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A Review of Biological Applications of Schiff base Metal Complexes

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ABSTRACT

Schiff bases synthesized from the condensation of an amino compound with carbonyl compounds and their complexes exhibit a wide range of biological activities, including antifungal, antibacterial, antiviral, antitumor and anticancer properties. In recent years, these complexes have attracted much attention due to their unique biological properties. Many reports are published on their applications in the biological activities of these compounds. The development of a new chemotherapeutic Schiff bases and their metal complexes is now attracting the attention of medicinal chemists. This review is nothing but a small attempt to show various examples of the most promising applied Schiff base complexes in biological fields.

INTRODUCTION

Hugo Schiff reported the condensation of primary amines with carbonyl compounds in 1864 and the product was known as the Schiff base. Schiff bases of aliphatic aldehydes are readily polymerized and hence unstable in nature but their aromatic varieties are more stable due to the conjugation system. The Schiff base complex has been the subject of study for its interesting magnetic properties in the fields of condensed matter physics, physical chemistry, as well as inorganic chemistry since its discovery. When metal centers are present in an unsaturated coordination environment, some additional linkers can bridge the metal centers to form polynuclear complexes. Primarily for inorganic chemists, the imine group (-RC=N-)1 in Schiff base compounds appears to be a point of interest as they are widely used in designing molecular ferromagnets, in catalysis, in biological modeling applications, in liquid Used in the form of crystals. As heterogeneous catalysts and also in self-assembling cluster complexes.

The Schiff base derived from the condensation of carbonyl compounds and amino acids provides an amazing class of ligands that coordinate with the metal ion by the azomethine nitrogen. The presence of a C=N linkage in the ligand system is essential for biological activities. The lone pair residing on the sp2 hybridized nitrogen atom of the azomethene linkage plays an important role to show biological activities.

These classes of complexes have also attracted much attention because of their active part in metalloenzymes and biomimetic model compounds. They are often found inside natural proteins and enzymes. It has been observed that the N atom has an important role in the coordination of metals as the active site of many metallobiomolecules.

Transition metal complexes of ligands containing some heterogeneous atoms such as oxygen, nitrogen and sulfur donors show carcinostatic, antitumor, antiviral, antifungal and antibacterial activities. These facts generate considerable interest in the chemistry of these complexes.

Therefore, the research area encompassing these types of metal complexes is very broad and includes many interdisciplinary fields such as bioinorganic chemistry, catalysis, photochemistry and magneto chemistry. Again, with developments in inorganic chemistry research people have new ideas about the versatile use of metal complexes as therapeutic agents and as drugs for the treatment of many human diseases. Schiff base metal complexes, especially the synthesis of transition metal ions, with different molecular topologies and sets of donor atoms are becoming an emerging area of research due to their potential applications in pharmaceuticals, antibacterial, antifungal, anticancer and anti-inflammatory actions.

In conclusion, heterocyclic Schiff base ligands and their metal complexes have been the subject of extensive investigation due to their widespread use in the biological field.

The present paper reviews the use of Schiff base metal complexes in their antifungal, antibacterial, antiviral, antitumor and anticancer activities.

BIOLOGICAL SIGNIFICANCE OF SCHIFF BASE COMPLEXES

Advances in bioinorganic chemistry increase interest in Schiff base complexes, taking into account the idea that many of these complexes can serve as models for biologically important species. Thus, we report them in the following:

ANTIFUNGAL AND ANTIBACTERIAL PROPERTIES:

Certain complexes involving copper(II) have been intensively studied for their antifungal and antibacterial properties. Their antifungal properties were evaluated by three phytopathogenic fungi, A. Solani, F. Equisetti and M. Against Phaseolina. Two pathogenic bacteria, E. coli and S. Their antibacterial properties have also been tested again against Aureus. ME Hussain et al. Based on their study reported a detailed test result. Their study has verified that these copper(II) complexes are generally associated with A. Solani, F. Equisetti and M. phaseolina, compared to either free ligands or the commercially available antifungal agent nystatin. Again the copper(II) complex of benzoylpyridine Schiff base ligands in the organism F. are found to

be quite active towards equity. Investigations show that the given complex is active against the organism S. aureus, but the presence of E. coli remains unaffected.

A series of 2-acetylpyridine thiosemicarbazone (A) derivatives were found to have significant anti-malarial activities. A 2-pyridylcylidene moiety and the presence of a thiocarbonyl or selenocarbonyl group (as opposed to a carbonyl group) appear to play an essential role in showing anti-malarial activity. Again the presence of some bulky groups at the N position of the thiosemicarbazone enhances the anti-malarial activity. Intensive study has shown that these thiosemicarbazide ligands become more active when attached to a metal ion. Sarayan et al. 20 reported that iron complexes of some α-N-heterocyclic thiosemicarbazones act as more active inhibitors of ribonucleotide reductase or in intensity of antitumor activities than free ligands. It is noteworthy in this context that Das and Livingstone reported the antitumor properties of several transition-metal complexes of methyl 3-[1-(2-pyridyl)ethylidine]carbodithioate (B). Derivatives of chloro-Ni(II) and Cu(II)B were found to be active against P388 leukemia.

It is well known that some drugs have higher activity when administered as metal complexes than as free ligands. Ramesh and Sivagamasundari reported a group of hexa-coordinated ruthenium(II) complexes that showed a fair amount of antifungal activity.

These Schiff base ligands and their ruthenium chelates were studied in vitro to explain their antifungal activities against Aspergillus flavus at four different concentrations. The results reiterated the same fact that ruthenium chelates are more toxic than their parent ligands against the same microorganisms under the same experimental conditions. The toxicity of ruthenium chelates increases with an increase in concentration. A possible explanation of this greater toxicity of metals on their respective free ligands can be considered in the light of Tweedy's chelation theory. As a result of chelation, the polarity of the metal ion decreases because the positive charge of the metal ion is shared by the ligand and the -electron is delocalized over the entire chelate ring. And this would increase the lipophilic character of the central metal atom, which then allows for its greater permeability through the lipid layers of the cell membrane. Thus lipophilicity is an important factor that modulates antimicrobial activity. In addition, the presence of azomethine (>C=N) group can form a hydrogen bond with the active centers of cell components, which interferes with normal cell processes.

Mohammed et al. reported that the Schiff base metal complex derived from 2-thiophene carboxaldehyde and 2-aminobenzoic acid and Fe(III) or Co(II) or Ni(II) or UO2(II) gave an excellent anti-inflammatory action against Escherichia coli, Pseudomonas aeruginosa and Staphylococcus pyogenes showed antibacterial activity. The Fe(III), Cu(II), Zn(II) and UO2(II) complexes can inhibit the growth of E. coli. Thus, these complexes can be applied

appropriately to prevent some common diseases caused by E. coli. Fe(III), Co(II), Cu(II), Zn(II) and UO2(II) using Schiff base complexes to again inhibit the growth of Gram-positive bacterial strains (Staphylococcus pyogenes and P. aeruginosa).

In the year 2007, Gabla et al. 20 reported that platinum(II) Schiff base complex containing salicaldehyde and 2-furaldehyde interacted with o- and p-phenylenediamine in E. coli, Bacillus subtilis, P. aeruginosa, has antibacterial properties against Staphylococcus aureus. Here also the same observation arises that platinum(II) complexes are more active antimicrobials against one or more microorganisms than the preceding Schiff base ligands.

In this context, it has been reported that some novel Schiff base metal complexes of sulfametrol and verrealdehyde have excellent antimicrobial behavior against bacteria E. coli (Gram-negative bacteria) and S. aureus (Gram-positive bacteria). The reason for their greater toxicity may be the sulfonic OH, OCH3, S and CH3CH2CH groups, which can interact with the double membrane. 2-Aminomethylthiophenyl- 4-bromosalicylaldehyde Schiff base and its metal complexes have been reported for their antimicrobial activities.

In conclusion, it can be said that the antibacterial activity of the compounds is related to the cell wall structure of bacteria. Some antibiotics inhibit a step in the synthesis of peptidoglycan, a polymer consisting of sugar and amino acids that make up the cell wall outside the plasma membrane of bacteria.

Nair et al., Antibacterial activity of some Schiff base complexes of Co(II), Ni(II), Cu(II) and Zn(II) incorporating indole-3-carboxaldehyde and m-aminobenzoic acid by the disc diffusion method examined. He explained that the activity of metal complexes depends on the effect of metal ions on normal cell membranes. When metal ions are chelated by some chelating ligand, polar and non-polar properties occur simultaneously. And this dual nature increases the permeability of metal ions to the cells and tissues of various bacteria. Nair et al reported that Cu(II) and Co(II) are more active than Ni(II) and Zn(II) in their antibacterial activities.

Shaker et al. Synthesized a series of Fe(II) Schiff base complexes of the ligand obtained from the condensation of amino acids and sodium 2-hydroxybenzaldehyde-5-sulfonate. The complexes were characterized by elemental, electronic, IR spectral analysis and conduction measurements. Their antibacterial activities were tested against Bacillus cereus, P. aeruginosa and Micrococcus bacteria.

Literature surveys show that cobalt complexes demand a lot of attention due to their amazing antibacterial properties. In this regard, Co(II) complexes, due to their aqueous stability, availability and simplicity of synthesis, are more studied than Co(III) complexes. The Co(III) ion can be stabilized with N, O and S donor atoms in the presence of certain polydentate

ligands and in the aqueous phase. Co(III) shows kinetic inertia in water in the presence of NH3 as a ligand.

The Co(III) complex of a new hybrid amine-imine-oxime ligand derived from the condensation reaction of diacetylmonoxime with benzidine was reported to have antibacterial activity against Bacillus subtilis. But it has no activity against Staphylococcus aureus or the Gram-negative bacteria Escherichia coli and Enterobacter fecalis.

NK Choudhary and P Mishra reported an important observation. They synthesized Schiff base ligands by condensation of amoxicillin trihydrate and nicotinaldehyde and used Co 2, Ni 2, Cu 2 and Zn 2 as central metal ions. Metal complexes were tasted in vitro for antibacterial assay. It was found that the new compound was more potent than amoxicillin and the control drug amikacin. The complexes were shown to have high activity against all bacterial pathogens at their high concentrations. The reason behind their greater activity is chelation. Schiff bases with metal ions that provide stability and greater sensitivity against bacterial pathogens. The structural component containing additional C=N bond with the N,O donor atom coordinates the metal ion and as a result the polarity of the complex decreases. This allows their efficient permeation through the lipid layer of bacterial organisms and destroys their activity.

ANTIVIRAL ACTIVITIES

Isatin has long been known for its biological activity in mammals. Isatin's Schiff base and Mannich base show a wide range of pharmacological properties, including antibacterial, anticonvulsant, anti-HIV, antifungal and antiviral activity. In 2007, A. Jarahpur et al. reported a group of Schiff bases of isatin and 5-fluoroisatin regarding their antiviral activities.

Generally, cobalt(III) ion is not stable in aqueous solution. It can be stabilized in aqueous solution in the presence of a chelating N,O donor ligand environment. This cobalt(III) complex of such ligands was found to be important because of their antibacterial or antiviral activities. In 1998, Epstein and colleagues reported a series of Co(III) complexes (1D) containing the following types of N,O donor ligands for their use in the treatment of blindness in industrialized countries, known as epithelial herpetic keratitis.

Initially, the drug was applied to a rabbit eye model infected with herpes simplex virus type 1 (HSV-1) and found to be an active inhibitor of HSV-1 replication in vitro. There is some evidence that these chains of complexes prevent virus entry by inhibiting membrane fusion. Complex 1d inhibited plaque formation by vesicular stomatitis viruses VSV and VZV (varicella-zoster virus).

The activity of CTC-96(1d) against adenovirus in cell culture model and adenovirus kerato conjunctivitis in rabbit model was reported by Epstein in 2006. Butcher et al. One drug is synthesized by Redox Pharmaceutical Corporation and is known commercially as doxovir™. These Co(III) Schiff base complexes have the ability to inhibit Sp1, a DNA binding zinc finger protein and are used in the treatment of human immunodeficiency virus type 1 (HIV-1).

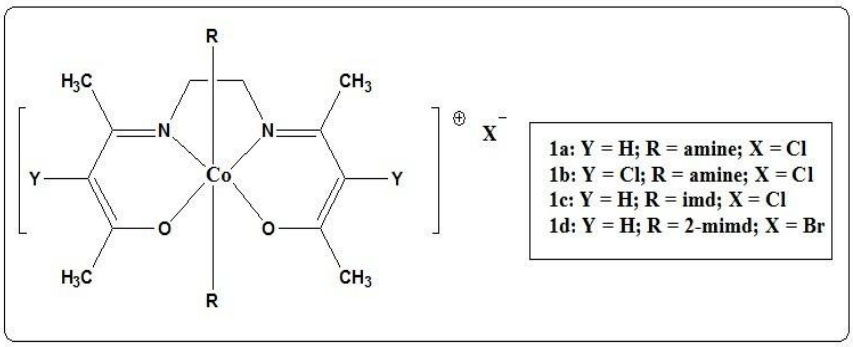

Figure 1. Structure of CTC-type cobalt(III) complexes (imd = imidazole, 2-mimd = 2-methylimidazole).

ANTI-CANCER ACTIVITIES

Cancer is a group of diseases that involve abnormal cell growth with the potential to attack or spread to other parts of the body. It appears as the most dire diagnosis of a serious public health problem worldwide. Currently, chemotherapy is the main approach for both localized and metastasized cancers. But all these curative effects of existing chemotherapy drugs have serious side effects. In this regard, many researches continue over the past five decades to develop more effective drugs to treat cancer patients.

In the past few years, organic compounds containing Schiff base as the main part of their structure have attracted much attention due to their anticancer properties. Metal complexes of Schiff base ligands in particular have attracted the attention of chemists because they are used as potent drugs or diagnostic agents. Metal complexes can offer unique mechanisms of drug action due to the wide range of coordination numbers, geometry and kinetic properties that are not possible with pure organic molecules. Rosenberg and colleagues invented cisplatin, one of the best-selling anti-cancer drugs worldwide. After that, several reports have been published to date, where metal complexes of Schiff bases have been used as anticancer agents.

In the year 2017, a report was published by Subin Kummer, where a series of metal complexes of Schiff bases derived from vanillin and acetoacetanilide with ethylenediamine were tested and found that the high inhibitory concentration (IC50) value of the copper complex is approximately 49 micro/ml. Dalton lymphoma ascites cell induced solid tumor models and

Ehrlich's ascites carcinoma cell induced ascites tumor models were mainly used for antitumor studies.

Five ternary complexes of rare earth ions with O-phenanthroline and the Schiff base salicylaldehyde L-phenylalanine were used to test the anticancer effect of the complexes with a K562 tumor cell. Complex K562 can inhibit tumor cell growth, generation and induce apoptosis. This inhibition can be accelerated by increasing the dose.

Zhang et al. 20 reported that three metal complexes (Cu2, Zn2, Cd2) of a ligand derived from 2-acetylpyridine and L-tryptophan have anti-cancer activities on MDA-MB-231 breast cancer cells.

A series of compounds were reported by Yang et al. with the general formula Ln(HL)3•3.5H2O (where Ln(III) = La, Eu, Gd, Tb, Dy, Ho and Er) 33. Among them, the complex of La and Eu has the most potential in anti-tumor Has activity against leukemia cells (L1210) with percentage inhibition of 87.1 and 78.5%, respectively.

Afrasiabi et al. Some Cu(II), Ni(II), Pd(II) and Pt(II) complexes of ortho-naphthaquinone thiosemicarbazone (NQTS) have been reported and in vitro anti-cancer activities against MCF7 human breast cancer cell lines rated. Among the complexes, Ni(II) complexes were tested as the most potent IC50 value of 2.25 μM.

Zhong et al. Some mononuclear complexes of Cu(II), Mn(II), Co(II), Ni(II) with bis-Schiff base ligands from 2,3-butanedione and thiosemicarbazide explained their synthesis and anti-cancer activities. The cytotoxicity assay was performed against five different cell types (HL-60, Spca-1, Tb, MGC, K562). Among them, the Cu(II) complex was found to have the highest anti-tumor activity.

Chakraborty et al. Synthesized a Schiff base copper complex of a tridentate ligand containing two pyridines and an imine nitrogen donor atom, and the complex has anticancer activities. The IC50 values of this compound were found to be 4.29 ± 0.42, 6.34 ± 0.58 and 5.32 ± 0.38 μM against the MCF7, PC3 and HEK 293 cell lines, respectively.

CONCLUSION

Schiff bases present a very important class of organic compounds due to their ability to form complexes with transition metal ions and of their pharmacological properties. The complexes have been of much interest over the last years, largely because of their various applications in biological processes and potential applications in designing new therapeutic agents. But still it needs to explore the biological applications of these transition metal complexes, already synthesized and to synthesize new complexes with more properties accordingly.

REFERENCES

1. Ramesh R. and Sivagamasundari (2003) M. Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry. 33: 5: 899–910,
2. Da Silva, C. R., Maniero, M. G., Rath, S., Guimaraes J. R.(2011) J. Adv. Oxid. Technol. 14: 1.
3. Hossain, M.E., Alam, M. N., Begum, J., Akbar Ali, M., Nazimuddin, M., Smith, F.E. (1996) Inorg. Chim. Acta 249: 207-213.
4. Das, M.; Livingstone, S. E. Br. (1978) J. Cancer, 37: 466. b) John P. Scovill, Daniel L. Klayman, and Charles F. Franchino (1982) J. Med. Chem., 25: 1261-1264.
5. Tweedy, B.G. Phytopathology (1964), 55: 910–917.
6. Singh Jadon, S.C.; Gupta, N.; Singh, R.V. (1995) Indian J. Chem., 34 (A):733–736.
7. Mohamed G.G, Zayed M.A, Abdallah S.M. J. Mol. Struct. (2010) 979: 62
8. Gaballa, A.S., Asker, M.S., Barakat, A.S., Teleb, S.M. (2007) Spectrochim Acta; 67A:114e21.
9. El-Sherif, A.A., Eldebss, T.M.A. (2011) Spectrochim Acta; 79A: 1803e14.
10. Nair, M.S., Arish, D., Joseyphus, R.S. (2012) J Saud Chem Soc; 16:83.
11. Shaker, A.M., Nassr, L.A.E., Adam, M.S.S., Mohamed, I.M.A. (2013) J Korean Chem Soc;5:560.
12. Ahmed M. Abu-Dief, Ibrahim M.A. Mohamed, (2015) Beni-suef university journal of basic and applied sciences 4: 119.
13. Mohamed, G. G, Omar, M. M., Hindy, A.M.M. (2005) Spectrochim Acta;62A:1140 e50
14. Kaya, M., Yenikaya, C., Colak, A.T., Colak, F (2008) Russ. J. Gen.Chem., 78: 1808–1815.
15. Chaudhary, N. K., Mishra, P. (2017) Bioinorganic Chemistry and Applications, Article ID 6927675.
16. Chang, E. L., Simmers, C., Andrew Knight, D. (2010) Pharmaceuticals 3: 1711-1728.
17. Jarrahpour, A., Khalili, D., De Clercq, E., Salmi, C., Michel Brunel, J. (2007) Molecules, 12: 1720-1730,
18. Asbell, P.A., Epstein, S.P., Wallace, J.A., Epstein, D., Stewart, C.C, Burger, R.M. (1998) Cornea 17: 550–557.
19. Schwartz, J.A., Lium, E.K., Silverstein, S.J. (2001) J. Virol., 75:4117–4128.
20. Epstein, S.P., Pashinsky, Y.Y., Gershon, D., Winicov, I., Srivilasa, C., Kristic, K.J., Asbell, P.A. (2006) BMC Opthalmol., 6: 22.
21. Redox Pharmaceutical Cooperation Home Page.(2010).
22. Louie, A.Y., Meade, T.J. (1998) Proc. Natl. Acad. Sci. USA, 95: 6663–6668
23. Kumar, K. S., Ganguly, S., Veerasamy, R., De Clercq, Erik. (2010) European Journal of Medicinal Chemistry, 45: 5474-5479,
24. Mehmood, R.K., Parker, J., Ahmed, S., Qasem, E., Mohammed, A.A., Zeeshan, M., Jehangir, E. (2014) World J. Oncol., 5: 97-108.
25. Subin kuamr, K., Priya varma, V. N., Reena, K. K., Aravindakshanj.(2017) Pharm. Sci. & Res. 9, 8: 1317-1323

26. Dongfang et al., 2008.
27. Zhang et al., 2012
28. Yang, Z.Y., Yang, R. D., Li, F.S., Yu, K.B. (2000) Polyhedron., 19: 2599-2604.
29. Garcıa-Friaza, G., Fernandez-Botello, A., Perez, J.M., Prieto, M.J., Moreno, V. (2006) J. Inorg. Biochem. 100: 1368- 1377.
30. Afrasiabi, Z., Sinn, E., Chen, J., Ma, Y., Rheingold, A.L., Zakharov, L.N., Rath, N., Padhye, S. (2004) Inorg. Chim. Acta., 357: 271-278.
31. Rehman, W., Badshah, A., Khan, S., Tuyet, L.T.A. (2009) Eur. J. Med. Chem., 44: 3981-3985.
32. Chakraborty, A., Kumar, P., Ghosh, K., Roy, P. (2010) Eur. J. Pharmacol., 647: 1-12.
33. El-Sherif, A. A.; Eldebss, T. M. A. (2011) Spectrochim. Acta A., 79: 1803-1814.