Metal complexes of hydrazones and their biological, analytical and catalytic applications: A review

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Abstract. This is the first comprehensive review of the biological activity of hydrazone-transition metal complexes. Hydrazones gained much attention because of their antifungal, antibacterial, anticonvulsant, and analgesic, anti-inflammatory, antimalarial, antimicrobial, antituberculosis, anticancer, and antiviral activities. Additionally, some of the hydrazones were used in treatment of iron overload diseases. One application, which reflects the importance of hydrazone complexes, is their use in detection and determination of metals and some organic constituents in pharmaceutical formulations. This review will provide an overview of the biological, analytical and catalytic applications of this category of complexes.

Keywords: Hydrazones, Transition metal complexes, biological, analytical, catalytic application

1. Introduction

Hydrazones are versatile ligands and considered as azomethine compounds and described by the following general structure $R_2C=NNR_2$. They are distinguished from other members of this class (imines, oximes, etc.) by the presence of interlinked nitrogen atoms. The hydrazone group occurs in organic compounds and can be classified into two types a and b (Fig. 1). The compounds of type a are named hydrazones whereas compounds of type b are termed azines.

1.1. Nomenclature of hydrazones

Hydrazones are usually named after the carbonyl compounds from which they are derived. Thus, the reaction of benzaldehyde and phenylhydrazine gives benzaldehyde phenylhydrazone. For instance,

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the name originally used is benzalidenephenylhydrazone. Many 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 [1].

1.2. Preparation of hydrazones

Hydrazones, in general, are prepared by refluxing the stoichiometric amounts of the appropriate hydrazine and aldehyde or ketone dissolved in a suitable solvent. The resulting hydrazone usually crystallizes out on cooling [1].

1.3. Types of hydrazone ligands

The hydrazone ligands are classified according to the number of hydrazonic groups into monohydrazone which are characterized by the presence of one hydrazonic group (one interlinked nitrogen atom) (Fig. 2 (a)), dihydrazone ligands, which are characterized by the presence of two hydrazonic groups (two interlinked nitrogen atoms) (Fig. 2 (b)) and trihydrazone ligands, which are characterized by the presence of three hydrazonic groups (three interlinked nitrogen atoms) (Fig. 2 (c)). Hydrazone ligands can also be classified according to the number of functional groups involved in the complexation process into bidentate, tridentate, tetradentate, pentadentatehexadentate, octadentate, and nondentate.
1.4. Mode of bonding of hydrazone ligands with transition metals

The bonding of hydrazone ligands with transition metals may proceed according to one of the following paths. The first one leads to formation of complexes in which the hydrazone react with transition metal in the ketonic form (Fig. 3 (a)) whereas the second one hydrazone react in the enolic form (Fig. 3 (b)), 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 [2].

2. Applications of hydrazone and metal complexes

Hydrazone ligands and their metal complexes have been attracted many authors due to their wide applications in biological, pharmaceutical, analytical, catalytic and industrial fields.

2.1. Biological applications

Hydrazones and their coordination compounds play important roles in treatment of different diseases. The biological activity of hydrazone may be attributed to the formation of stable chelates with transition metals present in the cell, thus many vital enzymatic reaction cannot take place in the presence of hydrazone. On coordination, the activity of hydrazone increases. This enhancement in the activity may be rationalized on the basis that their structures mainly possess an additional C=N bond. Moreover, 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 during the coordination. This process, in turn, increases the lipophilic nature of the central metal atom, which favors its permeation more efficiently through the lipid layers of the microorganism, thus destroying them more aggressively. On the other hand, the inhibition of the growth of the microorganisms may be due to the inhibition of the glucose uptake, inhibition of RNA and/or protein synthesis.

2.1.1. Anti-tumour activity

Cancer is the growth of abnormal cells in the body in an uncontrolled manner. There are many different kinds of cancer. It can be developed in almost any organ or tissue, such as lung, colon, breast, skin, bones, or nerve tissues. Chemotherapy is the most common way of treatment of different kinds of malignant tumors. The need for new promising antitumor agents is increasing worldwide. Hydrazone ligands and their complexes have wide applications as anti-tumour, 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 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 [3]. The second mechanism depends on preventing uptake of iron from transferrin of the neoplastic cells. This activity may be ascribed to producing cytotoxic oxygen radicals [3].

Examples of hydrazones and their complexes which have antitumor activity are the pyridoxal isonicotinoyl hydrazone ligands and their iron(III), gallium(III) and copper(II) complexes. These class of ligands have distinct activity against certain mammary tumors and leukemias in mice. Since they have affinity and selectivity for iron in the cell [3]. The activity of these ligands are similar to the deferiprone drug (DFO) but it is orally effective, economical to synthesize and has high Fe chelation efficiency in a wide variety of biological models. Moreover, DFO does not have anti-proliferation property due to its poor efficiency for penetration of cell membranes and short half-life time in plasma [4].

An important example of effective anti-tumour hydrazone is isonicotinoyl hydrazone derivatives as 2-hydroxy-1-naphthaldehyde isonicotinoyl hydrazone and its iron complexes [5–7], and di-2-pyridyl ketone isonicotinoyl hydrazone and its analogues [8, 9]. These ligands have iron chelation efficiency, are anti-proliferative agents, and have potential for the treatment of cancer. Several isothiazolehydrazones found to be inactive against viruses, but showed cytotoxicity at micromolar concentration against the human lymphocytes that support HIV-1 growth. They possess anti-retroviral activity and anti-proliferation activities against panel of human cell lines such as hematological tumour, skin melanoma, lung squamous, carcinoma, breast adenocarcinoma, hepato cellular and prostate carcinoma [10]. Aroyl hydrazones of pyridoxal and salicylaldehyde hydrazone classes are potent inhibitors of DNA synthesis and cell growth in a number of human and rodent cell lines and shown in vitro lymphoproliferation [11, 12]. 2-Benzoxazolyl and 2-benzimidazolyl hydrazones derived from 2-acetyl pyridine inhibit cell proliferation and colon cancers [13]. Cyanacetic acid hydrazones of 3- and 4-acetylpyridine also act as potential anti-tumor and capable of inhibiting the replication of hepatitis-C virus [14]. Hydrazones derivatives of 2,6-dimethylimidazol[2,1-b]-[1,3,4]thiazole-5-carboxyhydrazide and the derivatives of hydrazine primidones have anti-cancer against lung, breast, renal, leukemia, colon, and ovarian cancers [15, 16]. Organotin(IV) complexes of 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxy benzoilhydrazone (Fig. 4) have been synthesized and structurally characterized. Structural analyses reveals that complexes show similar monomeric structure, in which the tin center is coordinated with the enolic tridentate ligand (L) in the ONO chelate mode and exhibits five-coordinated trigonal bipyramidal geometry. All compounds exhibit in vitro antitumor activity toward human colon cancer cells (HCT-8), lung cancer cells (AS549) and human promyelocyticfima leukemic cells (HL-60). The results indicate that both

![Fig. 4. Structures of tin complexes 2-hydroxy-1-naphthaldehyde 5-chloro-2-hydroxy benzoilhydrazone derivatives.](image-url)
alkyl groups bound with tin centers and the structural of organotin compounds have significant effect on their in-vitro antitumor activities [17].

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 anticancer. Recently, nine new SIH analogues (Fig. 5) derived from aromatic ketones with improved hydrolytic stability were developed. Their antiproliferative potential evaluation in MCF-7 breast adenocarcinoma and HL-60 promyelocytic leukemia cell lines. Seven of the tested substances showed selectivity greater than parent agent towards the latter cancer cell lines compared to non-cancerous H9c2 cardiomyoblast-derived cells [18].

A series of trisubstituted 3,5-triazine-2,4,6-tris(oxy)tris(benzene-4,1-diyl)tris(methanylylidene) tri(benzohydrazide) derivatives (Fig. 6) have in-vitro antiproliferative activity. The activities of these hydrazone ligands against human liver carcinoma (HepG2) and human cervix carcinoma (HeLa) cell lines showed that these compounds exhibited lower activity against HepG2 cell lines but reasonably moderate in-vitro cytotoxicity against HeLa cell lines [19].

Copper(II) complex of 2-hydroxy naphthaldehyde-2-pyridylhydrazone ligand (Fig. 7) was prepared and characterized. The cytotoxic activity of the ligand and its complex were measured in-vitro against the HeLa cells and showed that, the complex has cytotoxic effect with HeLa cells (LD50 = 4.97 μM) [20].

In-vitro antioxidant and cytotoxicity effect of three organoruthenium(II) carbonyl complexes with benzoic acid pyridine-2-ylmethylenedithiazone, benzoic acid (1-pyridin-2-yl-ethylidyne)hydrazide and benzoic acid (phenyl-pyridin-2-yl-methylene)hydrazide (Fig. 8) have been studied. The results showed that these metal complexes could serve as potential antioxidants where as the cytotoxicity experiments revealed that the complexes possess selective activity against both human cervical cancer cell line HeLa, human skin cancer cell line A431 with a preference to inhibit the proliferation of the later, thereby proved that the selected compounds could serve as promising candidates in anti-tumour applications. The significant result of this work showed that the activities of ruthenium organometallic hydrazone complexes increase withinserting substituents of the phenyl ring at the azomethine carbon of the ligand which led to an increased interaction with biomolecules such as free radicals and tumour cell lines than the rest of the complexes without such a phenyl ring in that position [21].
Fig. 6. Structures of tri-substituted 3,5-oxido-2,4,6-triyltris(oxytris(benzene-4,1-diylmethanylylidene))tri(benzoylhydrazide) derivatives (X = H, Br, Cl, F, OCH₃, CH₃, NO₂ or NH₂).

Fig. 7. Geometry of Cu(II) complex of 2-hydroxy naphthaldehyde-2-pyridyldihydrazone ligand.
Fig. 8. Structures of organoruthenium(II) carbonyl complexes of benzoic acid, (phenyl-2-ylmethylene)hydrazide, benzoic acid (1-pyridin-2-yl-ethylidene)hydrazide.

Fig. 9. Trans palladium complexes of benzaldehyde, 2,3-dimethoxybenzaldehyde, 4-chlorobenzaldehyde, and 4-hydroxybenzaldehyde (1,3-dimethyl-4-nitro-1H-pyrazol-5-yl) hydrazone.

The cytotoxic effect of trans palladium complexes of benzaldehyde (1,3-dimethyl-4-nitro-1H-pyrazol-5-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. 9) against the fast growing head and neck squamous carcinoma cells SQ20B and SCC-25 have been studied. The influence is dose dependent and varies by cell type. Some complexes had higher clonogenic cytotoxic effect than cisplatin when tested on SQ20B cell line [22].

Comparative cytotoxic activities of three 2-oxo-quinoline-3-carbaldehyde hydrazone ligands (Fig. 10) and their Cu(II) complexes were studied. The results showed that the three Cu(II) complexes exhibited more effective cytotoxic activities against HL60 cells and HeLa cells than corresponding ligands. Moreover, the most active compound is copper complex of the third ligand which may be explained on the basis of the difference in the terminal functional group (3,4-dimethylpyrrol heterocycle) relative to other group [23].

Anti-cancer activities of the N-(1-phenyl-3-methyl-4-propyl-pyrazolone-5)-salicylidene hydrazone (Fig. 11) and its copper(II) complex showed that both ligand and its copper complex are potent anti-
cancer agent against ovarian cancer cells (OVCAR3) and liver cancer cells (Hep-G2). The results of the effect on the resistant of Hep-G2 revealed that the copper complex was an active compound with lethal concentration (IC50) value 5.0 \( \mu \text{g/ml} \). An IC50 of 35.1 \( \mu \text{g/ml} \) found for ligand, which was not as good as the complex. This enhancement of activity of complex may indicate that the coordination improve the anti-cancer activity of the compound. Meanwhile, the anti-cancer activities of the tested compounds on Hep-G2 were better than that on OVCAR3. Besides, the efficacy on resisting to cancer cell of the copper complex is more powerful than that of the ligand, which shows that the coordination improves the anti-tumor activity of the compound [24].

Several biological activities of 6-acetyl-cyclohex-3-enecarboxylic acid [1-pyridin-2-yl-1-(pyridyn-2-ylamino)methylidene] hydrazide (Fig. 12) were examined in-vitro. They were suppression of phytohemagglutinin A (PHA)- induced proliferation of human peripheral blood mononuclear cells (PBMC) and their effects on tumor necrosis factor alpha (TNF-\( \alpha \)) and interleukin 6 (IL-6) production. The cytotoxic activity of Cu(II) complex was determined with respect to 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 [25].
The inhibitory effects of end-to-end thiocyanato-bridged zig-zag polymers of Cu(II), Co(II) and Ni(II) complexes of N’-(1-(pyridin-2-yl)ethylidene)acetohydrazide ligand (Fig. 13) on human cell cancer. Such as lung carcinoma cells (A549 cells), human colorectal carcinoma cells (COLO 205 cells and HT-29 cells), and human hepatocellular carcinoma cells (PLC5 cells) revealed that the Cu(II) complex had the strongest population growth inhibition of human colorectal carcinoma cells (COLO 205 cells and HT-29 cells). Moreover, the 50% inhibitory concentration (IC50) showed the highest activity for this complex with IC50 value of 22.7 ± 0.5 μM (COLO 205 cells) and 24.7 ± 2.5 μM (HT-29 cells), respectively. The Cu(II) complex could be further tested by an in-vivo model to justify if it is effective for prevention of human cancer and showed the highest inhibitory activity in human colorectal carcinoma cells (COLO 205 cells and HT-29 cells) [26].

Hydrazones also play an important role in improving the anti-tumor selectivity and toxicity profile of anti-tumour agents by forming drug carrier systems employing suitable carrier proteins [27].

2.1.2. Anti-mycobacterial activity

Tuberculosis (TB) is one of the most common infectious diseases known to population. Nearly one-third of the world’s population is infected with *Mycobacterium tuberculosis* with new infections occurring at a rate of about one per second [28]. In that respect the World Health Organization (WHO)
estimates that about 30 million persons will be infected within the next 20 years. Every year, approximately 8 million of those infected people develop active TB, and almost 2 million of them die from the disease [29–32]. The distribution of tuberculosis is not uniform across the globe: about 80% of the population in many Asian and African countries test positive in tuberculin tests, while only 5–10% of the United States population tests positive [33]. So that developing of new drugs for treatments of these diseases is considered as a challenge to scientists. One of the most important compounds that play a significant part in therapy of these diseases is the hydrazones [29–32]. For example, isonicotinoyl hydrazone derivatives and their nickel and copper complexes have anti-mycobacterial activity in-vitro and/or in-vivo against M. tuberculosis H37 Rv [34–37]. Whereas the copper complexes of isonicotinoyl hydrazide is the most effective first-line antitubercular compound used in the DOTS program advocated by WHO [38–40]. The second example is the diclofenac acid hydrazones derivatives, which were found to be more active than parent drug diclofenac. The most effective hydrazones is derived from 1-cyclopropyl-6-fluoro-8-methoxy-7-[[N4-(2-(2-(2,6-dichlorophenylamino) phenyl) acetyl)-3-methyl]-N1-piperazinyl]-4-oxo-1,4-dihydro-3-quinoline carboxylic acid which is more active than fluoroquinolones, ciprofloxacin or gatifloxacin [41].

Anti-microbial and anti-tubercular activities of trigonal bipyramidal and tetrahedral Co(II), Ni(II), Cu(II) and Zn(II) complexes of N'-(1-(2-oxo-2H-chromen-3-yl)ethylidene)isonicotinohydrazide screened using serial broth dilution method and Minimum Inhibitory Concentration (MIC). Zn(II) complex has shown significant antifungal activity with an MIC of 6.25 μg/mL while Cu(II) complex is noticeable for antibacterial activity at the same concentration. Anti-TB activity of the ligand has enhanced on complexation with Co(II) and Ni(II) ions [42].

Anti-tubercular and anti-microbial activities of synthesised and characterized distorted square planar transition metal complexes of salicylhydrazone of anthranilhydrazide investigated. Metal complexes in general have exhibited better antibacterial and antifungal activity than the free ligand and in few cases better than the standard used. Among the bacterial strains used, the complexes are highly potent against Gram-positive strains compared to Gram-negative. Anti-tubercular activity exhibited by the Co(II) complex is comparable with the standard used [43].

Series of benzofuran-3-carbohydrazide and its analogs screened for in-vitro anti-tuberculosis (anti-TB) activity against M. tuberculosis H37Rv strains by using resazurin assay utilizing microtiterplate method (REMA). These compounds also showed good anti-fungal activity against Candida albicans. The synthesized N-benzylidene benzofuran-3-carbohydrazide and its analogs show promising activity against M. tuberculosis. The inhibition of M. tuberculosis at concentrations as low as 2 and 8 μg/mL indicates that these compounds can act as leads for development of newer anti-TB compounds [44].

Hydrazine derived from 3-(4-chlorophenyl)-4-substituted pyrazoles have been synthesised and were tested for anti-tubercular activity in-vitro against M. tuberculosis H37Rv strain, anti-fungal activity against a pathogenic strain of fungi and antibacterial activity against gram positive and gram-negative organisms. Among them tested, many compounds showed good to excellent antimicrobial and antitubercular activity. The results suggest that hydrazones, 2-azetidinones and 4-thiazolidinones bearing a core pyrazole scaffold would be potent antimicrobial and antitubercular agents [45].

Anti-tubercular activities against M. tuberculosis H37Rv of synthetic five coordinate square-pyramidal copper(II) complexes of 2-(2-benzoylhydrazono), 2-(2-(2-hydroxy benzoyl) hydrazono)-2-(2-isonicotinyl hydrazono) and 2-(2-nicotinoyl hydrazono) propanone acid (Fig. 15) were investigated. The result of antibacterial activity against M. tuberculosis H37Rv strain indicates percent inhibition ranging from 6% to 92%. Compounds containing isonicotinoyl group are the most active among the group [46].
Fig. 14. Structure representation of (a) Trigonal bipyramidal and (b) tetrahedral Co(II), Ni(II), Cu(II) and Zn(II) complexes of N’-(1-(2-oxo-2H-chromen-3-yl)ethylidene)isonicotinohydrazide.

Fig. 15. Structure of square-pyramidal Cu(II) complexes of (a) 2-(2-benzoylhydrazono)-, (b) 2-(2-hydroxy benzoylhydrazone), (c) 2-(2-isonicotinoyl hydrazono) and (d) 2-(2-nicotinoyl hydrazono) propanoic acid.

Fig. 16. Metal conjugation of the carboxamidrazole ligands with copper and iron ions.
Some metal ions are essential for biological functions, other metal ions are poisons to our bodies and a large number of them and their complexes are used as drugs or diagnostic agents for treatment of a variety of diseases [45]. Metal conjugation of the carboxamidrazone ligands with copper and iron ions results in significant enhancement in their anti tubercular activities against *M. tuberculosis*. Copper was more active rather than iron ion. It may be due to the increase in liposolubilities of metal conjugates contribute to their easy permeability through the mycobacterial cell wall. On the other hand, the carboxamidrazone moiety may interfere with the copper transport by chaperone proteins through up regulation of oxidative stress [47].

2.1.3. Anti-microbial activity

Hydrazone ligands and their complexes act as anti-microbial agents against gram negative, gram positive bacteria, fungi and yeast [48–50]. The biological activities of the metal complexes are governed by the following factors: (i) the chelate effect of the ligands, (ii) the nature of the donor atoms, (iii) the total charge on the complex ion, (iv) the nature of the metal ion, (v) the nature of the counter ions that neutralize the complex, and (vi) the geometrical structure of the complex [51]. Furthermore, chelation reduces the polarity of the metal ion because of partial sharing of its positive charge with the donor groups and possibly the \( \pi \)-electron delocalization within the completely chelate ring system that is formed during coordina-

These factors increase the lipophilic nature of the central metal atom and hence increasing the hydrophobic character and liposolubility of the molecule favoring its permeation through the lipid layer of the bacterial membrane. This enhances the rate of uptake/entrance and thus the anti-bacterial activity of the testing compounds. The metal complexes of some hydrazones showed higher activity than the parent hydrazones such as gadolinium complexes of N-(2-propionic acid) salicyloyl hydrazone and manganese(III), cobalt(III), iron(III) and chromium(III) complexes of benzyl \( \alpha \)-monooxide substituted benzoyl hydrazones [53, 54]. Sometimes the activity of the complexes is less than the parent ligand such as hafnium(IV) complexes of acetyl ferrocenyl hydrazone derivatives. Some ligands showed higher activity towards fungi whereas the complexes showed higher toxicity toward some types of bacteria than the parent ligands [55]. The anti-microbial activity of some hydrazone ligands and their corresponding complexes may be close or equal to the standard drug which used as reference, such as the thiazolyl...
hydrazone derivatives [56], hydrazone of 4-fluorobenzoic acid hydrazide and 3-acetyl-2,5-disubstituted-1,3,4-oxidazolines [57], diflunisal hydrazone-hydrazone [31] as well as copper(II) and cadmium(II) complexes of amino acid (N-benzoyl) hydrazide and amino acid (N-nicotinoyl) hydrazide [58] have activities are equal or close to fluconazole, ceftriaxone, cefepime and ampiciline drugs respectively. The type of the metal has a pronounced effect on the anti-microbial activity of the complexes, for example the activity of copper(II), nickel(II), cobalt(II) and zinc(II) complexes of 3-salicylidenehydrazono-2-indolinone was found to be decreased in the order Zn(II)>Cu(II)>Co(II)>Ni(II) [59]. 4-(((3-hydroxy naphthalene-2-yl)methylene)amino)-6-methyl-3-thioxo-3,4-dihydro-1,2,4-triazin-5(2H)-one (Fig. 17) and its Cu(II), Ni(II), Co(II), Zn(II), Cd(II), VO(IV) and UO2(VI) complexes. Antimicrobial screening of the free ligand and its complexes indicated that metal complexes have more activity than their ligands against the tested bacteria [60].

The anti-bacterial activities of Nickel(II), palladium(II), platinum(II) complexes of salicylaldehyde methanesulfonylhydrazone, 2-hydroxyacetophenonemethanesulfonyl hydrazone and 2-hydroxy-3-ethoxybenzaldehydemethanesulfonylhydrazone have been determined in vitro against gram positive bacteria; S. aureus ATCC 25923, Bacillus cereus RSKK 709, and gram negative bacteria; Pseudomonos aeruginosa ATCC 27853, E. coli ATCC 35268 by paper disc diffusion and microdilution broth methods. The biological activity screening showed that metal complexes have more activity than their ligands against the tested bacteria [61].

The anti-microbial activity of copper(II), nickel(II), platinum(II) and palladium(II) complexes with 2-hydroxy-1-naphthaldehyde-N-methylpropanesulfonylhydrazone compounds (Fig. 19) was screened against three Gram-positive B. subtilis, S. aureus and B. cereus and three Gram-negative bacteria E. coli, P. aeruginosa, Y. enterocolitica. The results of anti-microbial studies indicate that Pt(II) and Pd(II) complexes showed the most activity against all bacteria [62].
Fig. 19. Structure of Cu(II), Ni(II), Pt(II) and Pd(II) complexes of 2-hydroxy-1-naphthaldehyde-N-methyl propane sulfonyl hydrazone compounds.

Fig. 20. Structure representation of Ni(II), Co(II) and Cu(II) complexes of 2-((2-phthalazin-1-yl)hydrazono)methyl)phenol ligand

2-((2-phthalazin-1-yl)hydrazono)methyl)phenol ligand and its Ni(II), Co(II) and Cu(II) complexes (Fig. 20) were screened for their anti-microbial activities using the disc diffusion method against Gram positive (S. aureus, B. subtilis) and two Gram negative (E. coli, P. aeruginosa) bacteria at concentration of 20 mg/ml in DMSO as solvent and fungi: Aspergillus flavus and C. albicans using amphotericin as standard material. The hydrazone ligand is biologically active and its activity may be arise from the hydroxyl groups which may play an important role in the anti-bacterial activity, as well as the presence of imine group which imports in elucidating the mechanism of transformation reaction in biological systems. The synthesized compounds were found to be more toxic compared with their parent hydrazone ligand against them same microorganism and under the identical experimental conditions. The increase in biological activity of the metal chelates may be due to the effect of the metal ion on the normal cell process [63].
The square planar Ni(II) and Cu(II) and tetragonal Co(II) complexes derived from benzil bis(carbonylhydrazine) (Fig. 21) were structurally and pharmaceutically studied. Anti-fungal activity of these compounds was examined against the opportunistic pathogens, i.e., Alternaria brassicae, Aspergillus niger and Fusarium oxysporum and led to the conclusion that the free ligand has growth inhibition capacity against the tested fungal strains and this efficacy is positively affected by the complex formation [64].

Hydrazone complexes of Co(II), Ni(II), Cu(II), Pd(II), Cd(II), Zn(II) and U(VI)O$_2$ with 3-(2-(1-(2-hydroxyphenyl)hydrazinyl)-3-oxo-N-(thiazol-2-yl)propanamide (Fig. 22) have been synthesized. The ligand and its complexes have been screened for their antibacterial (E. coli and Clostridium sp.) and antifungal activities (Aspergillus sp. and Stemphylium sp.) by MIC method. From the results, the Ni(II), Co(II), Cu(II), Cd(II), Zn(II), Pd(II) and U(VI)O$_2$ metal complexes shown potential antimicrobial activities against all the bacterial and fungal strains. Amongst all the compounds tested, Pd complex demonstrated the most potent antibacterial and antifungal activity (90%) at the higher concentration of 1.5 mg/ml. In general, all the metal complexes possess higher antimicrobial activity than the ligand. This enhancement of activity may be due to the change in structure due to coordination and chelating tends to make metal complexes act as more powerful and potent bacteriostatic agents [65].

2.1.4. Anti-malarial

Tropical diseases constitute a major world health problem and offer an extraordinary challenge for drug discovery [66, 67]. Malaria is the most widespread, and one of the most severe, tropical parasitic diseases and it continues to be a major cause of mortality and morbidity in poor regions in the developing world. It is endemic in most of the tropical regions of the planet causing 1–3 million deaths annually, mostly children under 5 years. The disease is caused by protozoa of the genus Plasmodium and it is transmitted through the bite of female Anopheles mosquito. Mortality from malaria has doubled in the last 20 years mainly due to the development of resistance of malarial parasites to anti-malarial drugs, particularly to the first-line
drug chloroquine [68, 69]. Several organic compounds have been used as antimalarial drugs, including quinine, chloroquine, hydroxychloroquine, mefloquine, primaquine, proguanil, cotrimoxazole, doxycycline, sulfadoxine, pyrimethamine, atovaquone, lumefantrine, artesunate and amodiaquine.

Some hydrazones ligands showed a pronounced anti-malarial activity more than the desferrioxamine drug. Acylhydrazone derivatives (Fig. 23) showed the ability to inhibit the growth of a chloroquine resistant strain of *Plasmodium falciparum*. Some of these new compounds are significantly more active than desferrioxamine (DFO) [70]. N1-aryliden-N2-quinolyl- and N2-acrydinylhydrazones derivatives were synthesized and tested for their anti-malarial properties. These compounds showed remarkable anti-plasmodial activity *in vitro* especially against chloroquine-resistant strains. This potent biological activity makes them promising lead structures for the development of new antimalarial drugs [71].

The anti-malarial activity of novel aroylhydrazones (Fig. 24) and thiosemicarbazones Fe chelators investigated using the chloroquine-sensitive, 3D7, and chloroquine-resistant, 7G8, strains of *Plasmodium falciparum in vitro*. The new ligands were significantly more active in both strains than the Fe chelator was in widespread clinical use, desferrioxamine (DFO). The most effective chelators examined were 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone and 2-hydroxy-1-naphthylaldehyde-4-phenyl-3-thiosemicarbazone. These result indicated that, these class of lipophilic chelators might have potential as useful agents for the treatment of malaria [72].
2.1.5. Anti-convulsant

Epilepsy is most common neurological disorder, second to stroke. The number of drugs useful for the treatment of epilepsy is remarkably small. New epileptic drugs have been developed that may constitute novel and effective therapies for epilepsies [73]. It was found that both 2-oxobenzoxazoline and 2-oxobenzothiazoline hydrazone derivatives exhibited remarkable anticonvulsant activity. 5-chloro-2(3H)-benzoxazolinone-3-acetyl-2-(o-methoxybenzaldehyde) hydrazone, 5-chloro-2(3H)-benzoxazolinone-3-acetyl-2-(o-methylbenzaldehyde) hydrazone, 5-chloro-2(3H)-benzoxazolinone-3-acetyl-2-(p-methyl-benzaldehyde) hydrazone, and 5-chloro-2(3H)-benzoxazolinone-3-acetyl-2-(p-nitrobenzaldehyde) hydrazone were significantly active than phenytoin (a commercial antiepileptic drug) in the tests [73, 74].

In general, the biological results revealed that, the acetylhydrazones provided a good protection against convulsions while the oxamoylhydrazones were significantly less active [75, 76]. Fifteen new hydrazones of (2-oxobenzoxazoline-3-yl)acetohydrazide (Fig. 25) were synthesised and their antiepileptic activity was tested in scPTZ test. The 4-fluoro derivative was found to be more active than the others [75, 77].

GABA hydrazones (Fig. 26) were designed and synthesized and evaluated for their anticonvulsant properties in different animal models of epilepsy such as MES, scPTZ, subcutaneous strychine (ScSTY) and intraperitoneal picrotoxin (IpPIC) induced seizure tests. Some of the compounds were effective in these models [75, 78].
The hydrazones along with semicarbazones and thiosemicarbazones which are derived from pyridyl ketones have been found to be nonneurotoxic antiepileptic drugs and are potent orally active. Their use has been proposed in the treatment of convulsive disorders such as epilepsy, in the treatment of stroke and other neurological disorders such as Parkinson’s disease [79]. They act as excitatory amino acid antagonists and inhibitors of L-glutamate neurotransmission. These compounds afford protection in the maximal electroshock seizure (MES) model in both mice and rats, by either route, intraperitoneal and oral. The study represents them as glutamate antagonists. Hydrazones in addition to Schiff and Mannich bases of isatin were evaluated for anticonvulsant activity by maximal electroshock method (MES) and metrazol-induced convulsions (MET) at different dose levels [80]. Neurotoxicity of the compounds was also noticed at the same dose levels. Eight compounds of the series denoted significant anticonvulsant activity at 30 mg/kg dose level. 3-(4-chloro-phenylimino)-5-methyl-1,3-dihydro-indol-2-one showed to be the most potent compound of the series with 87% protection at 100 mg/kg and an ED(50) of 53.61 mg/kg (MET).

2.1.6. Antiviral activity
HIV infection and AIDS represent one of the first diseases for which the discovery of drugs was performed entirely via a rational drug design approach. Current treatment regimens are based on the use of two or more drugs that belong to group of inhibitors termed as highly active antiretroviral therapy (HAART). Some thiourea compounds were reported to be non-nucleoside inhibitors (NNIs) of the reverse transcriptase (RT) enzyme of the human immunodeficiency virus (HIV). Hydrazones have been reported to be the potent inhibitors of ribonucleotide reductase activity. N-Arylaminoacetylhydrazones and O-acetylated derivatives of sugar N-arylaminoacetyl hydrazones were synthesized and evaluated for their antiviral activity against Herpes simplex virus-1 (HSV-1) and hepatitis-A virus (HAV). Some compounds revealed the highest antiviral activity against HAV-27 and HSV-1 [75, 81].

2.2. Pharmaceutical applications
2.2.1. Anti-inflammatory activity
Hydrazones and their complexes showed an activity as anti-inflammatory and analgesic activity. The tellurium complexes of phenyl and acetyl hydrazide have mild anti-inflammatory activity compared to
Fig. 27. Geometries of metal complexes of pyridine-2-ethyl-(3-carboxylideneamino)-3-(2-phenyl)-1,2-dihydroquinazolin-4(3H)-one.

Fig. 28. Structure of 6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted benzal) hydrazone derivatives.

R₁ = H, CH₃ or OCH₃; R = 3-ClC₆H₄, 4ClC₆H₄, 2C₂H₅N

phenylbutazone [82]. The hydrazone derived from sulphonylhydrazide and 2-acetyl-, 4-acetylpyridine or indol aldehyde have anti-inflammatory and analgesic activity equals or close to that of aspirin [83]. inflammatory and analgesic activity of Cu(II), Ni(II), Zn(II), Mn(II), Co(II), Cd(II) complexes of pyridine-2-ethyl-(3-carboxylideneamino)-3-(2-phenyl)-1,2-dihydroquinazolin-4(3H)-one (Fig. 27) showed that the synthesized complexes were found to be more active than free ligand [84].

6-substituted-3(2H)-pyridazinone-2-acetyl-2-(p-substituted benzal) hydrazone derivatives (Fig. 28) were synthesized as analgesic and anti-inflammatory agents. Compounds in which R₁ is hydrogen were exhibited more potent analgesic activity than ASA. Also these derivatives demonstrated anti-inflammatory activity as well as standard compound indomethacin. Side effects of the compounds were examined on gastric mucosa. None of the compounds showed gastric ulcerogenic effect compared with reference nonsteroidal anti-inflammatory drugs (NSAIDs) [85].

2.2.2. Hydrazones in treatment of iron overload diseases

All living cells, whether prokaryotic or eukaryotic, need a supply of iron for reduction of oxygen (respiration), reduction of carbon dioxide (photosynthesis), reduction of dinitrogen or other fundamental biological processes. Excessive amounts of iron may become very toxic to the human body and, eventually,
is fatal for vital cell structure. Iron overload may be defined as an excess in total body iron stores. The normal iron concentration in the human body ranges between 40 and 50 mg/kg of body weight. Most of this iron is present in hemoglobin and in myoglobin. Only a few hundred milligrams of iron are stored in enzymes such as cytochrome c oxidase that, however, are essential to human life. Humans have very limited capacity for excretion of excess iron; in particular, they lack any effective means to protect cells and tissues against iron overload. Consequently, any increase in iron intake may cause in a short time an increase in body iron stores. Iron balance is normally regulated by controlling iron absorption in the proximal small intestine. In the category of patients affected by chronic anaemia, who need regular blood transfusions in order to sustain their normal growth and development during childhood, β-thalassemia major (BTM) constitutes one of the most serious public health problems in the Mediterranean area, in the Middle East, in the Indian subcontinent, in Southeast Asia and, in particular, in the island of Sardinia. BTM is an autosomal recessive disease, characterized by absent or decreased synthesis of the β-globin gene. The number of thalassemic children requiring regular blood transfusions and a program of iron chelation has been estimated to be 100 000 world-wide. Although desferrioxamine has been demonstrated to be
a safe drug when administered in the presence of an elevated body iron burden, serious complications may arise because of long-term chelation, mainly in young patients with low body iron stores. At the basis of desferrioxamine, toxicity is the fact that, like other chelators, desferrioxamine is not completely iron-selective. It may due to depletion of other trace elements, such as zinc, copper, manganese, cobalt; a direct toxic effect of free desferrioxamine; depletion of iron from critical iron-dependent enzymes, such as cytochrome c oxidase. So chemist need to develop a new selective iron chelator [86]. One of the most effective compounds is hydrazone chelators such as pyridoxal isonicotinoyl hydrazone, salicylaldehyde benzoyl hydrazone derivatives which are effective iron chelators in vivo and in vitro, and are of interest for the treatment of secondary iron overload (Fig. 29) [87–90].

Desferrioxamine (DFO), is expensive and cumbersome since the drug requires long subcutaneous infusions and it is not orally active. So chelator, 2-pyridylcarboxaldehyde, 2- thiophenecarboxyl hydrazone derivatives (Fig. 30) were designed and shown to have high Fe chelation efficacy in vitro [91, 92].

Di-2-pyridyl ketone isonicotinoyl hydrazone and a range of its analogues comprise a series of monobasic acids that are capable of binding iron (Fe) as tridentate (N,N,O) ligands (Fig. 31) [93].
Fig. 33. Structure of bis(2-hydroxybenzylidene)oxalohydrazide.

The diarylhydrazone (N,N-bis-picolinoyl, N-4-aminobenzoyl-N-picolinoyl, N-3-bromo-benzoyl-N-picolinoyl and N-(4-bromobenzoyl)-N-picolinoyl hydrazone) are considered as a good chelator for iron(III) so that they act as orally effective drugs for treatment of iron overload or genetic diseases β-thalassemia. They have been demonstrated a greater iron chelation efficacy than deferiprone (DFO) [94, 95].

2.3. Catalytic applications

Coordination chemistry of hydrazones has been a subject of competitive research since they exhibit a wide range of catalytic activities in some polymerization as well as oxidation processes. For example, the palladium complexes of 2-acetylpyridine or 2-formylpyridine benzoyl hydrazones as well as titanium complexes of hydrazone catalyze the polymerization of phenylacetylene [96] and olefine [97] respectively. The nickel(II) complexes of benzoyl hydrazone derivatives catalyze the oligmerization of ethylene with methyaluminoxane [98]. Manganese(II), cobalt(II), nickel(II) and copper(II) complexes of bis(salicylaldiminato) hydrazone catalyze the oxidation of cyclohexene with tert-butylhydroperoxide [99]. Another example is the catalytic activity of copper(II) complexes of picolyl hydrazone derivatives toward ascorbic oxidation of vitamin C [100].

The catalytic potential of oxovanadium(V) complexes of tridentate hydrazone ligands, 3-hydroxy-N-(2-hydroxy-3-methoxybenzylidene)-2-naphthohydrazide, 3-hydroxy-N-(2-hydroxy benzylidene)-2-naphthohydrazide and N-(5-bromo-2-hydroxybenzylidene)-3-hydroxy-2-naphthohydrazide (Fig. 32) has been tested for the oxidation of cyclooctene using H2O2 as the terminal oxidant. The complex of 3-hydroxy-N-(2-hydroxy benzylidene)-2-naphthohydrazide showed the most powerful catalytic activity in oxidation of various terminal, cyclic and phenyl substituted olefins. Excellent conversions have been obtained for the oxidation of cyclic and bicyclic olefins [101].

The catalytic potential of dinuclear vanadium, copper, manganese and titanium complexes of dichelating ligands, bis(2-hydroxybenzylidene)oxalo- and bis(2-hydroxybenzylidene)terephthalohydrazide (Fig. 33) were evaluated for oxidation of hydrocarbons including cycloalkanes, cyclic alkanes and benzylalcohol using H2O2 as terminal oxidant. Of the studied aroylhydrazone complexes, titanium complex of bis(2-hydroxy benzylidene)oxalohydrazide showed the best selectivity and activity as catalyst (Fig. 34) [102].

Molybdenum complexes of salicylidene 2-picoloyl hydrazone ligand (Fig. 35) have been synthesized and characterized. The complexes were evaluated for epoxidation catalysis with tert-butyl hydroperoxide (tert-BuOOH). The molybdenum complex exhibited high catalytic activity for the epoxidation of olefins, whereas the peroxy analogue is inert to reaction with olefins, thus ruling out the peroxide compound as the intermediate responsible in the molybdenum complex catalyzed epoxidation with tert-BuOOH [103].
Fig. 34. Structure of bis(2-hydroxybenzylidene)terephthalohydrazide.

Fig. 35. Geometry of molybdenum complexes of salicylidene 2-picoloyl hydrazone ligand.

Fig. 36. Structure of distorted square-planar palladium complexes of substituted pyridoxal hydrazone ligands.

\[ R = \text{H, Cl, Br, OCH}_3, \text{NO}_2 \]

Fig. 36. Structure of distorted square-planar palladium complexes of substituted pyridoxal hydrazone ligands.
The synthetic distorted square-planar palladium complexes of substituted pyridoxal hydrazone ligands [36]. The catalytic efficiency of the one of the palladium(II) hydrazone complexes was determined in Suzuki Miyaura cross-coupling reaction and was found to be excellent. This facile, mild and general protocol represents, to a certain extent, a new advance in Suzuki Miyaura cross-coupling reactions (aryl bromides with phenylboronic acid) [104].

The aquasoluble Fe(III) complexes of 5-chloro-3-(2-(4,4-dimethyl-2,6-dioxocyclohexylidene) hydrazinyl)-2-hydroxy-benzenesulfonic acid and 3-(2-(2,4-dioxopentan-3-ylidene)hydrazinyl)-2-hydroxy-5-nitrobenzenesulfonic acid, were synthesized and fully characterized including by X-ray crystal structural analysis. In the channels of the water-soluble 3D networks of 3 and 4, the uncoordinated water molecules are held by oxygen atoms of the carbonyl and sulfonyl groups, and by the water ligands. The Fe(III) coordination environment resembles that in the active sites of some mononuclear non-heme iron-containing enzymes. The complexes show a high catalytic activity for the peroxidative oxidation (with aqueous H2O2) of C5–C8 cycloalkanes to the corresponding alcohols and ketones under mild conditions [105].

The pseudo-octahedral nickel complexes of N-(1-(thiophen-2-yl)ethylidene) benzohydrazide ligand (Fig. 37) is reported and discussed. The catalytic activity of this complex for the oligomerization of ethylene indicate that it provide ethylene dimers and trimers as primary products with a turnover frequency (TOF) of 31200 mol of C2H4 per mol. of Ni and per hour [106].

2.4. Analytical applications

In the field of analytical chemistry, hydrazones were used in detection, determination and isolation of compounds containing carbonyl group. Recently, they have been extensively used in detection and determination of several metals [107], such as the micro determination of gold by N-cyanoacetylacetaldelde hydrazone [108], lanthanides by aryl hydrazones [109], molybdenum by 2,4-dihydroxy acetophenone benzoyle hydrazone [110]. They are used in sensitive determination of uramiium(VI) by o-hydroxy-1-naphthaldehyde isonicotinoyl hydrazone[111] or o-hydroxy propophenate isonicotinoyl hydrazone [112]. Hydrazones are also used in the spectrophotometric determination of
titanium in mineral or rock using 1,2 cyclohexanedione bis-benzoyl hydrazone [113], and determination of copper and iron in ores, alloys and in their mixture in pharmaceutical formulation by biacetyl(2-pyridyl) hydrazone thiourea-carbazone [114]. Hydrazones are also used in photometric determination of sub-nanograms level of cobalt(II), chromium(III) Iron(III) by oxidative coupling reaction of 3-methyl-2-benzothiazolinone hydrazone with N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxaniline or N,N-dimethylaniline respectively [115–117]. 2,4-Dihydroxybenz-aldehyde isonicotinoyl hydrazone is used in direct, rapid and derivative spectrophotometric determination of thorium, titanium and zinc in potable water or pharmaceutical formulations [118–120]. 3.5-Dimethyl-4-hydroxy-2-aminoaceto-phenone isonicotinoyl hydrazone is used in facile flow injection spectrophotometric detection of gold(III) in water or pharmaceutical sample [121]. Substituted quinolyl and benzothiazolyl hydrazones used as metallochromic indicators in the EDTA titration of copper(II) [122]. Complexes of hydrazones are used also in radiometric determination of metals such as determination of copper and iron by labeled cobalt (60Co) complexes of α-hydroxybenzaldehyde isonicotinoyl hydrazone [123, 124]. Some hydrazone ligands are used in the extraction of metals, such as substituted 2-thiophenealdehyde-2-benzothiazolyl hydrazones, which used as analytical reagent for extraction of trace of copper [125]. 2,2-pyridyl mono-2-quinolyl hydrazone are used in liquid-liquid extraction of copper(II), nickel(II) and cobalt(II) [126]. Benzilimono-(2-quinolyl) hydrazone and dicetyl bis-(2-pyridyl) hydrazone are used in the extraction of copper(II), nickel(II) and cobalt(II) [127–129]. It is used in the high performance chromatographic separations of some complexes [130]. Poly acrolein isonicotinic acid hydrazone resin was used for separation and concentration of palladium and platinum in the road dust [131]. The hydrazone derivatives of dialdehyde cellulose were used in sewage wastewater treatment. They act as good and active coagulants for removing the total suspended solids (TSS), chlorine, iron and chromium [132].

2.4.1. Spectrophotometric determination of some active species in pharmaceutical formulations

Some hydrazones are considered as analytical reagents used in spectrophotometric determination of some organic constituents in pharmaceutical formulations such as spectrophotometric determination of acetaminophen and phenobarbital [133], acyclovir [134], antidepressant [135], nortriptyline hydrochloride [136], propranolol [137], labetalol hydrochloride [138] and clozapine [139] using 3-methylbenzothiazolin-2-one-hydrazone. In that respect 2-hydroxybenzaldehyde hydrazone and p-diethylaminosalicylaldehyde hydrazone are used in determination of iron(II) in antiamaenic formulations [140, 141].Nimesulide either in pure form or in pharmaceutical formulations is determined using of 3-methyl-2-benzothiazolinone hydrazone hydrochloride in presence of FeCl₃ [142].

3. Conclusions

Development of new metal complexes suitable for therapeutic, analytical and catalytic applications is a recent research priority. One of the most significant compounds category is the hydrazone ligands and its metal complexes, which represent a resource of probabilities for new design due to its peerless structure of hydrazone itself and its mode 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, anti-convulsant and in treatment of iron overload diseases due to their selective chelating ability to iron or other transition metal necessary for enzymatic reaction in the cell. In addition to hydrazone, metal complexes of it are also strongly required because of the coordination reduces the polarity of the metal ion mainly because of the partial sharing of its positive charge with the donor atom within the
chelate ring system, which formed during the 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 more aggressively. However, hydrazone and its complexes exhibit a wide range of catalytic activities in some polymerization as well as oxidation processes and are used in detection, determination and isolation of compounds containing carbonyl group, metal and as analytical reagents used in spectrophotometric determination of some species in pharmaceutical formulations.

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