (Shi et al., 2007; Ye et. al., 2007; Chandra et al., 1997; Thangadurai and Ihm, 2004; Temiz et al., 1998). Disulfide-containing compounds are reported to possess wide variety of biological activities including anti HIV (Sharmeen et al., 2001), antibacterial (Turos et al., 2008; Bhowon et al., 2001), antifungal, inhibition of blood platelet aggregation (Okachi et al., 1985). It has been reported that the presence of aromatic or heteroaromatic groups such as pyridine, furan and thiophene (Thangadurai and Ihm 2004; Li-Xia et al., 2006) enhances the antibacterial activity. The electron donating or electron withdrawing properties of the different substituents on the phenyl ring also influence the antibacterial or antifungal activity (Yalcin et al., 1992; Thangadurai and Natarajan 2001; Mazumder et al., 2005).

In the present work, a series of Schiff bases having different substituents on the phenyl ring have been selected as the target structures for the comparison of antimicrobial effects.

MATERIALS AND METHODS

All the chemicals used were AR/GR grade. The microorganisms were clinical strains obtained from the Central laboratory, Victoria Hospital, Mauritius. Schiff bases 1-7 were synthesised by reacting bis(2-aminophenyl)disulfide with the corresponding aldehydes (Bhowon et al., 2005) while **8** and **9** by the reaction of vanillin and 2-aminophenol or 2-aminobenzoic acid (Uppiah et al., 2009).

The ligands were screened *in vitro* for their antibacterial activities against the gram-positive bacteria *Staphylococcus aureus,*

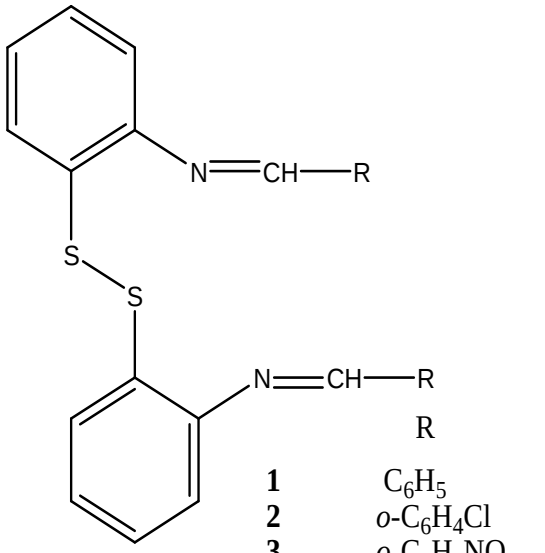
Enterococcus faecalis and gram-negative bacteria *Pseudomonas aeruginosa* and antifungal activity against *Aspergillus niger* and *Candida albicans* using the agar disc diffusion method. Bacteria were cultured in Mueller Hinton Agar and the fungi *C. albicans* in Sabouraud Dextrose while *A. niger* was in Potato Dextrose. 10 µL of the compounds (**1-9**) dissolved in DMSO was placed on the sterile paper disc (5 mm) and transferred onto the surface of the agar containing the microorganism. The petri dishes for bacteria and *C. albicans* were incubated at 37ºC for 24 hrs and 48 hrs for *A. niger*. The diameter of the zone of inhibition was recorded and tests were run in duplicates. DMSO was used as negative control. Ampicillin (8 mg/mL) was used as positive control for bacteria and Nystatin (0.08 mg/mL) for fungi.

RESULTS

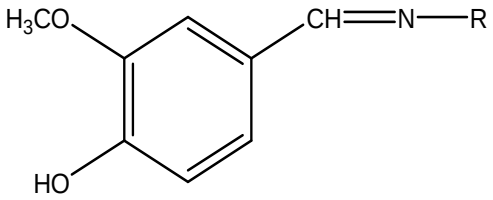
The structures of the Schiff bases were confirmed by the analytical and spectral data. The results are summarized in Table 1. The Schiff bases (**1-9**) (Figure 1) were evaluated for their antibacterial and antifungal activity against gram positive *S. aureus*, *E. faecalis* and gram-negative *P. aeruginosa* bacteria and the fungi *A. niger* and *C. albicans*. The results of antibacterial and antifungal activities of the compounds at 100 mg/mL are given in Figure 2 and 3. Table 2 comprises the *in vitro* results of antibacterial and antifungal activities of the compounds under study expressed as minimum inhibitory concentrations (MICs) ranging from 1 to >100 mg/mL.

DISCUSSION

Aromatic substituents at different positions in the compounds **(1-9)** having different electronic characteristic and lipophilicity influence the biological activity.



R	
1	C_6H_5
2	*o*-C_6H_4Cl
3	*o*-$C_6H_4NO_2$
4	*m*-$C_6H_4OCH_3$
5	*p*-$C_6H_4OCH_3$
6	*o*-C_5H_5N
7	*o*-C_4H_3O



R	
8	*o*-C_6H_4OH
9	*o*-C_6H_4COOH

Figure 1: Structures of Schiff bases.

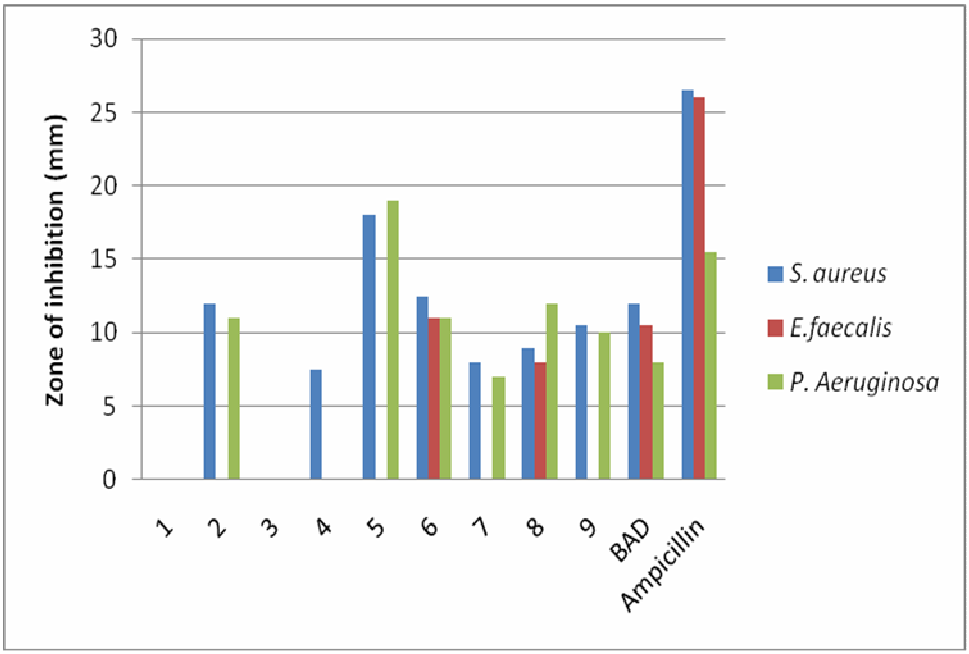


Figure 2: Antibacterial activity of the compounds at 100 mg/mL.

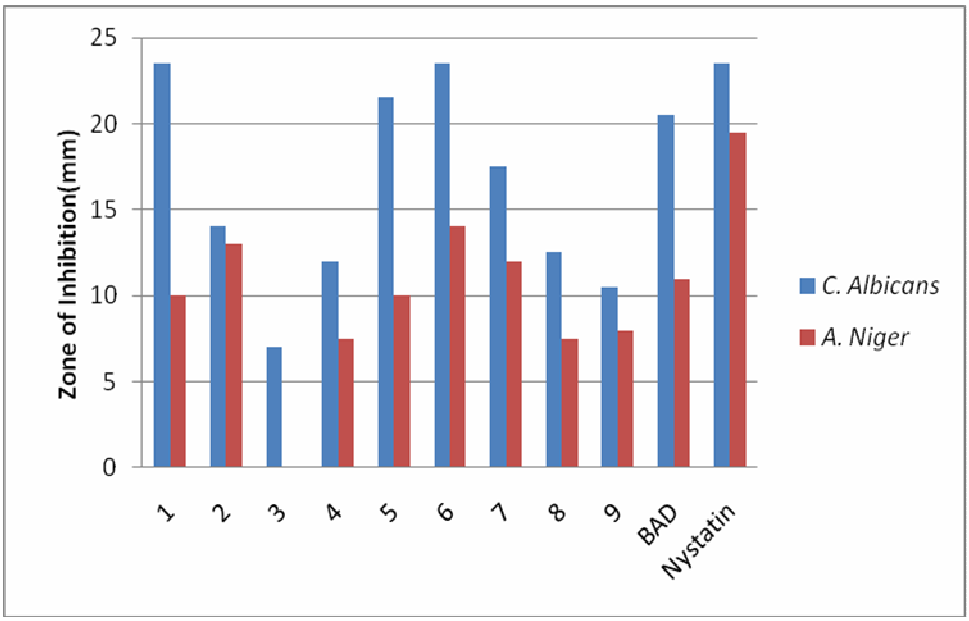


Figure 3: Antifungal activity of the compounds at 100 mg/mL.

Table 1: Analytical and spectral data of the Schiff bases **1-9**.

Compound	**M.P.**	**IR (cm^{-1}) υ(C=N)**	**^{1}H NMR**
1 bis(benzyldiimino) phenyl disulfide	140	1624	8.51(s, 2H), 8.01-7.87(m, 4H), 7.57-7.54(m, 6H), 7.28-7.22(m, 8H)
2 bis(*o*-chlorobenzyldiimino) phenyl disulfide	173	1610	8.98(s, 2H), 8.40(d, 2H), 7.66(d, 2H), 7.26-6.58(m, 12H)
3 bis(*o*-nitrobenzyldiimino) phenyl disulfide	168	1620	8.59(s, 2H), 8.36(m, 4H), 8.15(m, 4H), 7.64(m, 2H), 7.26-7.13(m, 6H)
4 bis(*m*-methoxybenzyldiimino) phenyl disulfide	165	1615	
5 bis(*p*-methoxybenzyldiimino) phenyl disulfide	170	1619	8.42(s, 2H), 8.05(d, 4H), 7.65(d, 2H), 7.16-6.99(m, 10H), 3.89(s, 6H)
6 o,o'-(N,N-dipicolinyldene)diazadiphenyldisulfide]	140	1623	8.67-8.65(d, 2H), 8.60(s, 2H), 8.34-8.30(d, 2H), 7.82-7.75(t, 2H), 7.62-7.58(d, 2H), 7.36-7.31(t, 2H), 7.19-7.04(m, 6H)
7 bis(*o*-furyldiimino) phenyl disulfide	108	1620	8.28(s, 2H), 7.68-7.61(m, 4H), 7.15(td, 4H), 7.05(m, 4H), 6.5(m, 2H)
8 N-*o*-hydroxyphenyl (vanillaldimine)	154	1626	8.82(s,1H), 7.26(d, 2H), 7.08(d, 2H), 6.95-6.86(m, 3H), 6.34(s, 1H), 5.58(s, 1H), 3.81(s, 3H)
9 4-[(4-hydroxy-3-methoxy benzylidine (amino) benzoic acid	164	1624	9.74(s, 1H), 7.66(d, 1H), 7.41(d, 1H), 7.38(s,1H), 7.19(t, 1H), 6.95 (d,1H), 6.71(d, 2H), 6.47(t, 1H), 3.81(s, 3H)

Table 2: The *in vitro* antimicrobial activity of the compounds 1-9 and standard drugs (MIC in mg/mL).

Compound	**Microorganism**				
	S. aureus	***E.faecalis***	***P. aeruginosa***	***C.albicans***	***A.niger***
1	>100	>100	>100	0.05	100
2	100	>100	100	10	100
3	>100	>100	>100	100	>100
4	100	>100	>100	10	100
5	1	>100	1	0.05	1
6	10	10	10	0.025	1
7	100	>100	100	10	10
8	10	100	1	10	100
9	100	>100	10	10	100
BAD	100	100	100	1	10
Ampicillin	<8	<8	<8		
Nystatin				<0.08	<0.08
DMSO	-	-	-	-	-

The presence of a strong electron withdrawing group (NO_2) connected on the benzene ring reduced the antibacterial activity. It may be suggested that the presence of a highly electronegative group is having a negative inductive effect as it is pulling electrons away from the Schiff base (Mazumder et al., 2005). **5** having a methoxy (OCH_3) group in the para position exhibited greater antibacterial activity against *S. aureus* and *P. aeruginosa* compared to **4** where OCH_3 is in the meta position. This is due to the fact that there is considerable conjugative effect in para compared to meta position. Although Cl is an electron withdrawing it donates electron to the system by mesomeric effect and therefore **2** having ortho Cl was active against *S. aureus* and *P. aeruginosa.*

Based on the results obtained, the structure of disulfides was modified by introducing heterocyclic moieties containing oxygen and nitrogen donor groups. The compound containing pyridine moiety showed good bacterial inhibition against *S. aureus, E. faecalis,* and *P. aeruginosa.* Surprisingly, the introduction of furan moiety **7** showed little activity on *S. aureus* and *P. aeruginosa.*

In order to evaluate the importance of disulfide linkage, compounds **8, 9** with no sulfur linkage but containing lipophilic groups such as OH, COOH were investigated and they showed MICs value in the range of 1 to >100 mg/mL. The presence of liphophilic and pyridine group showed enhanced activity against *E. faecalis.*

The antifungal activity of compounds **1-9** showed a similar trend as that observed for antibacterial activity. The presence of electron withdrawing groups such as Cl and NO_2 causes a significant reduction against the tested fungal strain by about 45 to 70% respectively. The presence of electron donating group such as methoxyl group at the meta position reduces the activity compared to **1** while at para position comparable activity was observed. Replacing the phenyl moiety by the pyridine ring, an enhanced activity was observed for *C. albicans* and *A. niger* having MIC values of 0.025 mg/mL and 1 mg/mL respectively. Absence of disulfide linkage in compounds **8, 9** showed a reduction of antifungal activity.

Conclusion

The structure-activity relationship of these Schiff base derivatives indicated that the presence of electron withdrawing groups decreases the activity while the presence of methoxy group at para position plays an important role in eliciting inhibition of all bacteria and fungi assayed. The high efficacy exhibited by compound **6** clearly reveals that the presence of pyridine enhanced the activity considerably. The presence of disulfide linkage is important for antifungal activity.

ACKNOWLEDGMENTS

The authors wish to thank Central Laboratory, Victoria Hospital for providing clinical strains of bacteria and fungi.

REFERENCES

Bhowon MG, Laulloo SJ, Ramnial T. 2001. Antibacterial activity of Ruthenium(II) benzamide complexes. *Trans. Met. Chem.*, **26**: 329-332.

Bhowon MG, Laulloo SJ, Dowlut M, Curpen S, Jumnoodoo V. 2005. Synthesis and characterization of bis(2-aminophenyl)disulfide diimine derivatives and their ruthenium complexes. *Trans. Met. Chem.*, **30**: 35-39.

Chandra S, Jadon S, Saxena C, Singh RV. 1997. Characterization and biological evaluation of ruthenium(III) complexes of 2-fluorophenyl imines. *Trans. Met. Chem.*, **22**: 385-388.

Li-Xia Z, Yi L, Li-Hua C, Yan-Jun H, Jun Y, Pei-Zhi H. 2006. Inhibitory study of some novel Schiff base derivatives on *Staphylococcus aureus* by microcalorimetry. *Thermochimica Acta*, **440**: 51-56.

Mazumder UK, Gupta M, Karki SS, Bhattacharya S, Rathinasamy S, Sivakumar T. 2005. Synthesis and pharmacological activities of some mononuclear Ru(II) complexes. *Bioinorganic and Medicinal Chemistry*, **13**: 5766-5773.

Okachi R, Niino H, Kitaura K, Mineura K, Nakamizo Y, Murayama Y, Ono T, Nakamizo A. 1985. Synthesis and antibacterial activity of 2,2'-dithiobis(benzamide) derivatives against Mycobacterium species. *J. Med. Chem*., **28**: 1772-1779

Shi L, Ge HM, Tan SH, Li HQ, Song YC, Zhu HL, Tan RX. 2006. Synthesis and antimicrobial activities of Schiff bases derived from 5-chlorosalicyaldehyde. *Eur. J. Med. Chem.*, **42**: 558-564.

Sharmeen L, Mcquade T, Heldsinger A, Gogliotti R, Domagala J, Gracheek S. 2001. Inhibition of the early phase of HIV replication by an isothiazolone. PD 161374. *Antiviral Research.*, **49**: 101-114.

Thangadurai TD, Natarajan K. 2001. Tridentate Schiff base complexes of ruthenium(III) containing ONS donor atoms and their biocidal activities. *Trans. Met Chem*., **26**: 717-722.

Thangadurai TD, Ihm SK. 2004. Novel bidentate ruthenium(III) Schiff base complexes: Synthesis, spectral, electrochemical, catalytic and antimicrobial studies. *Trans. Met. Chem*., **29**: 189-195.

Temiz Ö, Ören I, Şener E, Yalçin I, Uçarturk N. 1998. Synthesis and microbiological activity of some novel 5- or 6-methyl-2-(2,4-disubstituted phenyl) benzoxazole derivatives. *Il Farmaco.*, **53**: 337-341.

Turos E, Revell KD, Ramaraju P, Gergeres DA, Greenhalgh K, Young A, Sathyanarayan N, Dickey S, Lim D, Alhamadsheh M, Reynolds K. 2008. Unsymmetric aryl-alkyl disulfide growth inhibitors of methicillin-resistant *Staphylococcus aureus* and *Bacillus anthracis*. *Biorg. Med. Chem*., **16**: 6501-6508.

Uppiah DJN, Bhowon MG, Laulloo SJ. 2009. Solventless synthesis of imines derived from diphenyldisulphide diamine or *p*-vanilin. *E-Journal of Chemistry*., **6**(S1): S195-S200.

Ye XX, Chen ZF, Zhang AJ, Zhang LX. 2007. Synthesis and biological evaluation of some novel Schiff bases from 1, 2, 4-Triazole. *Molecules.*, **12**: 1202-1209.

Yalcin I, Oren I, Sener E, Akin A, Ucarturk N. 1992. The synthesis and the structure-activity relationship of some substituted benzoxales, oxazolo(4,5-b)pyridines, benzothiazoles and benzimidazoles as antimicrobial agents. *Eur. J. Med. Chem.*, **27**: 401-406.