Antimicrobial Potential of Dithiocarbamates Complexes

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Dithiocarbamates and their metal complexes have shown promising antimicrobial activities; the mechanisms responsible for the antimicrobial activity include their ability to act as enzyme inhibitors for (i) fungal, protozoan, and bacterial carbonic anhydrase and (ii) metallo-beta-lactamase (MBL) in antibiotic resistant bacteria, particularly Gram-negative bacteria.

Keywords: antibacterial therapeutics ; antifungal activity ; dithiocarbamate ; metal dithiocarbamates ; sulfur compounds ; metal-based drugs ; mechanism of action

1. Introduction

Dithiocarbamates are mono-anionic 1,1-dithiolate ligands of the general chemical formula of $R(R')CNS_2^{(-)}$for R, R' = H, alkyl, and aryl. A zinc complex of the bifunctional dithiocarbamate ligand, ethylenebis (dithiocarbamate), $\{Zn(S_2CN(H)CH_2CH_2N(H)CS_2)\}_n$, known as Zineb®, has been employed as a fungicide since the 1940s[1]. Other biological roles of dithiocarbamates are also summarized in the literature [2][3]. Prompted by the antibiotic resistance that poses a significant threat to public health, the medicinal use of dithiocarbamates and their metal complexes as antimicrobial agents is actively explored.

2. Antimicrobial Activity of Dithiocarbamates and Their Complexes

The water-soluble salts of dithiocarbamate have shown antibacterial properties. The subsequent study to investigate the coadministration of zinc chloride with pyrrolidine dithiocarbamate, for example, suggested $(CH_2)_4NCS_2^{(-)}$ facilitated the entry of zinc ions into the bacteria cells followed by the inhibition of glycolysis of microorganisms [4]. Inspired by the findings above, in addition to the ability of dithiocarbamates to form stable complexes with different metals, the antimicrobial activities of dithiocarbamates and their metal complexes were widely studied.

Early work has established the importance of metal ions to improve the biocidal efficacy of the dithiocarbamate anion. Besides, lipophilicity is yet another factor that may influence the bioavailability of a dithiocarbamate complex, as well as the inclusion of judiciously selected ancillary ligand(s) to enhance the bioefficacy. Ferrocene, for instance, can impart increased cell permeability and lipophilicity in addition to its ability to induce oxidation in various species such as DNA and proteins [5][6]. The above led to the study of transition metal complexes bearing functionalized dithiocarbamates for the evaluation of their antimicrobial activities. Indeed, there is a wide range of metal dithiocarbamates prepared and assessed for their antimicrobial properties. The recent review on the antimicrobial properties of dithiocarbamates, contributed by the authors of this entry, has carefully summarised the antimicrobial studies conducted on metal dithiocarbamates to work as a handy reference to those interested in a related study [7].

3. Possible Mechanisms of Action

To date, evidence shows that the mechanisms responsible for the antimicrobial activity of dithiocarbamates include their ability to act as enzyme inhibitors for (i) fungal, protozoan, and bacterial carbonic anhydrase and (ii) metallo-beta-lactamase (MBL) in antibiotic resistant bacteria, particularly Gram-negative bacteria.

Carbonic anhydrases are a group of metalloenzymes that catalyze the conversion of carbon dioxide to bicarbonates and proton. Like carbon dioxide, bicarbonate, and protons play important roles in various physiological processes, the use of carbonic anhydrase inhibitors was demonstrated to have antimicrobial application[8] in key microbial pathogens such as *Mycobacterium tuberculosis*[9], *Cryptococcus neoformans*, *Candida albicans*, *Candida glabrata*[10], and *Leishmania major* promastigotes[11].

MBLs are produced by a group of multidrug-resistant Gram-negative nosocomial bacteria, including *Enterobacter* spp., *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*[12], conferring resistance to carbapenems, such as imipenem and meropenem, employed as the last resort antibiotics for extended-spectrum beta-lactamase (ESBL) producing drug-resistant bacteria[13]. Multiple dithiocarbamates were shown to restore the activity of carbapenems *K. pneumoniae*[13][14], *Escherichia coli*[13][15] and *P. aeruginosa*[14].

4. Conclusions

In summary, the evaluation of metal dithiocarbamates has presented evidence for their potential use as antimicrobial agents. The versatility of the dithiocarbamate ligand enables the possibility to fine-tune crucial biological indicators such as lipophilicity by varying the heavy element center, the dithiocarbamate ligand, and even co-ligands. Overall, dithiocarbamates and their complexes presented promising bioactivities and exhibited great potential for their use as antimicrobial agents.

References

1. Guardiola, F.A.; Cuesta, A.; Meseguer, J.; Esteban, M.A.; Risks of using antifouling biocides in aquaculture.. *Int. J. Mol. Sci.* **2012**, *13*, 1541–1560, .
2. Lal, N.; Dithiocarbamates: A versatile class of compounds in medicinal chemistry. *Chem. Biol. Interface* **2014**, *4*, 321–340, .
3. Bala, V.; Gupta, G.; Sharma, V.L.; Chemical and medicinal versatility of dithiocarbamates: An overview. *Mini Rev. Med. Chem.* **2014**, *14*, 1–12, .
4. Kang, M.S.; Choi, E.K.; Choi, D.H.; Ryu, S.Y.; Lee, H.H.; Kang, H.C.; Koh, J.T.; Kim, O.S.; Hwang, Y.C.; Yoon, S.J.; et al. Antibacterial activity of pyrrolidine dithiocarbamate. *FEMS Microbiol. Lett.* **2008**, *280*, 250–254, .
5. Patra, M.; Gasser, G.; The medicinal chemistry of ferrocene and its derivatives.. *Nat. Rev. Chem.* **2017**, *1*, 0066, .
6. Verma, S.K.; Singh, V.K.; Synthesis and characterization of ferrocene functionalized transition metal dithiocarbamate complexes: Investigations of antimicrobial, electrochemical properties and a new polymorphic form of [Cu{k2S,S-S2CN(CH2C4H3O)CH2Fc}2]. *J. Organomet. Chem.* **2015**, *791*, 214–224, .
7. Yeo, C.I.; Tiekink, E.R.T.; Chew, J.; Insights into the Antimicrobial Potential of Dithiocarbamate Anions and Metal-Based Species. *Inorganics* **2021**, *9*, 48, .
8. Supuran, C.T.; Carbonic anhydrase inhibitors and activators for novel therapeutic applications. *Future Med. Chem.* **2011**, *3*, 1165–1180, .
9. Aspatwar, A.; Hammaren, M.; Parikka, M.; Parkkila, S.; Carta, F.; Bozdag, M.; Vullo, D.; Supuran, C.T.; . In vitro inhibition of Mycobacterium tuberculosis β-carbonic anhydrase 3 with Mono-and dithiocarbamates and evaluation of their toxicity using zebrafish developing embryos.. *J. Enzyme Inhib. Med. Chem.* **2020**, *35*, 65–71, .
10. Monti, S.M.; Maresca, A.; Viparelli, F.; Carta, F.; De Simone, G.; Mühlschlegel, F.A.; Scozzafava, A.; Supuran, C.T.; Dithiocarbamates are strong inhibitors of the beta-class fungal carbonic anhydrases from Cryptococcus neoformans, Candida albicans and Candida glabrata.. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 859–862, .
11. Pal, D.S.; Mondal, D.K.; Datta, R.; . Identification of metal dithiocarbamates as a novel class of antileishmanial agents.. *Antimicrob. Agents Chemother.* **2015**, *59*, 2144–2152, .
12. Codjoe, F.S.; Donko, E.S.; Carbapenem resistance: A review. *Med. Sci.* **2018**, *6*, 1, .
13. Zhang, E.; Wang, M.M.; Huang, S.C.; Xu, S.M.; Cui, D.Y.; Bo, Y.L.; Bai, P.Y.; Hua, Y.G.; Xiao, C.L.; Qin, S.; et al. NOTA analogue: A first dithiocarbamate inhibitor of metallo-β-lactamases. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 214–221, .
14. Chen, C.; Yang, K.-W.; Wu, L.-Y.; Li, J.-Q.; Sun, L.-Y; Disulfiram as a potent metallo-β-lactamase inhibitor with dual functional mechanisms. *Chem. Commun.* **2020**, *56*, 2755–2758, .
15. Wang, M.-M.; Chu, W.-C.; Yang, Y.; Yang, Q.-Q.; Qin, S.-S.; Zhang, E; Dithiocarbamates: Efficient metallo-β-lactamase inhibitors with good antibacterial activity when combined with meropenem. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 3436–3440, .

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