CHAPTER - VI

BIOLOGICAL ACTIVITIES OF COMPLEXES

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The biological activity (antibacterial / antifungal) of a compound or complex is attributed to the result of interlinked chemical reactions or the observed manifestation of an interference with a delicately balanced system of interdependent chemical and physical process. The biological activity of complex depends on combination of factors like steric, electronic and pharmacokinetic aspects. It is well known that metal complexes show considerable antibacterial and antifungal activity. Transitional metal complexes have remarkable potential for inhibiting growth of various pathogenic microorganisms. A possible explanation for the biological activity of the complexes has been explained by Sreevastav using chelation theory [1]. Chelation reduces considerably the charge of the central metal ion by partial sharing its positive charge with the donor groups or ligands and facilitates π-electron delocalization over the whole chelate ring. This increases the lipophillic character of metal chelate which favours its permeation through lipid layers of fungus or bacteria membranes. Further more the mode of action of the compounds may involve the formation of a hydrogen bond through the –N=C- group of the ligand with the active centers of the fungal or bacterial cell constituents resulting in the interferences with the normal cell processes. In case of Schiff bases which contain azomethine group ortho to the hydroxy group are known to yield chelates which possess good bactericidal or fungicidal properties.

8-Hydroxyquinoline, a well known analytical reagent was found to have antibacterial activity due to its chelating ability with trace metal ions, which are essential for the bacterial growth and bacterial function [2]. The falconoid 5,7-dihydroxy flavones (chrysin) exhibited a significant antibacterial activity against a number of gram positive and gram negative organisms [3]. Flavonoid molecules like nobiletin, tangeritin, cabrevin and quercetin have also exhibited anti fungal activity [4]. Ahmad et al. [5] reported that the use of metals in therapeutic drugs have become increasingly important over the last couple of decades resulting in a variety of exciting and valuable drugs such as cisplatin and auranofin. The coordination chemistry of metallodrugs is strongly dependent on

understanding the thermodynamics (equilibria and structures) and kinetics of the reactions of metal complexes under physiological relevant conditions. They further explained the biocoordination chemistry of several metallodrugs (gold antiarthritic, silver antibacterial, vanadium antidiabetic and bismuth antiulcer, drugs) and their possible mechanism of action. Various structure-activity relationships and biochemical aspects of metal binding to cellular targets have also been explained by them.

Phosphane and complexes of gold, silver and copper play an important role in the design and development of metal complexes for biomedical applications and for tumoricidal properties [6]. Affana et al. [7] synthesized five new organotin(IV) complexes with pyruvic acid isonicotinoyl hydrazone complexes, screened for their antimicrobial activities and found that the complexes are relatively active. Podunavac-kuzmanovic et al. [8] evaluated the antibacterial activities of cobalt(II) complexes with two series of benzimidazoles in vitro against three gram-positive bacterial strains (Bacillus cereus, Staphylococcus aureus, and Sarcina lutea) and one gram-negative isolate (Pseudomonas aeruginosa). The majority of the investtigated complexes displayed in vitro inhibitory activity against very persistent bacteria. They were found to be more active against gram-positive than gram-negative bacteria. Comparing the inhibitory activities of the tested complexes, the effect of chemical structure on the antibacterial activity is discussed.

Al-Fregi et al. [9] studied in-vitro evaluation of antibacterial activity of platinum and palladium complexes by growth inhibition and minimal inhibition concentration (MIC) against eight types of Pathogenic bacteria: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *β-hemolytic streptococci*, *viridance streptococci*, *Escherichia coli*, *Klebsiella* and *Pseudomonas aeruginosa*. and found complexes have a high antibacterial activity (1000μg/ml). Isab et al. [10] synthesized several complexes of AgCN with alkanediamine ligands (where the ligands are ethylenediamine, propane-1,3-diamine, butane-1,4-diamine, N,N'-dimethylethylenediamine, N,N'-di-iso-propyl-ethylenediamine, etc.) and studied the antimicrobial activity. The results showed that the former exhibits substantial antibacterial activities compared to its complexes.

Spnu et al. [11] prepared iron(II), cobalt(II), nickel(II), copper(II), zinc(II) and cadmium(II) complexes of the type ML_2Cl_2, where M is a metal and L is the Schiff base N-(2-thienylmethylene)methanamine and screened for their biological activity against Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa. The metal chelates were found to possess better antibacterial activity than that of free Schiff base. According to Wazeer et al. [12] complexes formed by the reactions of imidazolidine-2-thione (Imt), 1,3-diazinane-2-thione (Diaz) and 1,3-diazipane-2-thione (Diap) with cadmium(II) chloride in methanol showed substantial antimicrobial activity and $Cd(Diap)_2Cl_2$ complex exhibited substantial antibacterial activity compared to the corresponding Zn(II) complex.

El-Ajaily et al. [13] prepared Schiff base complexes derived from salicylaldehyde and o-pheneylenediamine with Cr(VI), Cr(III), Pb(II)) and TiO(IV) ions. The Schiff base and its new complexes were tested for antibacterial activity against gram positive bacteria; Staphylococcus aureus and gram negative bacteria; Salmonella, Escherichia coli including the resistance bacteria Pseudomonas aeruginosa. Anacona et al. [14] studied the preparation of [M(cefotax)Cl] complexes of Cefotaxime (Hcefotax) with transition metal ions Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Cd(II) and screened for antibacterial activity against several bacteria. The results are compared with the activity of cefotaxime and found that the complexes showed increased activity upon complexation and Cu complex showed pronounced activity.

Raman and Johnson Raja [15] synthesized three new copper complexes of mixed ligands derived from Schiff bases (condensation of p-aminoacetanilide and substituted benzaldehydes) with 1,10-phenanthroline. The in vitro biological screening effects of the investigated compounds were tested against the bacteria Escherichia coli, Staphylococcus aureus, and Salmonella typhi and the fungi Rhizopus stolonifer and Candida albicans by the serial dilution method. A comparative study of the MIC values of the Schiff bases and their copper complexes indicates that the metal complexes exhibited higher antibacterial activity than the free ligands. The DNA cleavage ability of the complexes was monitored by the gel electrophoresis technique. It was found that electron withdrawing group

substituted copper complex had higher DNA cleavage activity than the other copper complexes.

Eajpai et al. [16] prepared oxalatoamine cobalt (II) complexes with a view to study their pharmacological activities. Compounds showed depressant effect on central nervous system and acted as stimulants. Some complexes possessed weak anti-inflammatory activity, whereas some exhibited pronounced antipassive cutaneous anaphylaxis activity, The compounds studied showed neither much significant effect on central vascular system nor exhibited anti-arrhythmic and diuretic activity. The biological significance of vanadium complexes is examplified by its incorporation in natural products and enzyme in potent inhibitor of phosphoryl transfer [17]. Vanadium-containing compounds have their utility as insulin mimetic and antiamoebic agent. The potential of vanadium(V) complexes as antiamoebic agents have been marginally explored by Maurya et al. [18]. It is also suggested that vanadium could be considered as a representative of a new class of nonplatinum metal antitumor agents.

Mishra et al. [19] reported new bidentate or tridentate Schiff bases and their VO(II) and Co(II) complexes formed by the condensation of methyl isobutyl ketone with nicotinamide (mna) / 2-amino-4-chlorophenol (map) and 2-hydroxy acetophenone with nicotinamide (han) / isoniazide (hai). The complexes have been screened for their antimicrobial activity by the well diffusion technique using DMSO as solvent on different species of pathogenic bacteria / fungi, that is, *E. coli, S. aureus, S. fecalis,A. niger, T. polysporum*, and their antimicrobial potency was discussed. It was found that all the complexes are antimicrobially active and showed higher activity than the free ligand. Metal chelation affects significantly the antimicrobial/bioactive behavior of the organic ligands. Sreekanth et al. [20] recently studied the copper(II) complexes of 2-benzoylpyridine, N(4)-(butane-1,4-diyl)thiosemicarbazone and found that these compounds possess a broad spectrum of potentially useful chemotherapeutic activities such as antimalarial, antibacterial, antiviral and antileishmanial activities [21, 22].

Arion et al. [23] synthesized three ruthenium(III) complexes containing 1H-1,2,4-triazole and assayed the cytotoxicity in three human carcinoma cell lines SW480, HT29

(colon carcinoma), and SK-BR-3 (mammary carcinoma). Among these two compounds exhibited antiproliferative activity in vitro. Time-dependent response of all three lines to the compounds and a structure-activity relationship, i.e. higher activity of the trans-isomer than that of cis-species have been observed. Kadhim et al. [24] synthesized mono- and dinuclear Cu(I) and Cu(II) complexes of 1,3,4-mercapto-oxadiazole derivatives. The microbiological activity of the complexes was investigated against bacteria and fungi. All the complexes were active against *Candida albicans*, while the reactivity against bacteria varied. The antimicrobial activity of the $[Cu(MeO\text{-}OX)_2(H_2O)_2]_2$ complex was exceptionally better than that observed for any other metal complex against both bacteria and fungi.

In view of the above observations the antibacterial and antifungal activities of the three ligands namely flavonoid, triazine and shiff base and their metal complexes have been investigated in the present studies. The bacterial species *Klebsiella pnuemoniae, Escherichia coli, Bacillus subtilis* (gram negative species) and *Pseudomonas aeruginosa and Staphylococcus aureus* (gram positive species) and fungal organisms *Aspergillus niger, Rhizoptonia solani, Fusarium oxysporium* were used to correlate the effect of complexation on the biologal properties of compounds. The results of the antibacterial activities (Figures VI-1 to VI-3) and antifungal activities (Figures VI-4 to VI-6) are represented in the graphical form.

Anti Bacterial activity: The three ligands namely 3-(4-Dimethylamino-phenyl)-2-hydroxy-benzo[+]chromen-1-one (flavonoid), 5,6-Diphenyl-2H-[1,2,4]triazine-3-thione (triazine) and 4-Phenylazo-2-(thiazol-2-yliminomethyl)-phenol (Schiff base) and their metal complexes were moderate to highly active against the above said bacteria. In particular the schiffbase complexes showed higher activity towards gram positive bacteria, triazine and flavonoid complexes showed higher activity towards gram negative bacteria. The triazine complexes showed activity with all the baceria more or less equally. The over all data suggests that the metal complexes showed higher activity than the respective free ligands. Copper complexes of three ligands showed higher activity than the other complexes. Since copper salt has antimicrobial action a synergistic effect

of shiff base ligand and metal acting together may be the reason for higher antibacterial activity of the copper Schiff base complexes.

Anti Fungal activity: The three ligands flavonoid, triazine and schiff base and their metal complexes were moderately active against the fungal species. The Schiff base complexes showed good activity against fungi than the other triazine and flavonoid complexes, next followed the triazine complexes. Flavonoid complexes showed some what less activity than the triazine and schiff base complexes. The activity against the three ligands was less than their corresponding metal complexes which may be attributed by the process of complexation. Copper complexes of three ligands showed higher activity than the other complexes.

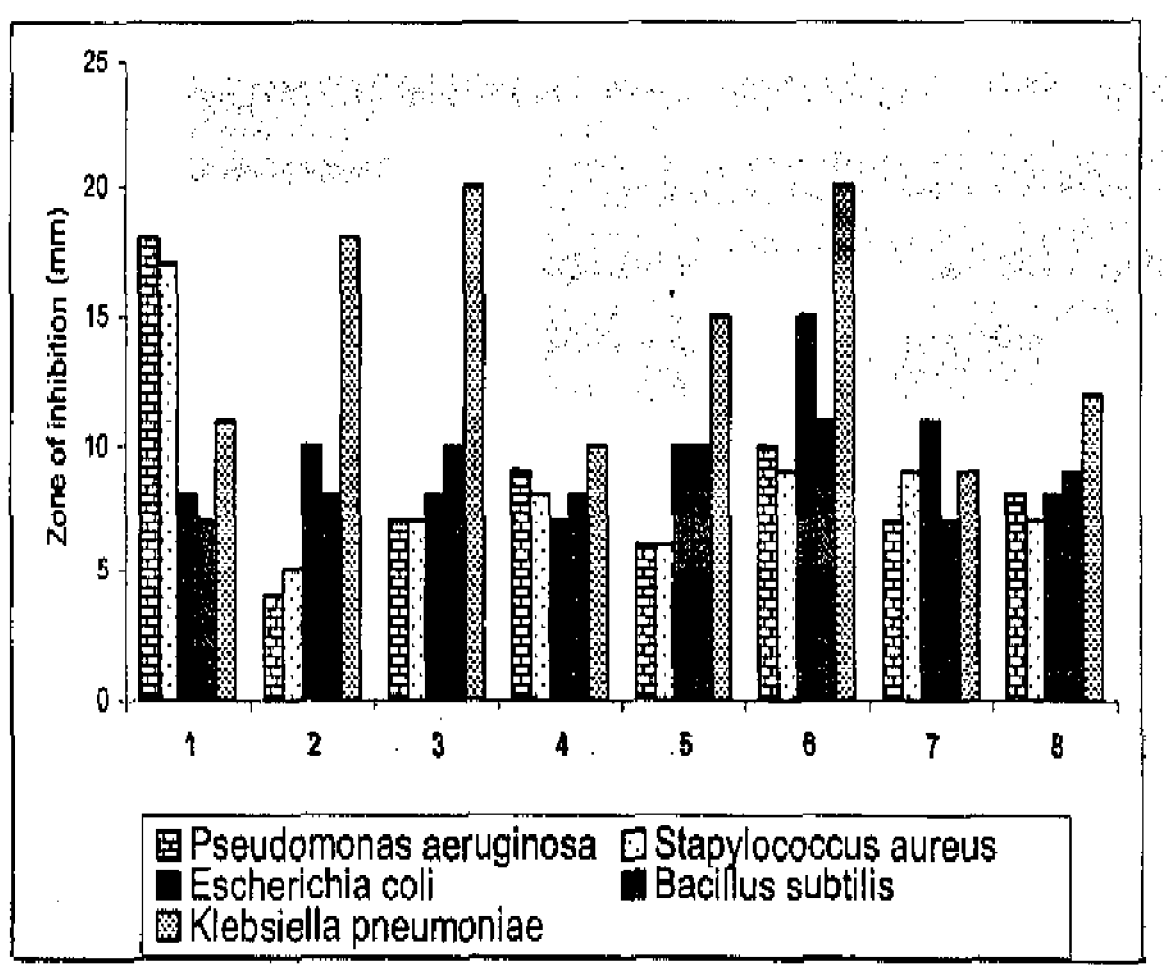

Figure VI-1: Antibacterial activity of flavonoid metal complexes
1)Flaconoid 2)Cr 3)Sn 4)Pb 5)Bi 6)Cu 7)U 8)Th

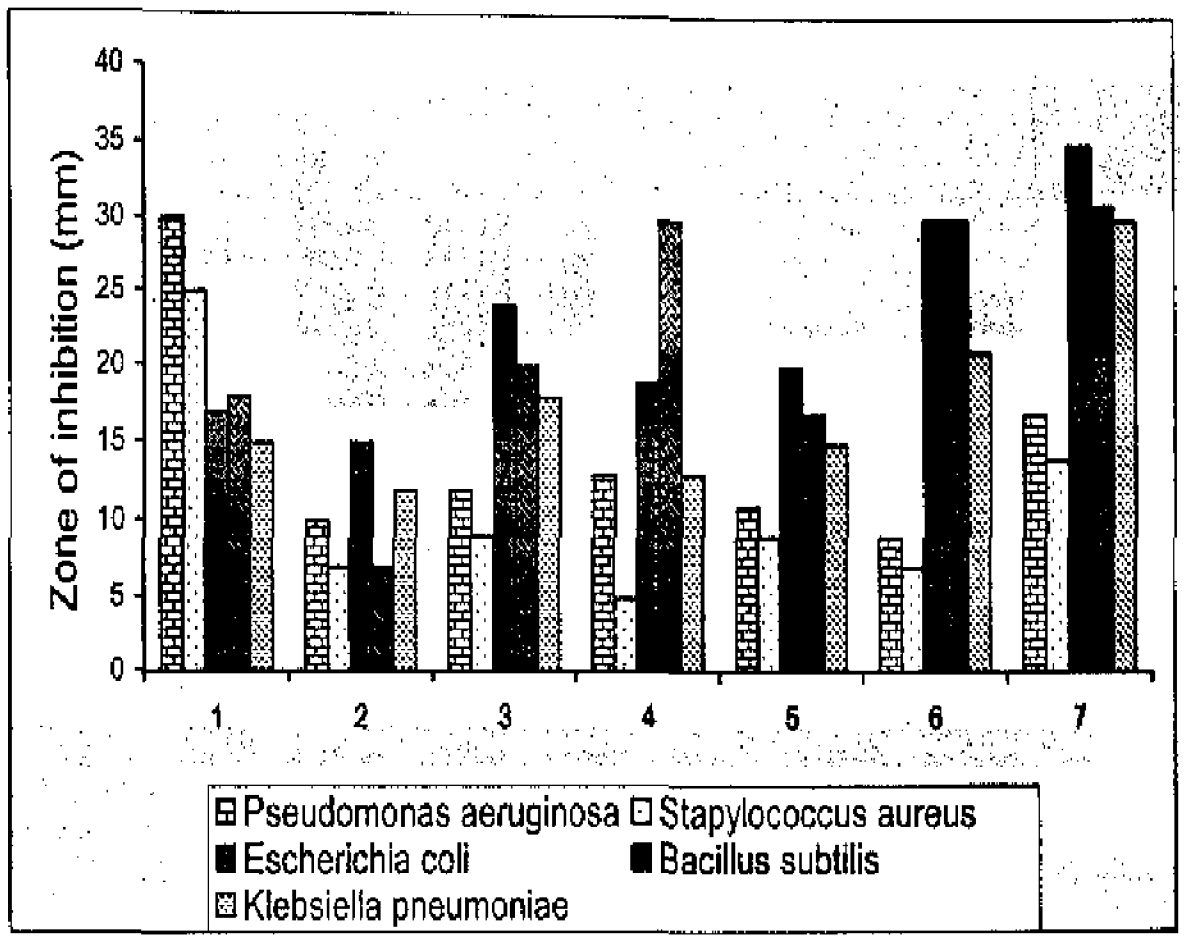

Figure VI-2: Antibacterial activity of Triazine metal complexes
1)Triazine 2)W 3)Sn 4)U 5)Th 6)Hg 7)Cu

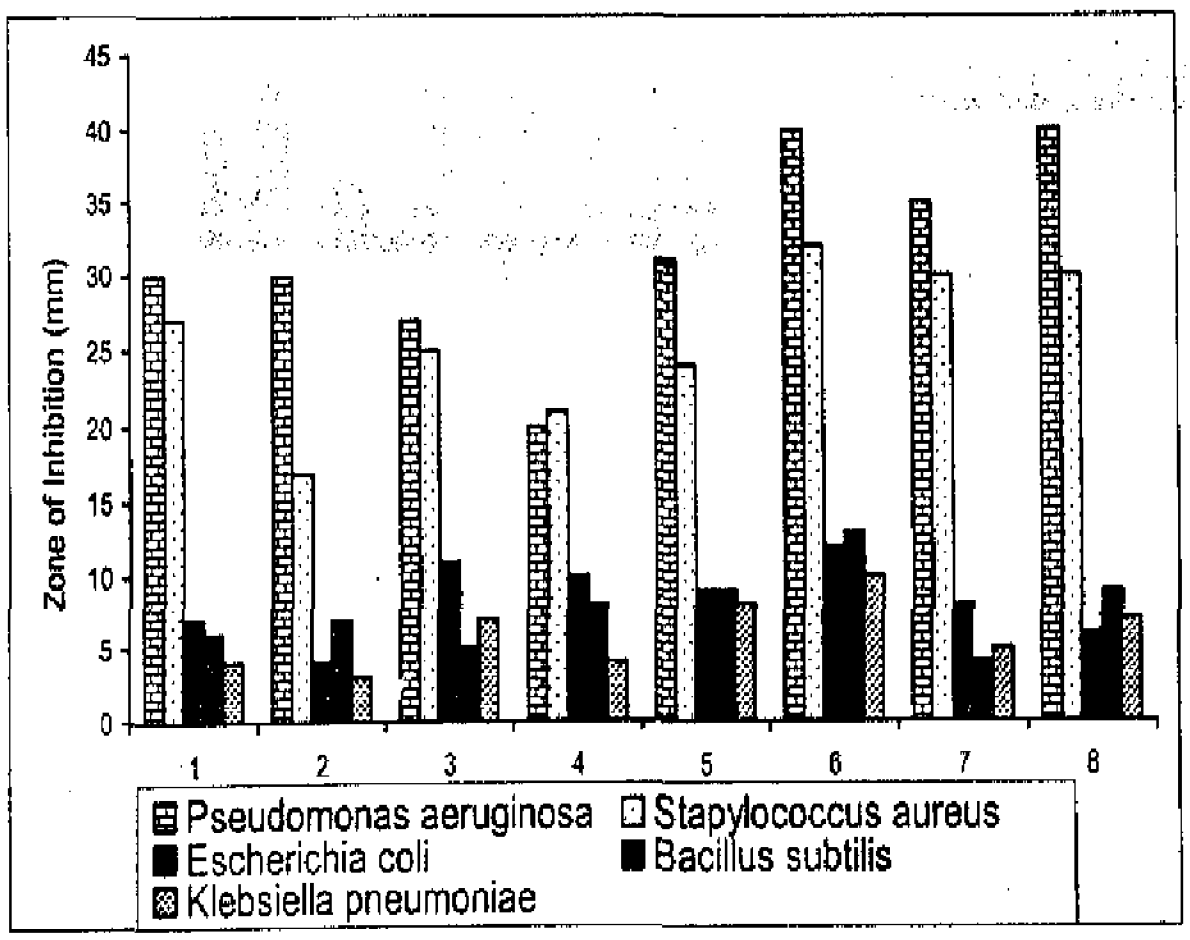

Figure VI-3: Antibacterial activity of Schiff base metal complexes
1)Schiff base 2)Th 3)Pb 4)Co 5)Cd 6)Cu 7)Sn 8)Hg

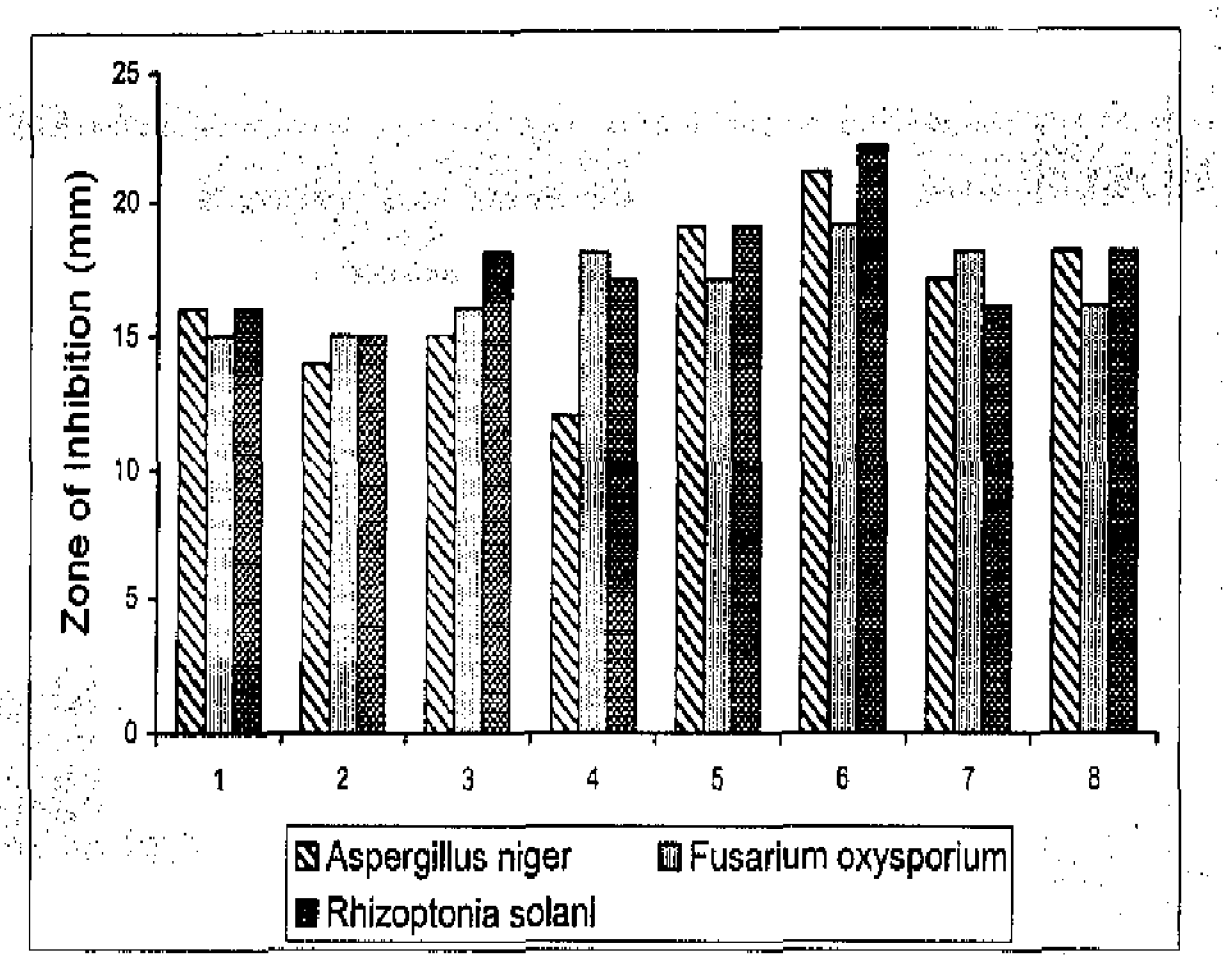

Figure VI-4: Antifungal activity of flavonoid metal complexes
1)Flaconoid 2)Cr 3)Bi 4)Pb 5)Sn 6)Cu 7)U 8)Th

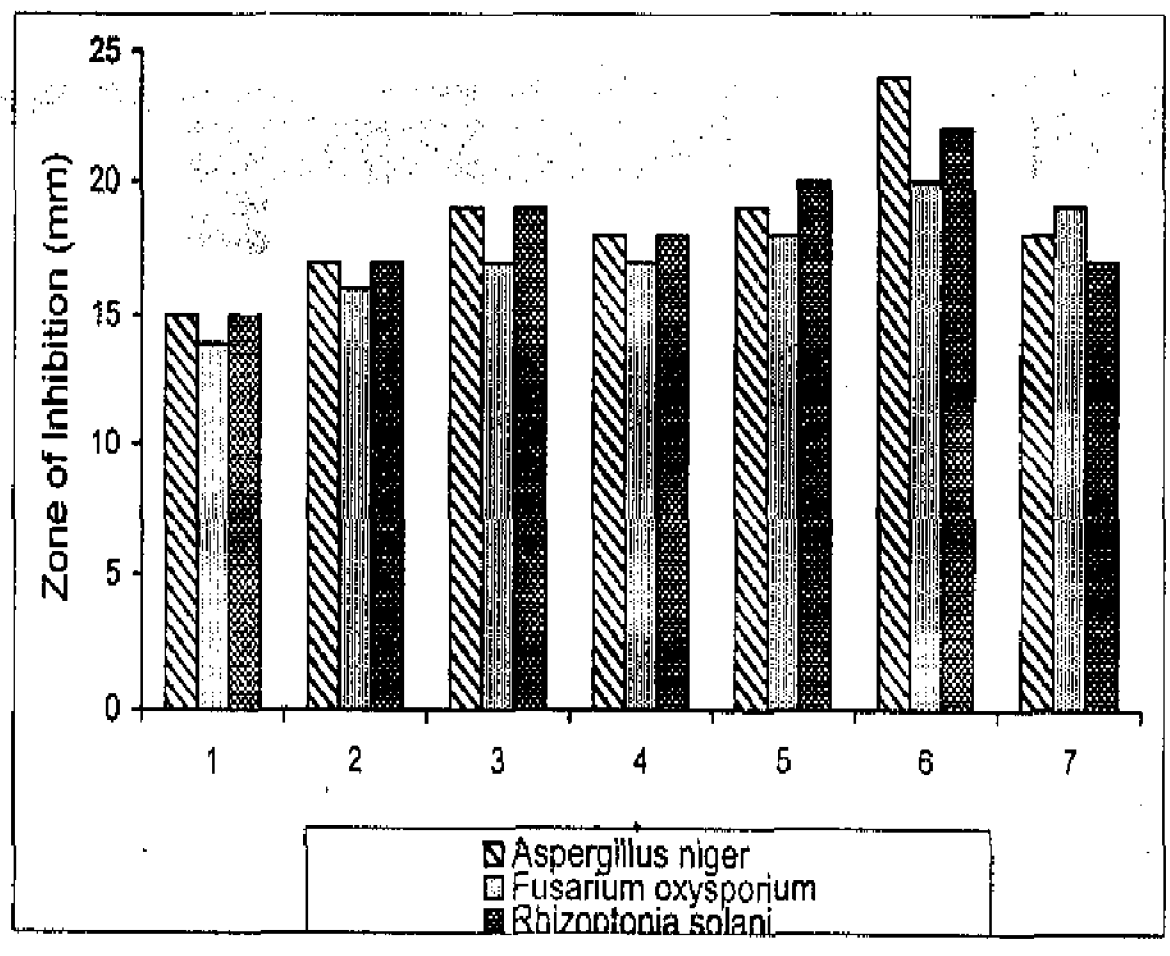

Figure VI-5: Antifungall activity of Triazine metal complexes
1)Triazine 2)W 3)Sn 4)U 5)Hg 6)Cu 7)Th

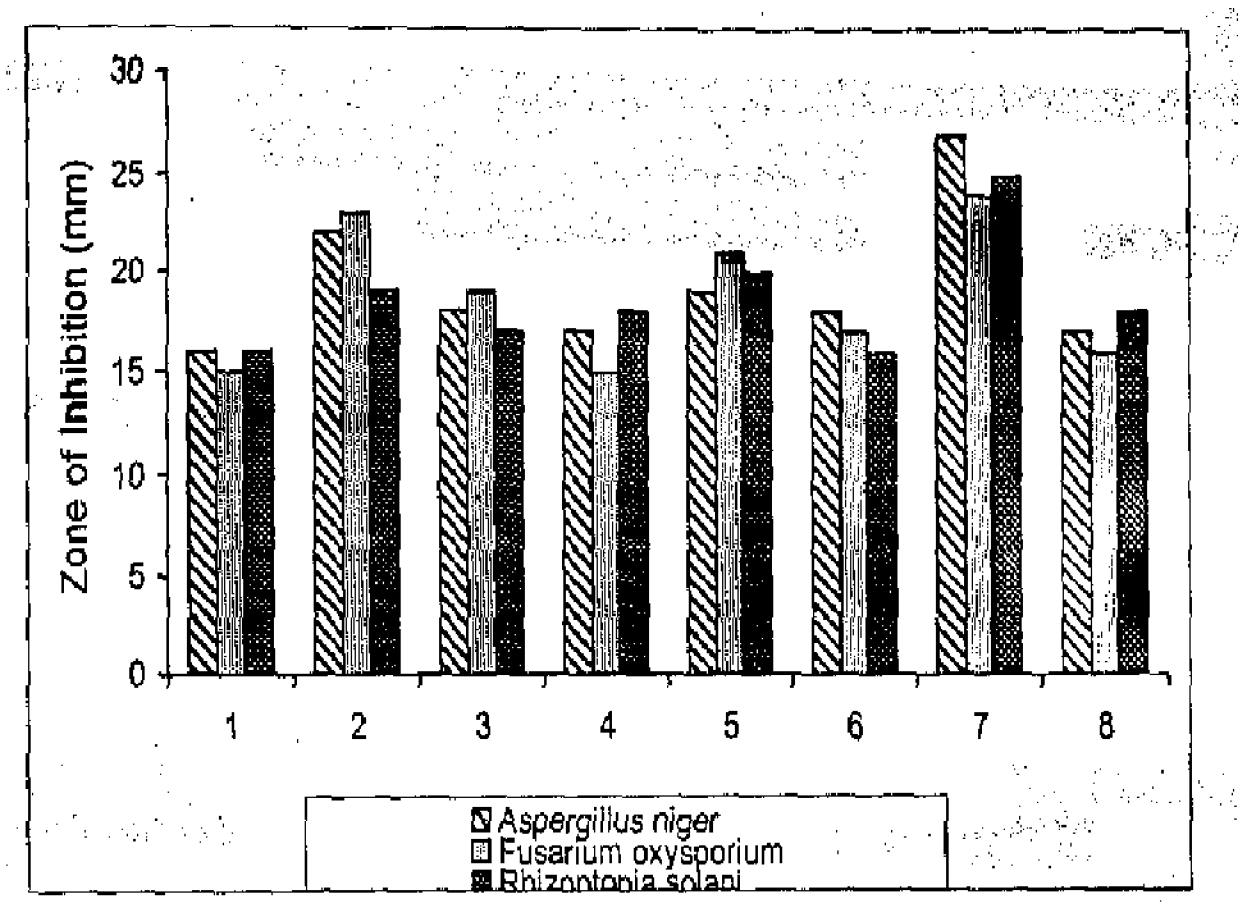

Figure VI-6: Antifungal activity of Schiff base metal complexes
1)Schiff base 2)Hg 3)Pb 4)Co 5)Sn 6)Cd 7)Cu 8)Th

REFERENCES

1. R. S. Sreevastav, *Inorg. Chim. Acta.*, 56, (1981), 256.
2. N. Sari, P. Gurkan and S. Arslan, *Trans. Met. Chem.*, 28, (2003), 468.
3. N. Quis, M.Rahman, *Phytotherapia*, 67, (1996).
4. A.B.Aziz, *Science*, 155, (1997), 1026.
5. N. Raman and S. Johnson Raja, *Journal of the Serbian Chemical Society*, 72(10), 2007, 983-992.
6. S. J. Berners-Price, R. J. Bowen, P. Galettis, P. C. Healy and M. J. McKeage, *Coordin. Chem. Rev.*, 185-186, (1999), 823-836.
7. M. A. Affana, B. A. Fasihuddina, Y. Z. Liewa, S. W. Fooa, and J. Ismailb. *J. Sci. Res.* 1(2), (2009), 306-316.
8. S. O. Podunavac-kuzmanovic, V. M. Leovac and D. D. Cvetkovic, *Journal of the Serbian Chemical Society*, 73(12), (2008), 1153-1160.
9. A. A. Al-Fregi, H. A. Abood and I. E. Al-Saimary *Internet Journal of Microbiology*, 4(1), (2007).
10. A. A. Isab, MIM. Wazeer, M. Fettouhi, B. A. Al-Maythalony, A. R. Al-Arfaj and N. O. Al-Zamil, *Inorganica Chimica Acta*, 360, (2007), 3719-3726.
11. C. Spnu, M. Pleniceanu, and C. Tigae *Journal of the Serbian Chemical Society*, 73(4), (2008), 415-421.
12. MIM. Wazeer, A. A. Isab and M. Fettouhi, *Polyhedron*, 26, (2007), 1725-1730.
13. M. M. El-Ajaily, F. A. Abdlseed and S. Ben-Gweirif, *E-Journal of Chemistry*, 4(4), (2007), 461-466.
14. J. R. Anacona and Gladys Da Silva, *J. Chil. Chem. Soc.*, 50(2), (2005), 447-450.
15. N. Raman and S. Johnson Raja, *Journal of the Serbian Chemical Society*, 72(10), (2007), 983-992.
16. S. K. Eajpai and (mrs) P. R. Shukla *Ind. J. Pharmac.* 7(4), (1975), 21-25.
17. M. R. Maurya, *Coordination Chemistry Reviews*, 237(1-2), (2003), 163–181.
18. M. R. Maurya, S. Khurana, Shailendra, A. Azam, W. Zhang, and D. Rehder, *European Journal of Inorganic Chemistry*, 2003(10), (2003), 1966–1973.
19. A. P. Mishra and Monika Soni *Metal-Based Drugs*, 1, (2008), 1-7.

20. A. Sreekanth, M.R.P. Kurup, *Polyhedron*, 22, (2003), 3321.

21. D. L. Klayman, J. M. Hoch, J. P. Scovill, C. Lambros, A. S. Dobeck, *J. Pharm. Sci.*, 73 (1984) 1763.

22. R. H. Dodd, C. Quannes, M. Robert Gero, P. Potier, *J. Med. Chem.*, 32, (1989), 1272.

23. V. B. Arion, E. Reisner, M. Fremuth, M. A. Jakupec, B. K. Keppler, V. Y. Kukushkin and A. J. Pombeiro. *Inorg. Chem.*, 42(19), (2003), 6024-31.

24. H. Kadhim, Al-obaidi, Basem F. Ali, Rajab Abu-El-Halawa and Anwar Abo-Amer, *Transition Metal Chemistry.* 29(7), (2004), 804-811.