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Synthesis, Characterization and Biological Activity of Hydrazones and Their Copper(II) Complexes †

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Abstract: The fundamental importance of copper as a redox-active metal essential to the functioning of several metabolic enzymes provides a wide range of its biological activity pathways. Copper(II) coordination compounds are known to exhibit potent antiproliferative, antibacterial, nuclease, anti-inflammatory and antimycobacterial activities. Hydrazones are organic ligands commonly used for complexation with copper(II) that possess antibacterial, antiviral and antifungal properties. Copper–ligand interaction might facilitate charge delocalization and increase net hydrophobicity of the system, resulting in its enhanced pharmacological activity. Coordination compounds of Cu(II) with 4,6-di-*tert*-butyl-2,3-dihydroxybenzaldehyde derived hydrazone, nitrofurantoin and ftivazide have been synthesized, characterized by means of elemental and XRD analysis, FT-IR, UV-Vis and NMR spectroscopy and tested for antibacterial activity in vitro on Gram-positive and Gram-negative bacteria.

Keywords: hydrazones; copper(II) complexes; antibacterial activity

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1. Introduction

Copper is an endogenous element that normally exists in two redox states—Cu(I) and Cu(II)—and readily forms coordination compounds with a wide variety of organic ligands. The pharmacological effect of copper(II) complexes with biologically active ligands can be either increased or altered due to the copper–ligand binding. In this review, the therapeutic action of various Cu(II) coordination compounds is summarized, including drug-based copper(II) complexes with commonly used antimicrobials, antibiotics and non-steroidal anti-inflammatory drugs. The physico-chemical properties and biological activity of copper(II) complexes obtained with nitrofurantoin, ftivazide and 4,6-di-*tert*-butyl-2,3-dihydroxybenzaldehyde derived hydrazones as antibacterial agents are discussed.

2. Medicinal Chemistry of Copper(II) Complexes

2.1. Physiological Role of Copper

Copper proves to be essential for the functioning of such enzymes as Cu/Zn superoxide dismutase, cytochrome *c* oxidase, monoamine oxidases, ferroxidases and metallothioneins [1]. This explains the indispensability of copper for the realization of cellular respiration, antioxidant defense mechanisms, hemoglobin and catecholamine biosynthesis, protein cross-linking and other biochemical processes. Hence, there are several biological pathways regulating the intracellular levels of copper, specifically the delivery of copper to the mitochondria, endosomes, lysosomes and golgi-apparatus by transporters CTR1, CTR2 and ATP7A/B and chaperones ATOX1 and COX17 [2]. This makes copper-based therapeutics by far more biocompatible than commonly known platinum-based antitumor agents, such as carboplatin or oxaliplatin.

2.2. Biological Activity of Copper(II) Complexes

The complexation of copper(II) with biologically active organic compounds offers the opportunity of enhancing the efficacy of antibacterial, antifungal, antiviral and anti-inflammatory agents by evading multidrug resistance of several pathogens. This might be due to the neutralization of an electrically charged metal ion, as well as the interaction with hydrogen bond acceptor atoms that are present in the initial chemical structure of ligands [3]. Copper(II) tends to form coordination compounds with organic ligands that possess N, O and S binding moieties. Such changes induce a considerable increase in the lipophilicity of the resulting molecule, facilitate its transport across the cell membrane and therefore enhance its biological activity, according to the Meyer–Overton theory. Moreover, the formation of a coordination compound significantly reduces the toxicity of both the ligand and the metal ion.

Copper(II) complexes are capable of either interacting directly with cellular enzymes or inhibiting DNA synthesis as a result of the damage caused by the intercalation of coordination compounds between its nucleobases, which suppresses DNA replication [4]. Thus, such compounds attack the main target of cytostatic agents and exert antiproliferative activity. The DNA dysfunction that occurs might as well be produced by oxidative damage [5]. In the cellular environment, the majority of Cu(II) complexes form a Cu(I) coordination compound with glutathione, which is able to generate superoxide anion radical in a Fenton-like reaction, thereby initiating ROS formation. In this way, the high redox activity of copper complexes contributes to the antiviral, antibacterial, antifungal and anti-inflammatory activity of its complexes.

Organic ligands coordinated by Cu(II) include N/O-donor ligands, such as Schiff bases, Mannich bases and hydrazones; N/S-donor ligands, such as thiosemicarbazones; N,N-donor ligands, such as 1,10-phenanthroline, 2,2′-bipyridine and benzimidazole derivatives; S/S-donor ligands, such as dithiocarbamates and pyridinethiones and N-, O- and S-donor ligands, such as hydroxylated derivatives of thiosemicarbazones [3,6,7]. For instance, benzimidazole-derived copper(II) complexes exert antitumour, anti-inflammatory and analgesic activities, whereas copper(II) pyrithione possesses antiproliferative properties.

2.3. Copper(II) Complexes with Existing Drugs

The biological activity, biocompatibility and versatile coordination chemistry of copper provide an opportunity for obtaining Cu(II) complexes with the drugs that already have clinical applications. It may imply either enhancement of the initial pharmacological effect of the ligand or acquisition of a novel therapeutic action by the complex. Copper(II) complexes with fluoroquinolones, 8-hydroxyquinoline derivatives, non-steroidal anti-inflammatory drugs and 5-nitroimidazole derivatives, as well as tetracycline, anthracycline, aminoglycoside antibiotics and carbapenems were synthesized (Table 1) [2,8–11].

Table 1. Drug-based copper(II) coordination compounds.

Ligand	Biological Activity	Reference
thiabendazole	antimicrobial	[12]
clofibrate, nicotinamide	antimicrobial	[13]
trimethoprim	antibacterial	[14]
doxorubicin	antiproliferative	[15]
kanamycin A, amikacin	antibacterial, nuclease, antiproliferative	[9]
doxycycline + 1,10-phenantroline tetracycline + 1,10-phenantroline	antiproliferative	[10]

Table 1. *Cont.*

Ligand	Biological Activity	Reference
ertapenem, meropenem	antibacterial	[11]
acyclovir	antiviral	[16]
metronidazole derivatives	antiproliferative	[17]
indomethacin	anti-inflammatory	[18]
piroxicam, isoxicam	anti-inflammatory, antiproliferative	[19]
fenoprofen	analgesic	[20]
diclofenac, mefenamic acid	antiproliferative	[21,22]
salicylic acid, diflunisal	anti-inflammatory	[23,24]
aspirin + N-(1,10-phenanthrolin-5-yl)-nonanamide	anti-inflammatory, antiproliferative	[25]
clioquinol	antiproliferative, antibacterial	[26]
cinoxacin	antibacterial	[27]
ciprofloxacin, enoxacin	antibacterial, nuclease	[28,29]
oxolinic acid + 1,10-phenantroline	antibacterial	[30]
isoniazid	antimycobacterial	[31]
elesclomol	antimycobacterial	[32]

2.4. Biologically Active Hydrazones as Ligands for Copper(II) Complexes

An important class of bidentate N/O-donor ligands that form coordination compounds with Cu(II) are acid hydrazones. Many of them possess antibacterial activity, for instance, 1,3,4-thiadiazole-, benzofuran- or benzimidazole-based hydrazone derivatives and thiazolidinone derivatives. Moreover, nitrofuran-based hydrazones, 1,2,4-triazole-3-mercaptoacetic acid hydrazones and pyridylmethyleneamino-derivatives of isonicotinoylhydrazones demonstrate antimycobacterial activity in the treatment of tuberculosis [33]. Imidazo [1,2-a]pyridine-, tetrazole- and benzofuran-based hydrazone scaffolds exert antifungal activity, whereas antiviral activity is observed for imidazole-amide- and sulfonamide-containing hydrazone derivatives.

Nitrofurantoin is a hydrazone that shows potent antibacterial activity when used in the therapy for urinary tract infections. Low concentrations of nitrofurantoin are known to inhibit β-galactosidase and galactokinase synthesis in *Escherichia coli* and β-galactosidase synthesis in *Klebsiella aerogenes*. Higher doses of nitrofurantoin induce the inhibition of enzymes of the citric acid cycle and disrupt the DNA, RNA, cell wall and protein synthesis in bacterial cells, as well as aerobic energy metabolism [34]. Intracellular nitroreductases capable of reducing the nitro group of nitrofurantoin occur in most major urinary tract pathogens and facilitate the generation of active intermediate metabolites that further interact with bacterial ribosomes and inhibit metabolic enzymes [35]. Therefore, nitrofurantoin possesses a broad spectrum of antibacterial activity and a quite low resistance rate of 2.3%, i.e., nearly 10 times lower than that of quinolones [36]. Nitrofurantoin is active against *E. coli*, Enterococci and *S. saprophyticus* and is applicable in the treatment of uncomplicated urinary tract infections, presenting an alternative to excessively used fluoroquinolones and cotrimoxazole.

A prominent example of hydrazones that possess antitubercular activity is ftivazide, i.e., isonicotinic acid vanillylidenehydrazide. It displays a potent and selective pharmacological effect against *Mycobacterium tuberculosis* and is used in the treatment of active tuberculosis. Ftivazide disrupts the synthesis of mycolic acids that constitute fatty acid-rich cell walls of mycobacteria and inhibits cell wall and cell membrane formation, as well as nucleic acid synthesis and energy metabolism.

Copper(II) complexes with (4,6-di-*tert*-butyl-2,3-dihydroxybenzylidene)isonicotinohydrazide, ftivazide and nitrofurantoin were synthesized by mixing copper(II) acetate with an appropriate ligand (1:2) in methanolic solution and isolated in the amorphous or poorly crystalline state, as judged from the reproducible results of diffuse XRD patterns [37]. The complexes were characterized by means of elemental analysis, FT-IR and UV-Vis spectroscopy, as well as biological methods. According to the data obtained, the coordination compounds correspond to the general formula $Cu(L)_2$ and the hydrazone ligands coordinate in the O,N-bidentate fashion (Figure 1).

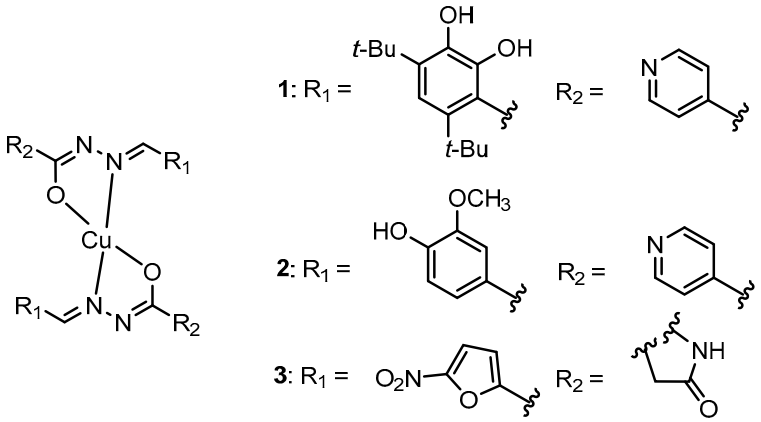

Figure 1. Plausible mode of coordination in the copper(II) complexes.

The hydrazones and their Cu(II) complexes have been screened for their antimicrobial activity against different species of bacteria (Table 2).

Table 2. Antibacterial activity of tested compounds.

Compound	MIC, μmol/mL			
	E. coli	*S. saprophyticus*	*B. subtilis*	*P. putida*
1	0.125	0.125	0.125	0.125
2	0.166	0.166	0.082	>0.166
3	0.047	0.023	0.023	0.093
Ftivazide	0.369	0.184	0.184	>0.369
Nitrofurantoin	0.052	0.052	0.052	0.210
Streptomycin	0.005	0.011	0.011	0.172
Tetracycline	0.007	0.014	0.014	0.112

The antibacterial (bacteriostatic) activity of the compounds was determined in vitro using the method of twofold serial dilutions in liquid broth. For each compound a minimum inhibitory concentration (MIC) was calculated. Streptomycin and tetracycline antibiotics were used as positive controls. The results of antibacterial screening demonstrate that Cu(II) complexes possess higher antibacterial activity compared to parent ligands.

3. Conclusions

Copper(II) complexes discussed in the present work exert a wide range of biological activities, from being antibacterial and nuclease to anti-inflammatory and antiproliferative. Their mechanism of action might involve intracellular ROS production in a Fenton-like

process and direct DNA damage through intercalation, as well as binding to metabolic enzymes of the cell. The results of antibacterial screening demonstrate the enhanced biological activity of Cu(II) complexes compared to uncomplexed ligands. This change in activity may be related to the fact that ligand modification has a pronounced effect on several physico-chemical characteristics of the complexes, in particular, their lipophilicity, which in turn increases the bioavailability of biocides.

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