

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, 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. 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 intracellular levels of copper, specifically the delivery of copper to mitochondria, endosomes, lysosomes and golgi-apparatus by transporters CTR1,

CTR2, ATP7A/B and chaperones ATOX1, 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 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 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 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, high redox activity of copper complexes contributes to 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; 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

Biological activity, biocompatibility and versatile coordination chemistry of copper provides 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, 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,	[9]

	antiproliferative	
doxycycline + 1,10-phenantroline	antiproliferative	[10]
tetracycline + 1,10-phenantroline		
ertapenem, meropenem	antibacterial	[11]
acyclovir	antiviral	[16]
metronidazole derivatives	antiproliferative	[17]
indomethacin	anti-inflammatory	[18]
piroxicam, isoxicam	anti-inflammatory, antiproliferative	[19]
fenopfen	analgesic	[20]
diclofenac, mefenamic acid	antiproliferative	[21,22]
salicylic acid, diflunisal	anti-inflammatory	[23,24]
aspirin + N-(1,10-phenanthrolin-5-yl)-nonana- mide	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, nitrofurantoin-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 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 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).

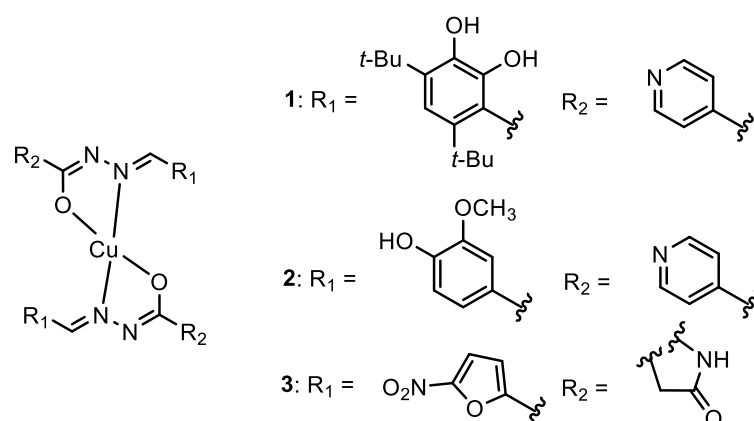


Figure 1. Plausible mode of coordination in the copper(II) complexes.

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, $\mu\text{mol/mL}$			
	<i>E. coli</i>	<i>S. saprophyticus</i>	<i>B. subtilis</i>	<i>P. putida</i>
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 antibacterial and nuclease to anti-inflammatory and antiproliferative. Their mechanism of action might involve intracellular ROS production in a Fenton-like process and the 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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References

1. Brewer, G.J. The risks of copper toxicity contributing to cognitive decline in the aging population and to Alzheimer’s disease. *J. Am. Coll. Nutr.* **2009**, *28*, 238–242. <https://doi.org/10.1080/07315724.2009.10719777>.
2. Wehbe, M.; Leung, A.W.Y.; Abrams, M.J.; Orvig, C.; Bally, M.B. A Perspective—can copper complexes be developed as a novel class of therapeutics? *Dalton Trans.* **2017**, *46*, 10758–10773. <https://doi.org/10.1039/c7dt01955f>.
3. Iakovidis, I.; Delimaris, I.; Piperakis, S.M. Copper and Its Complexes in Medicine: A Biochemical Approach. *Mol. Biol. Int.* **2011**, *2011*, 594529. <https://doi.org/10.4061/2011/594529>.
4. Wang, Y.; Zhang, X.; Zhang, Q.; Yang, Z. Oxidative damage to DNA by 1,10-phenanthroline/L-threonine copper (II) complexes with chlorogenic acid. *BioMetals* **2010**, *23*, 265–273. <https://doi.org/10.1007/s10534-009-9284-6>.
5. Gaetke, L.M.; Chow, C.K. Copper toxicity, oxidative stress, and antioxidant nutrients. *Toxicology* **2003**, *189*, 147–163. [https://doi.org/10.1016/s0300-483x\(03\)00159-8](https://doi.org/10.1016/s0300-483x(03)00159-8).
6. Krasnovskaya, O.; Naumov, A.; Guk, D.; Gorelkin, P.; Erofeev, A.; Beloglazkina, E.; Majouga, A. Copper Coordination Compounds as Biologically Active Agents. *Int. J. Mol. Sci.* **2020**, *21*, 3965. <https://doi.org/10.3390/ijms21113965>.
7. Duncan, C.; White, A.R. Copper complexes as therapeutic agents. *Metallomics* **2012**, *4*, 127–138. <https://doi.org/10.1039/c2mt00174h>.
8. Živec, P.; Perdih, F.; Turel, I.; Giester, G.; Psomas, G. Different types of copper complexes with the quinolone antimicrobial drugs ofloxacin and norfloxacin: Structure, DNA- and albumin-binding. *J. Inorg. Biochem.* **2012**, *117*, 35–47. <https://doi.org/10.1016/j.jinorgbio.2012.08.008>.
9. Szczepanik, W.; Kaczmarek, P.; Jeżowska-Bojczuk, M. Oxidative Activity of Copper(II) Complexes with Aminoglycoside Antibiotics as Implication to the Toxicity of These Drugs. *Bioinorg. Chem. Appl.* **2004**, *2*, 55–68. <https://doi.org/10.1155/S1565363304000056>.
10. Silva, P.P.; Guerra, W.; Silveira, J.N.; Ferreira, A.M.C.; Bortolotto, T.; Fischer, F.L.; Terenzi, H.; Neves, A.; Pereira-Maia, E.C. Two New Ternary Complexes of Copper(II) with Tetracycline or Doxycycline and 1,10-Phenanthroline and Their Potential as Antitumoral: Cytotoxicity and DNA Cleavage. *Inorg. Chem.* **2011**, *50*, 6414–6424. <https://doi.org/10.1021/ic101791r>.
11. Djoko, K.Y.; Achard, M.E.S.; Phan, M.D.; Lo, A.W.; Miraula, M.; Prombhul, S.; Hancock, S.J.; Peters, K.M.; Sidjabat, H.E.; Harris, P.N.; et al. Copper Ions and Coordination Complexes as Novel Carbapenem Adjuvants. *Antimicrob. Agents Chemother.* **2018**, *62*, e02280-17. <https://doi.org/10.1128/AAC.02280-17>.
12. Devereux, M.; McCann, M.; Shea, D.O.; Kelly, R.; Egan, D.; Deegan, C.; Kavanagh, K.; McKee, V.; Finn, G. Synthesis, antimicrobial activity and chemotherapeutic potential of inorganic derivatives of 2-(4'-thiazolyl)benzimidazole[thiabenzazole]: X-ray crystal structures of [Cu(TBZH)2Cl]Cl.H2O.EtOH and TBZH2NO3 (TBZH=thiabenzazole). *J. Inorg. Biochem.* **2004**, *98*, 1023–1031. <https://doi.org/10.1016/j.jinorgbio.2004.02.020>.
13. Moncol, J.; Kaliňáková, B.; Svorec, J.; Kleinova, M.; Koman, M.; Hudecova, D.; Melník, M.; Mazur, M.; Valko, M. Spectral properties and bio-activity of copper(II) clofibrates, part III: Crystal structure of Cu(clofibrate)₂(2-pyridylmethanol)₂, Cu(clofibrate)₂(4-pyridylmethanol)₂(H₂O) dihydrate, and Cu₂(clofibrate)₄(N,N-diethylnicotinamide)₂. *Inorg. Chim. Acta* **2004**, *357*, 3211–3222. <https://doi.org/10.1016/j.ica.2004.03.043>.
14. Simó, B.; Perelló, L.; Ortiz, R.; Castiñeiras, A.; Latorre, J.; Cantón, E. Interactions of metal ions with a 2,4-diaminopyrimidine derivative (trimethoprim). Antibacterial studies. *J. Inorg. Biochem.* **2000**, *8*, 275–283. [https://doi.org/10.1016/s0162-0134\(00\)00118-5](https://doi.org/10.1016/s0162-0134(00)00118-5).

15. Kheiriloom, A.; Mahakian, L.M.; Lai, C.Y.; Lindfors, H.A.; Seo, J.W.; Paoli, E.E.; Watson, K.D.; Haynam, E.M.; Ingham, E.S.; Xing, L.; et al. Copper–Doxorubicin as a Nanoparticle Cargo Retains Efficacy with Minimal Toxicity. *Mol. Pharm.* **2010**, *7*, 1948–1958. <https://doi.org/10.1021/mp100245u>.
16. Herrero, L.A.; Cerro-Garrido, J.C.; Terrón-Homar, A. A calorimetric study of 3d metal ions-acyclovir interactions. The 2-hydroxyethoxymethyl group of acyclovir mimics the role of ribose in deoxy-guanosine and guanosine promoting the coordination through N(7). *J. Inorg. Biochem.* **2001**, *86*, 677–680. [https://doi.org/10.1016/s0162-0134\(01\)00228-8](https://doi.org/10.1016/s0162-0134(01)00228-8).
17. Pellei, M.; Gandin, V.; Cimarelli, C.; Quaglia, W.; Mosca, N.; Bagnarelli, L.; Marzano, C.; Santini, C. Syntheses and biological studies of nitroimidazole conjugated heteroscorpionate ligands and related Cu(I) and Cu(II) complexes. *J. Inorg. Biochem.* **2018**, *187*, 33–40. <https://doi.org/10.1016/j.jinorgbio.2018.07.008>.
18. Sukul, A.; Poddar, S.K.; Haque, S.; Saha, S.K.; Das, S.C.; Al Mahmud, Z.; Abdur Rahman, S.M. Synthesis, Characterization and Comparison of Local Analgesic, Anti-Inflammatory, Anti-Ulcerogenic Activity of Copper and Zinc Complexes of Indomethacin. *Antiinflamm. Antiallergy Agents Med. Chem.* **2017**, *15*, 221–233. <https://doi.org/10.2174/1871523016666170217103402>.
19. Tamasi, G.; Serinelli, F.; Consumi, M.; Magnani, A.; Casolaro, M.; Cini, R. Release studies from smart hydrogels as carriers for piroxicam and copper(II)-oxicam complexes as anti-inflammatory and anti-cancer drugs. X-ray structures of new copper(II)-piroxicam and -isoxicam complex molecules. *J. Inorg. Biochem.* **2008**, *102*, 1862–1873. <https://doi.org/10.1016/j.jinorgbio.2008.06.009>.
20. Gumilar, F.; Agotegaray, M.; Bras, C.; Gandini, N.A.; Minetti, A.; Quinzani, O. Anti-nociceptive activity and toxicity evaluation of Cu(II)-fenopropfenate complexes in mice. *Eur. J. Pharmacol.* **2012**, *675*, 32–39. <https://doi.org/10.1016/j.ejphar.2011.11.049>.
21. Sayen, S.; Carlier, A.; Tarpin, M.; Guillon, E.A. A novel copper(II) mononuclear complex with the non-steroidal anti-inflammatory drug diclofenac: Structural characterization and biological activity. *J. Inorg. Biochem.* **2013**, *120*, 39–43. <https://doi.org/10.1016/j.jinorgbio.2012.12.002>.
22. Kovala-Demertzi, D.; Hadjipavlou-Litina, D.; Staninska, M.; Primikiri, A.; Kotoglou, C.; Demertzis, M.A. Anti-oxidant, *in vitro*, *in vivo* anti-inflammatory activity and antiproliferative activity of mefenamic acid and its metal complexes with manganese(II), cobalt(II), nickel(II), copper(II) and zinc(II). *J. Enzyme Inhib. Med. Chem.* **2009**, *24*, 742–752. <https://doi.org/10.1080/14756360802361589>.
23. Psomas, G.; Kessissoglou, D.P. Quinolones and non-steroidal anti-inflammatory drugs interacting with copper(ii), nickel(ii), cobalt(ii) and zinc(ii): Structural features, biological evaluation and perspectives. *Dalton Trans.* **2013**, *42*, 6252–6276. <https://doi.org/10.1039/C3DT50268F>.
24. Fujimori, T.; Yamada, S.; Yasui, H.; Sakurai, H.; In, Y.; Ishida, T. Orally active antioxidative copper(II) aspirinate: Synthesis, structure characterization, superoxide scavenging activity, and *in vitro* and *in vivo* antioxidative evaluations. *J. Biol. Inorg. Chem.* **2005**, *10*, 831–841. <https://doi.org/10.1007/s00775-005-0031-3>.
25. Shi, X.; Fang, H.; Guo, Y.; Yuan, H.; Guo, Z.; Wang, X. Anticancer copper complex with nucleus, mitochondrion and cyclooxygenase-2 as multiple targets. *J. Inorg. Biochem.* **2019**, *190*, 38–44. <https://doi.org/10.1016/j.jinorgbio.2018>.
26. Tardito, S.; Barilli, A.; Bassanetti, I.; Tegoni, M.; Bussolati, O.; Franchi-Gazzola, R.; Mucchino, C.; Marchiò, L. Copper-Dependent Cytotoxicity of 8-Hydroxyquinoline Derivatives Correlates with Their Hydrophobicity and Does Not Require Caspase Activation. *J. Med. Chem.* **2012**, *55*, 10448–10459. <https://doi.org/10.1021/jm301053a>.
27. Ruiz, M.; Perelló, L.; Ortiz, R.; Castiñeiras, A.; Maichle-Mössmer, C.; Cantón, E. Synthesis, characterization, and crystal structure of [Cu(cinoxacinat)₂].2H₂O complex: A square-planar CuO₄ chromophore. Antibacterial studies. *J. Inorg. Biochem.* **1995**, *59*, 801–810. [https://doi.org/10.1016/0162-0134\(94\)00068-1](https://doi.org/10.1016/0162-0134(94)00068-1).
28. Wallis, S.C.; Gahan, L.R.; Charles, B.G.; Hambley, T.W.; Duckworth, P.A. Copper(II) Complexes of the Fluoroquinolone Antimicrobial Ciprofloxacin. Synthesis, X-Ray Structural Characterization, and Potentiometric Study. *J. Inorg. Biochem.* **1996**, *62*, 1–16. [https://doi.org/10.1016/0162-0134\(95\)00082-8](https://doi.org/10.1016/0162-0134(95)00082-8).
29. Jiménez-Garrido, N.; Perelló, L.; Ortiz, R.; Alzuet, G.; González-Alvarez, M.; Cantón, E.; Liu-González, M.; García-Granda, S.; Pérez-Priede, M. Antibacterial studies, DNA oxidative cleavage, and crystal structures of Cu(II) and Co(II) complexes with two quinolone family members, ciprofloxacin and enoxacin. *J. Inorg. Biochem.* **2005**, *99*, 677–689. <https://doi.org/10.1016/j.jinorgbio.2004.11.016>.
30. Psomas, G.; Tarushi, A.; Efthimiadou, E.K.; Sanakis, Y.; Raptopoulou, C.P.; Katsaros, N. Synthesis, structure and biological activity of copper(II) complexes with oxolinic acid. *J. Inorg. Biochem.* **2006**, *100*, 1764–1773. <https://doi.org/10.1016/j.jinorgbio.2006.06.012>.
31. Bottari, B.; Maccari, R.; Monforte, F.; Ottana, R.; Rotondo, E.; Vigorita, M.G. Isoniazid Related Copper(II) and Nickel(II) Complexes with Antimycobacterial *In Vitro* Activity. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 657–660. [https://doi.org/10.1016/s0960-894x\(00\)00058-5](https://doi.org/10.1016/s0960-894x(00)00058-5).
32. Ngwane, A.H.; Petersen, R.D.; Baker, B.; Wiid, I.; Wong, H.N.; Haynes, R.K. The evaluation of the anti-cancer drug elesclomol that forms a redox-active copper chelate as a potential anti-tubercular drug. *IUBMB Life* **2019**, *71*, 532–538. <https://doi.org/10.1002/iub.2002>.
33. Mali, S.N.; Thorat, B.R.; Gupta, D.R.; Pandey, A. Mini-Review of the Importance of Hydrazides and Their Derivatives—Synthesis and Biological Activity. *Eng. Proc.* **2021**, *11*, 21. <https://doi.org/10.3390/ASEC2021-11157>.

34. McOsker, C.C.; Fitzpatrick, P.M. Nitrofurantoin: Mechanism of action and implications for resistance development in common uropathogens. *J. Antimicrob. Chemother.* **1994**, *33*, 23–30. https://doi.org/10.1093/jac/33.suppl_a.23.
35. Huttner, A.; Verhaegh, E.M.; Harbarth, S.; Muller, A.E.; Theuretzbacher, U.; Mouton, J.W. Nitrofurantoin revisited: A systematic review and meta-analysis of controlled trials. *J. Antimicrob. Chemother.* **2015**, *70*, 2456–2464. <https://doi.org/10.1093/jac/dkv147>.
36. Kashanian, J.; Hakimian, P.; Blute, M., Jr.; Wong, J.; Khanna, H.; Wise, G.; Shabsigh, R. Nitrofurantoin: The return of an old friend in the wake of growing resistance. *BJU Int.* **2008**, *102*, 1634–1637. <https://doi.org/10.1111/j.1464-410X.2008.07809.x>.
37. Loginova, N.V.; Koval'chuk-Rabchinskaya, T.V.; Ksendzova, G.A.; Gvozdev, M.Y.; Polozov, G.I. Redox-active metal complexes with hydrazone and thiosemicarbazone derivatives of 4,6-di-tert-butyl-2,3-dihydroxybenzaldehyde as novel antimicrobials for medicinal uses. In *Hydrazones: Uses and Reactions*; Østergaard, I.P.; Nova Science Publishers, Inc.: New York, NJ, USA, 2020; pp. 57–113.