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Biological activities of hydrazone Schiff bases and their some metal complexes : A Review

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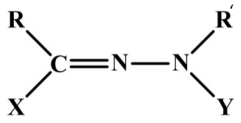
Abstract : Today, all over the world coordination chemistry comprises a large body of inorganic chemistry research and mainly the chemistry of transition metal complexes has fascinated and inspired chemists. Academic, commercial, and biochemical interest in metal complexes of organic chelating ligands continues to grow. This has resulted in the emergence of related fields such as organometallic chemistry, homogenous catalysis, and bioinorganic chemistry. Schiff bases have sparked the interest of chemists due to the complexation with metals. Hydrazones are an important class of ligands in coordination chemistry. This review focused on the biological activities of recently synthesized hydrazone metal complexes. Some hydrazones are used to detect and determination of metals and some organic constituents in pharmaceutical formulations. Chemists gained much attention toward the hydrazone complexes because of a wide range of biological applications like antifungal, antibacterial anticonvulsant, and analgesic, anti-inflammatory, antimalarial, antimicrobial, antituberculosis, antiviral, and anticancer activities.

(**Keywords:** Hydrazone Schiff bases, Metal complexes, Biological activities)

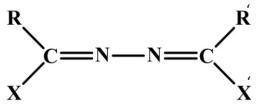
Introduction

Schiff bases containing the azomethine (–RC=N-) are generally formed by the condensation of a primary amine with an active carbonyl compound and were first reported by German chemist noble prize winner Hugo Schiff. They are stable and can tune the ligation aspects by varying denticity and basicity. Intensive research on the physicochemical properties and molecular structure of complexes with Schiff bases has provided interesting new results, which need to be surveyed and compared with earlier literature on these types of compounds. In the field of coordination chemistry, Schiff base ligands played an essential role, especially in the development of complexes because these compounds are capable of forming stable complexes with metal ions[1]. Schiff bases have gained much interest in the pharmaceutical fields due to their wide application of biological activities like anti-inflammatory[2-6], analgesic[7-9], antimicrobial[10,11], anticonvulsant[12], antitubercular[13], anticancer[14,15], antioxidant[16], anthelmintic[17], and so forth. Isatin Schiff and Mannich bases were also reported to demonstrate a broad spectrum of biological activities such as antibacterial, antifungal, antiviral, anti-HIV, antiprotozoal, and antihelminthic activities[18-20].

Hydrazones are versatile ligands and considered as azomethine compounds and described by the following general structure $R_2C = NNR_2$. They have possessed interlinked nitrogen atoms so that they are differing from other members of this class (imines, oximes, etc). The hydrazone group occurs in organic compounds and can be classified into two types:
(a) are named hydrazones (b) are termed azines



(a)



(b)

Fig. 1. Two types of compounds with N= C bonding, hydrazones a and azines b Where R and R' = H, alkyl, aromatic, heterocyclic group; Y = H, alkyl, aromatic, heterocyclic; X and X' = H, alkyl, aromatic, Hal, OR, SR, CN, SO_2R, NO_3, $NHNR_1R_2$, N= NR, COOR, $CONR_1R_2$, heterocyclic group.

Hydrazones are generally formed by the condensation reaction of various aldehydes or ketones with hydrazine. Several authors have recently reverted to this system which is, however, cumbersome when applied to more complex hydrazones. Bis-hydrazones of α-diketones are commonly called osazones[21]. Hydrazone ligands are classified according to the number of hydrazonic groups, which are characterized by the presence of one hydrazonic group (an interlinked nitrogen atom) (Fig. 2a), the dihydrazone ligand (two hydrazonic groups with two interlinked nitrogen atoms) (Fig. 2b) and the trihydrazone ligand (three hydrazonic groups with three interlinked nitrogen atoms) (Fig. 2c). Hydrazone ligands can be classified into bidentate, tridentate, tetradentate, pentadentate, hexadentate, octadentate, and nonadentate according to the number of functional groups involved in the complex process.

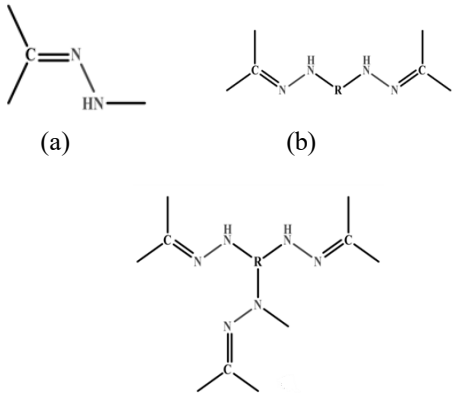


Fig. 2. Structure representation of mono- a, di- b and tri- c hydrazone ligands.

The bonding of hydrazone ligands with transition metals can proceed according to one of the following paths. The first one leads to the formation of complexes in which the hydrazone reacts with transition metal in the ketonic form (Fig. 3 a) whereas the second one hydrazone reacts in the enolic form (Fig. 3b), leading to the formation of two types of complexes. The mode of bonding of hydrazone and molecular structure of the resulted complexes depends on the nature of the metal ion, anion of the salt and alkalinity of the reaction medium[22].

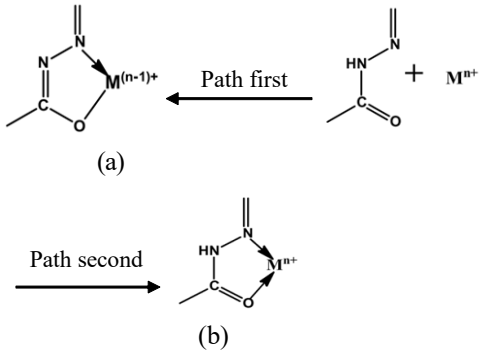


Fig. 3. Mode of bonding of hydrazone ligands with transition metals a- enolic, b- ketonic.

Many authors are gained much attention towards the hydrazone ligands and their metal complexes because of their wide applications in the field of biological, analytical, pharmaceutical, catalytic and industrial and also play important roles in the treatment of different diseases. According to the literature review hydrazones and their complexes represents an important place in medicinal chemistry.

2. APPLICATIONS OF HYDRAZONE AND METAL COMPLEXES

The biological activity of the hydrazone can be attributed to the formation of stable chelates with the transition metals present in the cell, thus many important enzymatic reactions cannot occur in the presence of the hydrazone. On coordination, the activity of the hydrazone increases. This increase in activity can be rationalized on the basis that their structures mainly contain an additional >C=N- bond. Coordination reduces the polarity of the metal ion because of the partial sharing of its positive charge with the donor atom within the chelate ring system, which formed the time of

coordination. This process, in turn, enhances the lipophilic nature of the central metal atom, which promotes its permeation more efficiently through the lipid layers of the microorganism, thus destroying them more aggressively. On the other hand, the inhibition of growth of the microorganisms may be due to the inhibition of glucose absorption, inhibition of RNA and/or protein synthesis.

Cancer is the uncontrolled growth of abnormal cells in the body and many different types of cancer occur in an organ or tissue such as lung, colon, breast, skin, bones, or nerve tissue. Chemotherapy is the most common method of treating various types of malignant tumors. The need for new promising antitumor agents is increasing worldwide. Hydrazone ligands and their complexes have wide applications as anti-tumor, anti-cancer, anti-neoplastic, and anti-proliferative agents. This activity may be due to one of two mechanisms. The first mechanism depends on the high ability of the hydrazone to chelate Fe(III) from the cell which is essentially in metabolic pathways that are involved in DNA synthesis of neoplastic cells so that chelation of iron inhibited the proliferation of the neoplastic cell[23]. The second mechanism depends on preventing the uptake of iron from transferrin of the neoplastic cells. This activity may be ascribed to producing cytotoxic oxygen radicals[23].

Examples of hydrazones and their complexes that have antitumor activity are the pyridoxal isonicotinoyl hydrazone ligands and their iron(III), gallium(III), and copper(II) complexes. These classes of ligands have distinct activity against certain mammary tumors and leukemias in mice. Since they have affinity and selectivity for iron in the cell[23]. This study revealed that complexation with metals increased the antiproliferative activities of chelators. Addition of iron(III) to some PIH analogs markedly depressed their activities, whereas it had little effect on others. The gallium(III) complex of PIH, but not its copper(II) complex, was more efficient than the apochelator at inhibiting[23] thymidine incorporation.

Aroyl hydrazones of pyridoxal and salicylaldehyde, a series of tridentate chelating agents, are potent inhibitors of DNA synthesis and cell growth in a number of human and rodent cell lines grown in culture and inhibit in vitro lymphoproliferation[24,25]. A copper(II) complex of the most potent chelators, salicylaldehyde benzoyl hydrazone (SBH), exhibited significantly greater inhibitory activity than SBH.

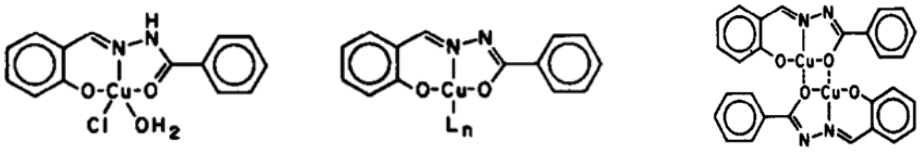


Fig. 4. Structures of copper(II) complexes of salicylaldehyde benzoyl hydrazone

Organotin(IV) complexes of 2-hydroxy-1-naphthaldehyde-5-chloro-2-hydroxy benzoylhydrazone have been synthesized by M. Hong[26] et al. All compounds exhibited in-vitro antitumor activity toward human colon cancer cells (HCT-8), lung cancer cells (A549) and human promyelocyticfina leukemic cells (HL-60). The results indicated that both alkyl groups bound with tin centers and the structure of organotin compounds have a significant effect on their in-vitro antitumor activities.

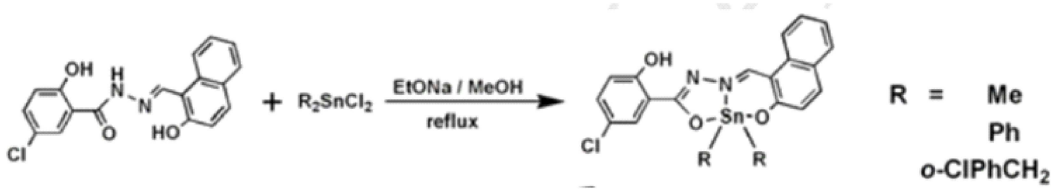
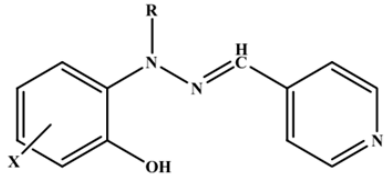


Fig.5. Structure of Organotin(IV) complexes of 2-hydroxy-1-naphthaldehyde5-chloro-2-hydroxy benzoylhydrazone

Salicylaldehyde isonicotinoyl hydrazone (SIH) is a lipophilic, orally active tridentate iron chelator providing both effective protection against various types of oxidative stress-induced cellular injury and anticancer action. However, its labile hydrazone bond that makes it prone to plasma hydrolysis represents the major limitation of SIH as an anticancer. Recently, a series of new SIH analogs derived from aromatic ketones with improved hydrolytic stability was developed. They analyzed their antiproliferative potential in MCF-7 breast adenocarcinoma and HL-60 promyelocytic leukemia cell lines. Seven of the tested substances showed selectivity greater than the parent agent towards the latter cancer cell lines compared to non-cancerous H9c2 cardiomyoblast-derived cells[27].



R= H, CH_3, C_2H_5, X= 0
R= CH_3, X = 4-OH, 4-OCH_3, 5-NO_2, 5-Cl, 6-OH, 4-OH-5-CH_3CO,

Fig. 6. Structures of Salicylaldehyde isonicotinoyl hydrazone (SIH) and its analogues

A series of tri-substituted 3,5-triazine-2,4,6-triyltris(oxy)tris(benzene-4,1-diyl)tris(methanylylidene)tri(benzohydrazide) derivatives have been synthesized by S. S. Machakanur[28] et al. The prepared compounds were tested for their antiproliferative activity in vitro against human liver carcinoma (HepG2) and human cervix carcinoma (HeLa) cell lines.

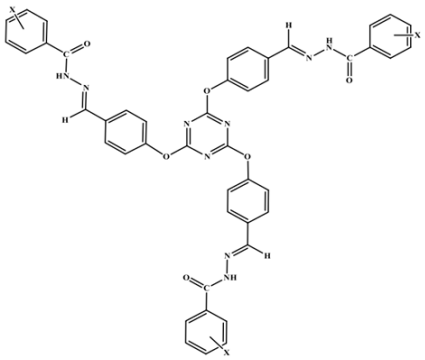


Fig. 7. Structures of tri-substituted 3,5-triazine-2,4,6-triyltris(oxy)tris(benzene-4,1-diyl)tris(methanylylidene)tri(benzohydrazide) derivatives (X= H, Br, Cl, F, OH, OCH_3, CH_3 NO_2 or NH_2)

A new luminescent copper(II) complex of 2-hydroxy naphthaldehyde-2-pyridylhydrazone ligand was prepared and characterized by S. Mukharjee[29] et al. The cytotoxic activity of the ligand and its complex was measured in-vitro against the HeLa cells and the complex showed a cytotoxic effect with HeLa cells (LD50 = 4.97M).

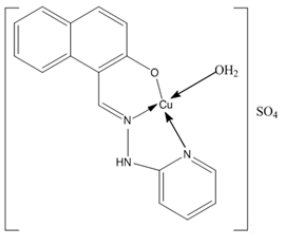


Fig. 8. Geometry of Cu(II) complex of 2-hydroxy naphthaldehyde-2-pyridylhydrazone

Organoruthenium(II) carbonyl complexes with benzoic acid pyridin-2-yl-methylenehydrazide, benzoic acid (1-pyridin-2-yl-ethylidene)hydrazide and benzoic acid (phenyl-pyridin-2-yl-methylene)hydrazide have been synthesized by D.R. Richardson[30]. The significant result of this work showed that the activities of ruthenium organometallic hydrazone complexes increase with inserting substituents of the phenyl ring at the azomethine carbon of the ligand which led to increased interaction with biomolecules such as free radicals and tumor cell lines than the rest of the complexes without such a phenyl ring in that position.

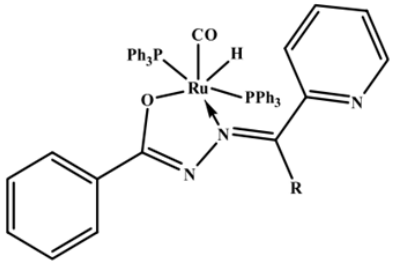


Fig. 9. Structures of organoruthenium(II) carbonyl complex

A.S. Abu-Surrah[31] et al. have synthesized trans palladium complexes of benzaldehyde (1,3-dimethyl-4-nitro-1H-pyrazol5-yl) hydrazone, 2,3-dimethoxybenzaldehyde (1,3-dimethyl-4-nitro-1H-pyrazol-5-yl) hydrazone, 4-chlorobenzaldehyde (1,3-dimethyl-4-nitro-1H-pyrazol-5-yl) hydrazone, and 4-hydroxybenzaldehyde (1,3- dimethyl-4-nitro-1H-pyrazol-5-yl) hydrazone(Fig. 10). The cytotoxic effect of these complexes against the fast-growing head and neck squamous carcinoma cells SQ20B and SCC-25 have been studied. The influence was dose dependent and varies by cell type. Some complexes had a higher clonogenic cytotoxic effect than cisplatin when tested on SQ20B cell line.

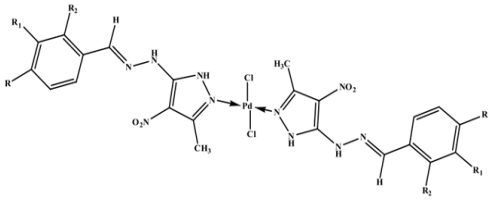


Fig. 10. Trans palladium complexes of benzaldehyde,2,3-dimethoxybenzaldehyde,4-chlorobenzaldehyde and4-hydroxybenzaldehyde (1,3-dimethyl-4-nitro-1H-pyrazol5-yl) hydrazone

Chin Liu[32] et al. have synthesized three novel 2-oxo-quinoline-3-carbaldehyde Schiff bases and their Cu(II) complexes and found that the Cu(II) complexes exhibited more effective cytotoxic activities against HL60 cells and HeLa cells than corresponding ligands.

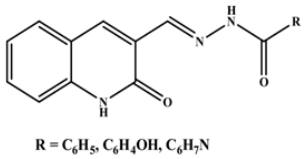


Fig. 11. Structure 2-oxo-quinoline-3-carbaldehyde hydrazone ligands

Y. Zhang[33] et al. have synthesized N-(1-phenyl-3-methyl-4-propyl-pyrazolone-5)-salicylidene hydrazone and Cu(II) complex and tested for anticancer activity. The testing results showed that the copper complex is more powerful than that of the ligand, which showed that the coordination effect improves the anti-tumor activity of the ligand.

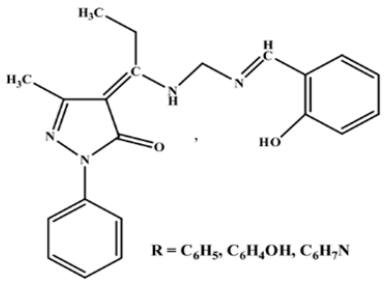


Fig. 12. Structure of N-(1-phenyl-3-methyl-4-propyl-pyrazolone-5)-salicylidene hydrazine

L. Maur[34] et al .have prepared 6-acetyl-cyclohex-3-enecarboxylic acid [1-pyridin-2-yl-1-(pyridyn-2-yloamin)methylidene] hydrazide and its Cu(II) complex. Synthesized Cu(II) complex was studied against the four carcinoma cell lines (SW 984, CX-1, L-1210, A-431). The studied complex exhibited significant cytotoxic effects (particularly against CX-1 colon carcinoma), comparable to those reported for cisplatin.

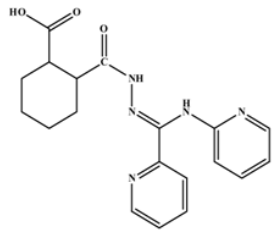


Fig. 13. Structure of 6-acetyl-cyclohex-3-enecarboxylic acid [1-pyridin-2-yl-1-(pyridyn2-yloamin)methylidene] hydrazide

A. Datta[35] et al. have synthesized tridentate hydrazone ligand, N'-[1-(pyridin-2-yl)ethylidene]acetohydrazide derived from the condensation of 2-acetylpyridine with acetic hydrazide and their complexes with Cu(II), Co(II) and Ni(II). The inhibitory effects of all the complexes on the cell population growth of human lung carcinoma cells (A549 cells), human colorectal carcinoma cells (COLO 205 cells and HT-29 cells), and human hepatocellular carcinoma cells (PLC5 cells) were determined by MTT assays and results revealed that the Cu(II) complex had the strongest population growth inhibition of human colorectal carcinoma cells (COLO 205 cells and HT-29 cells).

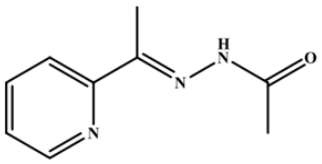


Fig. 14. Structure of N'-[1-(pyridin-2-yl)ethylidene] acetohydrazide ligand

P.A. Fatullayeva[36] synthesized 1-nicotinoyl-(2-hydroxybenzyl)hydrazine (L_1) by the reduction of 1-nicotinoyl-(2-salicylidene)hydrazone (L_2) in presence of $NaBH_4$. Co(II), Ni(II), and Cu(II) complexes with L_1 and L_2 have been prepared. These ligands and their complexes were screened for their fungicidal and antibacterial activity. The data has shown that 1-nicotinoyl-(2-hydroxybenzyl)hydrazine (L_1) shows higher antifungal and antibacterial activity. The Co(II) complex shows only antibacterial activity.

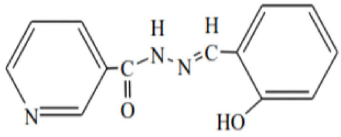


Fig.15. Structure of 1-nicotinoyl-(2-salicylidene)hydrazone

Inas Al-Qadsy[37] et al. developed (Z)-N'-(4-methoxybenzylidene)benzohydrazide Schiff base and its Ni(II) complex. The bio-efficacy of the Schiff base and Ni(II) complex (62.5–1000 µg/mL) against Gram-positive (*Staphylococcus aureus* and *Streptococcus pyogenes*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacterial and fungal (*Candida albicans*, *Aspergillus niger*, and *Aspergillus clavatus*) species has been examined. The results revealed that complex has higher activity against *S.aureus* and *S. pyogenes* (bacteria) and *A. niger* and *A. clavatus* (fungi) as compared to the parent Schiff base.

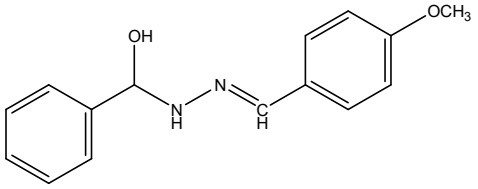


Fig.16.Structure of (Z)-N'-(4-methoxy benzylidene) benzohydrazide

A new series of metal complexes of Pd(II), Cd(II) and Cu(II, I) of polydentate Schiff base ligand, namely (Z)-2-(phenylamino)-N'-(thiophen-2-

ylmethylene) acetohydrazide have been prepared by S.A. Aly[38] et al.. The antibacterial study of the selected compounds was assayed against two pathogenic bacteria. Moreover, the complexes (CuII, I), Cd(II), Pd(II)) and the ligand revealed excellent antioxidant properties and could be useful in fighting the free radicals which occur in close connection with cancerous cells.

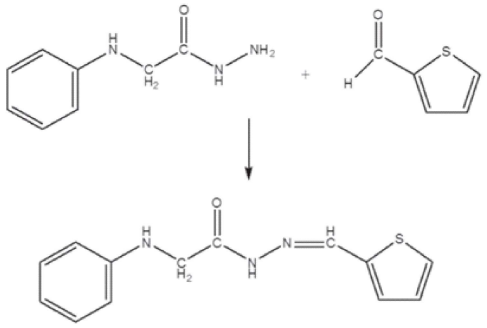


Fig.17. Synthesis of ligand(Z)-2-(phenylamino)-N'-(thiophen-2-ylmethylene) acetohydrazide

Hydrazones also play an important role in improving the anti-tumor selectivity and toxicity profile of anti-tumor agents by forming drug carrier systems employing suitable carrier proteins[39]. The overuse of chemicals against various infectious diseases has led to the rapid emergence of resistivity against different bacteria. Therefore, the search for antimicrobials is a never-ending task. Consequently, there has been immense research on hydrazones as antibacterial agents.

Conclusion

The study emphasizes the usage of hydrazones as a starting point for the creation of newer agents. As aforementioned, the moiety possesses an array of activities. Potential compounds with different biological activities can be synthesized utilizing proper synthesis and structure activity relationships. One of the most important chemical categories is hydrazone ligands and metal complexes, which provide a reservoir of possibilities for novel design owing to the matchless structure of hydrazone itself and its way of bonding with metal ions. This article review reveals that the hydrazone ligands are extremely needed because of their properties such as anti-tumor, anti-malarial, anti-bacterial, anti-fungal anti-mycobacterial, antiviral, anti inflammatory. Metal complexes of hydrazone are also highly required because coordination decreases the polarity of the metal ion, mostly due to the partial sharing of its positive charge with the donor atom inside the chelate ring system produced during coordination. This process, in turn, increases the lipophilic nature of the central metal atom, which favors its permeation more efficiently through the lipid layer of the microorganism thus destroying them.

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