

Review

Insights into the Antimicrobial Potential of Dithiocarbamate Anions and Metal-Based Species

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Abstract: Bacterial infection remains a worldwide problem that requires urgent addressing. Overuse and poor disposal of antibacterial agents abet the emergence of bacterial resistance mechanisms. There is a clear need for new approaches for the development of antibacterial therapeutics. Herein, the antibacterial potential of molecules based on dithiocarbamate anions, of general formula $R(R')NCS_2^{(-)}$, and metal salts of transition metals and main group elements, is summarized. Preclinical studies show a broad range of antibacterial potential, and these investigations are supported by appraisals of possible biological targets and mechanisms of action to guide chemical syntheses. This bibliographic review of the literature points to the exciting potential of dithiocarbamate-based therapeutics in the crucial battle against bacteria. Additionally, included in this overview, for the sake of completeness, is mention of the far fewer studies on the antifungal potential of dithiocarbamates and even less work conducted on antiparasitic behavior.



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1. Introduction

Dithiocarbamates are mono-anionic 1,1-dithiolate ligands of the general chemical formula of $R(R')CNS_2^{(-)}$ for $R, R' = H, \text{alkyl, and aryl}$, Figure 1a. These molecules are ubiquitous in coordination chemistry being able to coordinate practically every heavy element [1,2] by virtue of having two sulfur atoms available for chelation and a significant contribution of the dithiolate resonance structure, $R(R')C=N^{(+)}S_2^{(2-)}$, Figure 1b. The oxidation of one of the more common dithiocarbamate anions, the diethyl derivative, gives rise to the disulfide, $Et_2NC(=S)S-SC(=S)NEt_2$, commonly known as tetraethylthiuram disulphide [3]. This molecule is marketed as Antabuse[®] and Disulfiram[®], being a drug employed for the treatment of alcohol abuse [4]. In the realm of metal complexes, the 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 [5]; the crystal structure of this material has only recently been reported and revealed a two-dimensional polymer owing to the presence of both chelating and bidentate bridging ligands linked into the three-dimensional crystal via amine-N-H \cdots S (dithiocarbamate) hydrogen bonding [6]. These are but two examples of the prominent role that dithiocarbamates play in contemporary society with other biological roles summarized in the literature [7–10]. Of particular relevance to the present review on the antibacterial potential of dithiocarbamate derivatives are reviews on the potential medicinal applications of dithiocarbamate derivatives [11–13].

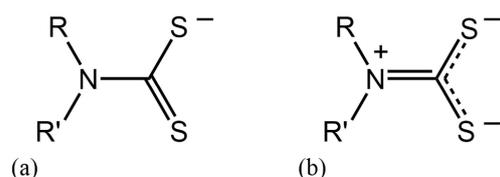


Figure 1. Chemical diagrams for (a) the dithiocarbamate anion and (b) the dithiolate canonical form. R, R' = H, alkyl, and aryl.

The world's population is facing a crisis in terms of bacteria being able to develop resistance to currently employed drugs. Since the first antibacterial agent, penicillin, developed by Sir Alexander Fleming [14], many synthetic drugs, usually organic molecules, have been developed as antibiotics. However, the overuse of antibacterial agents in patients and animal husbandry coupled with poor disposal practices have enabled bacteria to develop effective resistance mechanisms, a problem exacerbated by the rapid replication cycles of bacteria [15]. A similar observation in the rapid emergence of antifungal resistant species, among which are drug-resistant *Candida*, including multi-drug resistant *C. auris*, and azole-resistant *A. fumigatus*, which is recognized as driven by the extensive use of antifungal agents in the clinical and agricultural sectors. The emergence of drug-resistant fungal species severely impacts clinical outcomes as there are limited classes of antifungal agents currently available in the market [16,17]. Thus, there is clearly an urgent imperative to develop novel and effective antibiotics. A practical approach is to direct attention to metallodrugs, which offer new opportunities in drug discovery with enhanced potency and distinct mechanisms of action. While hardly a new concept [18], recent reviews have highlighted the potential of metal-based compounds in combating microbial infections, particularly bacterial infections [19–22]. Incidentally, Sir Alexander Fleming reported investigations on the antimicrobial potential of $K_2 [TeO_3]$ close to a century ago [23]; while not the first heavy element one might consider in the pharmacopeia, tellurium compounds exhibit a range of potential medicinal applications [24].

With the established medicinal use and potential of dithiocarbamate derivatives, the bacterial crisis, and the increasing appreciation of the role of metal-based drugs, it seems only natural that dithiocarbamates should be explored as potential antibacterial agents. Herein, after a brief survey of some basic dithiocarbamate chemistry, attention will be directed to describing preclinical studies investigating dithiocarbamates as antibacterial agents followed by a summary of possible biological targets and modes of action. The focus on antibacterial activity notwithstanding, there are a limited number of antifungal studies of dithiocarbamate derivatives and even fewer of antiparasitic activity. These results are also included and discussed herein to achieve a more comprehensive overview of the field.

2. Chemistry

The preparation of dithiocarbamates is generally facile and often involves the one-pot reaction of an amine with carbon disulfide in the presence of a base. This is an exothermic reaction and usually, an ice bath is recommended for the preparation of the dithiocarbamate salt, especially on a large scale. Alkali metal hydroxides, such as sodium hydroxide and potassium hydroxide, are commonly used bases, although tetraalkylammonium salts can also be used. The dithiocarbamate salts are often soluble in water and short-chain alcohols. Dithiocarbamates prepared from secondary amines possess greater stability compared to those prepared from primary amines (to generate $R(H)CNS_2^{(-)}$) and ammonia ($H_2CNS_2^{(-)}$). The reactions to generate heavy element dithiocarbamates are more often than not via simple metathesis.

Just as their synthesis is readily accomplished, characterization can be achieved through a variety of physicochemical characterization methods. In particular, infrared spectroscopy is useful as characteristic bands are observed in the ranges 1500–1400 and 1090–950 cm^{-1} due to $\nu(C-N)$ and $\nu(C-S)$, respectively. Similarly, characteristic UV absorptions are observed in solution in the ranges 330–360, 275–296, and 240–260 nm which are

ascribed to $n \rightarrow \pi^*$ (S(lone-pair) $\rightarrow \pi^*$), $\pi \rightarrow \pi^*$ (within S–C=S), and $\pi \rightarrow \pi^*$ (within N–C=S) transitions, respectively. It needs to be emphasized that heavy element dithiocarbamates can be prepared in high yields, are stable, and readily crystallized. This is borne out by a survey of the Cambridge Structural Database (version 5.42, November 2020) [25] where over 4300 crystal structure determinations of dithiocarbamate derivatives are curated.

3. Screening of Dithiocarbamates for Antimicrobial Activity

In this section, antibacterial activities are discussed before the less well explored antifungal/antiparasitic activities. In general, Section 3.1 collates the results of organic dithiocarbamate derivatives while heavy element compounds are summarized in Sections 3.2 and 3.3, with transition metal complexes discussed before main group element dithiocarbamates. There is no clear delineation other than this breakdown as many studies report the results of antimicrobial screening of more than one heavy element. However, generally, the discussion follows the order of the Periodic Table. Again, in general terms, mononuclear species are covered before multinuclear species. Finally, for compactness of discussion, an alphabetical listing of the full names of all microbes encountered in this survey as well as likely diseases and infections they are thought responsible for are given in the Appendix A at the conclusion of the review.

3.1. Organic Derivatives

A summary of antimicrobial activities along with antifungal activity when available, exhibited by reported $R(R') NCS_2^{(-)}$ and $Y(CH_2CH_2)_2NCS_2^{(-)}$ salts are presented in Table 1.

The water-soluble salt, pyrrolidine dithiocarbamate, $(CH_2)_4NCS_2^{(-)}$, showed antibacterial properties against *P. gingivalis*, *A. actinomycetemcomitans*, *S. aureus*, and *E. coli* [26]. Subsequently, Camps and Boothroyd reported the selective killing effects of $(CH_2)_4NCS_2^{(-)}$ on extracellular *T. gondii* parasites, effects ascribed to an oxidative mechanism [27]. Kang et al. investigated the implications of the coadministration of metal salts, namely MCl_x [for $x = 2$, $M(II) = Zn$ and Cu ; $x = 3$, $M(III) = Fe$] upon the inhibitory effect of $(CH_2)_4NCS_2^{(-)}$ against *P. gingivalis*, *A. actinomycetemcomitans*, and *F. nucleatum* [26,28]. It was found the coadministration of $ZnCl_2$ augmented the inhibitory properties towards the three studied bacteria while the presence of $CuCl_2$ blocked the growth-inhibitory activity of $(CH_2)_4NCS_2^{(-)}$ towards *A. actinomycetemcomitans*. On the other hand, the addition of $FeCl_3$ showed no effect against either *P. gingivalis* or *A. actinomycetemcomitans*. The authors proposed that $(CH_2)_4NCS_2^{(-)}$ facilitated the entry of zinc ions into the bacteria cells followed by the inhibition of glycolysis of microorganisms.

An interesting multifunctional dithiocarbamate zwitterion formulated as $R(R') NCS_2^{(-)}$, with $R = CH_2CH_2NH_3^{(+)}$ and $R' = CH_2C(=O)O^{(-)}$, as the potassium salt, that has multiple potential donor atoms for interaction with metal ions was reported to show significant antibacterial activity against the tested Gram-positive and Gram-negative bacteria [29]. It was proposed that the activity of this salt was due to its ability to form stable complexes with different metals, thereby readily interacting with metalloenzymes of the bacteria eventually leading to damage and death of the bacteria. Prompted by these findings, the antimicrobial activities of dithiocarbamates and their metal complexes were widely studied.

Table 1. Summary of antibacterial and antifungal activities exhibited by R(R')NCS₂⁽⁻⁾ and Y(CH₂CH₂)₂NCS₂⁽⁻⁾ salts. MIC = minimum inhibitory concentration.

Formulation/R(R')NCS ₂ ⁽⁻⁾	Method	Activity	Ref.
R = H; R' = Me	Broth dilution	MIC = 20 µg/mL against <i>B. cereus</i> ; limited antibacterial effects on probiotic bacteria <i>L. plantarum</i> and <i>L. mesenteroides</i>	[30]
R = H; R' = Ph	Disc diffusion	Active against 12 bacterial species and 10 fungi (zone of inhibition ranging 6–8 mm at MIC 1 × 10 ⁴ and 1.25 × 10 ⁴ µg/mL, respectively)	[31,32]
R = H; R' = Cy	Disc diffusion	Showed improved percentage of minimum inhibitory zone towards <i>A. flavus</i> , <i>A. carbonarius</i> , <i>A. niger</i> , <i>S. Typhi</i> , <i>B. subtilis</i> , <i>B. cereus</i> , <i>P. aeruginosa</i> , and <i>P. mirabilis</i> at increased concentration; showed no significant concentration effect on <i>A. fumigatus</i>	[32,33]
R = H; R' = CH ₂ CH ₂ N(CH ₂) ₅	Broth dilution/zebrafish model	Growth inhibition on <i>M. marinum</i> at approximate 18 µg/mL. Significantly inhibited bacterial growth in zebrafish larvae at approximate 73 µg/ml	[34] ^a
R = H; R' = N(CH ₂ CH ₂) ₂ NMe	Broth dilution	Growth inhibition on <i>M. marinum</i> at approximate 17 µg/ml	[34] ^a
R = R' = Me	Broth dilution/well diffusion	MIC = 20 µg/mL against <i>B. cereus</i> [28]. Greater activity towards Gram-positive bacteria (<i>S. aureus</i> and <i>B. subtilis</i>) than Gram-negative bacteria (<i>E. coli</i> and <i>P. aeruginosa</i>) compared to chloramphenicol [32]	[30,35]
R = Me; R' = CH ₂ CH(OMe) ₂ and R = Me; R' = 2-methyl-1,3-dioxolane	Broth dilution	The species with R' = CH ₂ CH(OMe) ₂ presented at least 6-fold greater activities against <i>A. flavus</i> , <i>A. niger</i> , and <i>A. parasiticus</i>	[36]
R = Me; R' = (1 <i>R</i> ,2 <i>S</i>)-1-methyl-2-phenyl-2-hydroxy]ethyl	Broth dilution	Mild activity towards <i>S. aureus</i> , <i>S. sciuri</i> , and drug-resistant bacterial strains: extended spectrum beta-lactamase producing <i>E. coli</i> , methicillin-resistant <i>S. epidermidis</i> , <i>S. haemolyticus</i> , and <i>S. simulans</i>	[37]
R = Et; R' = Et	Well diffusion/disc diffusion	Greater sensitivity towards Gram-positive bacteria than Gram-negative bacterial strains compared to chloramphenicol	[35,38]
R = Et; R' = Ph	Disc diffusion	Tested against 4 bacterial species: <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. Typhi</i> , and <i>S. aureus</i> ; zone of inhibition in the range 4–10 mm at 100 µg/mL; inactive towards <i>S. aureus</i> . Additionally, tested against 2 fungal organisms: <i>A. flavus</i> and <i>F. oxysporium</i> ; zone of inhibition in the ranging (range) 9–10 mm at 100 µg/mL	[39]
R = Ph; R' = Ph	Disc diffusion	Active against Gram-positive bacteria: <i>B. subtilis</i> , <i>S. aureus</i> , and <i>Rhodococcus</i> sp. with zone of inhibition in the range 12–22 mm; inactive towards Gram-negative bacteria namely, <i>E. coli</i> , <i>P. aeruginosa</i> , and <i>Enterobacter</i> sp. Active against 4 fungal organisms: <i>A. niger</i> , <i>A. flavus</i> , <i>C. albicans</i> , and <i>Acetomyces</i> sp.; zone of inhibition in the range 16–18 mm at 100 µg/mL	[40,41]

Table 1. Cont.

Formulation/R(R')NCS ₂ ⁽⁻⁾	Method	Activity	Ref.
Y(CH ₂ CH ₂) ₂ NCS ₂ ⁽⁻⁾			
Y = CMe	Well diffusion/tube diffusion	Active against 6 bacterial species: <i>E. coli</i> , <i>B. subtilis</i> , <i>S. flexneri</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>S. Typhi</i> with zones of inhibition in the range 12–20 mm. Active against 4 fungi: <i>T. longifusus</i> , <i>M. canis</i> , <i>F. solani</i> , and <i>C. glabrata</i> ; zone of inhibition in the range 10–38 mm	[42]
Y = CCH ₂ Ph	Well diffusion	Mild activity against <i>E. coli</i> , <i>S. Typhi</i> , <i>P. aeruginosa</i> , and <i>S. aureus</i> with zones of inhibition in the range 12–22 mm. Active against 5 fungi: <i>A. nigar</i> , <i>A. flavus</i> , <i>H. solani</i> , <i>A. solani</i> , and <i>Fusarium</i> sp.; range of inhibition: 12.6–43.5 mm at 200 µg/mL	[43]
Y = NMe	Broth dilution/well diffusion/agar dilution	Weak sensitivity towards 10 bacterial species (<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>E. faecalis</i> , <i>V. cholerae</i> , <i>S. pneumoniae</i> , <i>B. cereus</i> , <i>B. subtilis</i> , <i>S. flexneri</i> , and <i>S. Typhi</i>) and 5 fungi (<i>C. albicans</i> , <i>T. longifusus</i> , <i>M. canis</i> , <i>F. solani</i> , and <i>C. glabrata</i>).	[44–47]
Y = NC(=S)S(CH ₂) ₂ N(CH ₂) ₅	Broth micro-dilution	Active against 6 species of fungi (<i>C. albicans</i> , <i>C. neoformans</i> , <i>S. schenckii</i> , and <i>T. mentagrophytes</i> , <i>A. fumigates</i> , and <i>C. parapsilosis</i>)	[44]
Y = NC(=S)S(CH ₂) ₃ Me	Broth micro-dilution	Active against 4 species of fungi (<i>C. albicans</i> , <i>C. neoformans</i> , <i>A. fumigates</i> , and <i>C. parapsilosis</i>) and displayed spermicidal activity at minimum effective concentration (MEC) 31.6 mM	[44]
Y = CHCH ₂ Ph	Well diffusion	Tested against 4 bacterial species: <i>E. coli</i> , <i>V. cholerae</i> , <i>S. pneumoniae</i> , and <i>B. cereus</i> with zones of inhibition in the range 3–7 mm at 100 µg/mL	[45]
Y = NPh	Disc diffusion	Active against <i>S. Tyhimurium</i> , <i>P. aeruginosa</i> , <i>B. pumilus</i> , <i>S. aureus</i> , <i>C. albicans</i> , and <i>A. niger</i> . with zones of inhibition in the range 14–45 mm at 1750 µg/mL	[48]
Y = NC ₆ H ₄ NO ₂ -4	Disc diffusion	Showed activities against <i>B. pumilus</i> , <i>S. aureus</i> , <i>C. albicans</i> , and <i>A. niger</i> with zones of inhibition in the range 25–42 mm at 1000 µg/mL; inactive towards <i>E. coli</i>	[48]
Y = NC ₆ H ₄ F-4	Disc diffusion	Showed activities against <i>E. coli</i> , <i>S. Typhimurium</i> , <i>P. aeruginosa</i> , <i>B. pumilus</i> , <i>S. aureus</i> , <i>C. albicans</i> and <i>A. niger</i> with zones of inhibition in the range 23–42 mm at 2500 µg/mL	[48]
Y = O	Well diffusion	Tested against 4 bacterial species: <i>E. coli</i> , <i>V. cholerae</i> , <i>S. pneumoniae</i> , and <i>B. cereus</i> with zones of inhibition in the range 4–8 mm at 100 µg/mL	[45]

^a The MIC values reported for [39] were converted from µM to µg/mL for ease of comparison, hence the values reported herein are rounded to integers.

3.2. Transition Metal Dithiocarbamates

The study of the antimicrobial activities of transition-metal dithiocarbamates was initiated as early as 1987 by Manoussakis et al. [49]. Early work established the importance of metal ions to improve the biocidal efficacy of dithiocarbamate anions [50,51]. Owing to the presence of amine functionality in the beta-blockers, propranolol (Inderal[®]) and atenolol (Tenormin[®]), used for the regulation of blood-pressure and the treatment of heart conditions among other ailments, dithiocarbamate ligands L¹ and L² can be formed from these amines; the chemical diagrams of the dithiocarbamate ligands discussed in this review are shown in Figure 2. Indeed, Gölcü and colleagues explored the antibacterial

activities of these dithiocarbamates and various metal complexes. The antimicrobial activities of the complexes against 10 bacterial species surpassed those of dithiocarbamates alone. The work showed the copper(II) complex to exert no effect towards any of the microorganisms tested while the cobalt(II) complex exhibited the greatest activity [50,51]. A similar observation was made in the study of metal(II) complexes bearing mixed 4-chlorophenyl- and 4-bromophenyldithiocarbamates, formulated as $M(L^3)(L^4)$ for $M(II) = Co, Ni, Cu, Zn, Cd,$ and Hg , where the presence of the metal ion resulted in improved efficacy against selected bacteria (*E. coli*, *S. mercescens*, and *S. aureus*) compared with the free ligand [52]. However, the complexes exhibited weak to no activity towards the investigated fungi (*T. viride* and *M. albicans*).

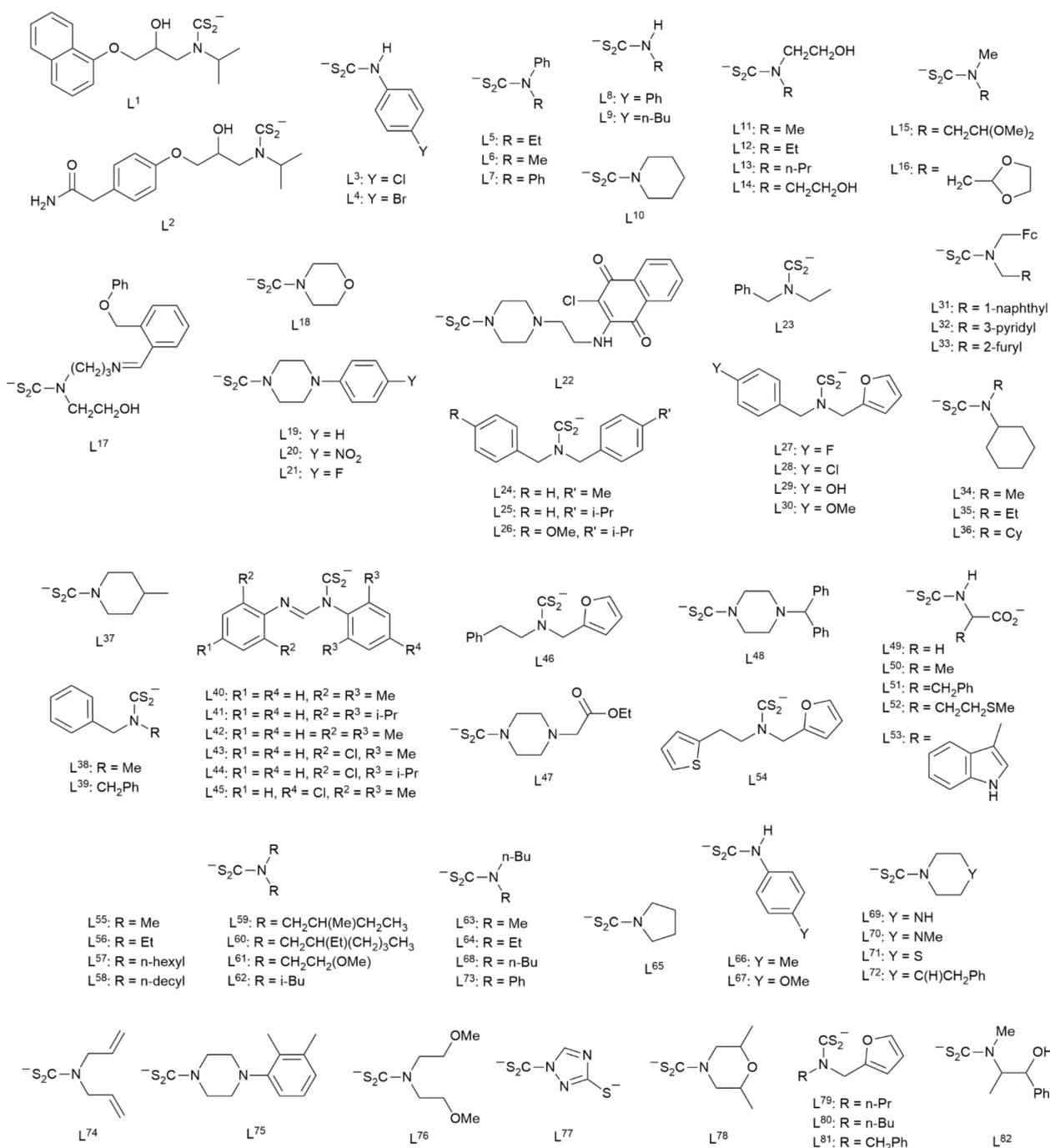


Figure 2. Chemical diagrams for dithiocarbamate anions L^1 to L^{82} discussed herein. Fc is ferrocenyl, $(C_5H_4)Fe(C_5H_5)$.

The antimicrobial activities of transition metal complexes comprising N-alkyl-N-phenyldithiocarbamate were explored against a range of microbial species [39,53]. In [39], where alkyl = ethyl, $M(L^5)_2$ complexes, for $M(II) = Mn, Co,$ and $Cu, Cr(L^5)_3,$ and $Pd(L^5)_2 \cdot 4H_2O$ showed a broad spectrum of bactericidal and fungicidal activity. Overall, the complexes displayed greater potency as antibacterial agents. Among the complexes screened, the palladium(II) complex proved to be ineffective for all the organisms tested. The copper(II) complex showed the greatest potency against *S. aureus* while the chromium(III) analog displayed the best activity against *P. aeruginosa*, and the manganese(II) complex was the most active towards *S. Typhi* and *E. coli*. These results suggest a metal-specific potency towards bacteria. Furthermore, metal complexes with alkyl = methyl showed comparable antibacterial activity to that of streptomycin, a standard antibiotic used as a control, towards *S. aureus* and *B. cereus* with $Co(L^6)_2$ having greater efficacy compared to the nickel(II) and copper(II) congeners [53]. In a related study, Ekennia et al. reported the antimicrobial properties of heteroleptic nickel(II) and zinc(II) complexes containing N-alkyl-N-phenyl dithiocarbamate and benzoate, formulated as $M(L^x)(O_2CPh)$ for $x = 5$ and 6 , the potency being assessed by agar and disc diffusion methods; the two complexes demonstrated moderate to high activity against the bacteria and fungi tested [54]. However, due to the distinct experimental methods adopted in the foregoing studies and the different metals present in the complexes, no direct correlation can be derived from the testing outcomes of [39,53,54].

Khan et al. evaluated the activities of the diphenyl dithiocarbamates, $M(L^7)_2$ for $M(II) = Ni, Cu$ and Zn [40]. Noteworthy from this study was that each of the metals exhibits a distinctive efficacy against four bacterial strains (*B. subtilis*, *P. aeruginosa*, *E. coli*, and *Rhodococcus* sp.) and four fungal strains (*A. niger*, *A. flavus*, *C. albicans*, and *Acetomyces* sp.) [40]. Among the evaluated complexes, the zinc(II) species was the most potent against all the bacterial species tested while the copper(II) derivative showed the highest antifungal activity; both zinc(II) and copper(II) derivatives also presented greater activity than the standards (ampicillin and fluconazole) employed in the study. On the other hand, Botha and colleagues evaluated the antimicrobial properties of another series of copper(II) dithiocarbamates, $Cu(L^{8-10})_2$ [55]. The aniline-derived $Cu(L^8)_2$ complex displayed promising antibacterial activities towards *E. coli*, *S. aureus*, *S. Typhi*, and *S. Typhimurium* while the piperidine-derived $Cu(L^{10})_2$ was the least active among the series. Tests were also conducted for antifungal activity with the $Cu(L^x)_2$ complexes with $x = 8$ and 9 exhibiting antifungal activities comparable to or greater than the standard antifungal drugs used as the control [55].

In order to delineate the importance of increasing hydrophilicity to enhance the bioavailability, de Lima and colleagues assessed a series of four copper(II) dithiocarbamates bearing an ethyl hydroxyl group, $Cu\{S_2CN(R)CH_2CH_2OH\}_2$ for $R = Me (L^{11}), Et (L^{12}), n-Pr (L^{13}),$ and $CH_2CH_2OH (L^{14})$ [56]. However, the research revealed the biocidal activity was not greatly impacted by the enhanced hydrophilicity; liposolubility in drug cell interactions was important as the less polar complex, $Cu(L^{13})_2$, showed the greater potency towards *C. albicans*. All four complexes were inert towards the bacterial strains *S. aureus* and *P. aeruginosa*.

In 2013, Ferreira et al. reported the in vitro antimicrobial activities of $Cu\{S_2CN(Me)R\}_2$, for $R = CH_2CH(OMe)_2 (L^{15})$ and 2-methyl-1,3-dioxolane (L^{16}), as well as of $Cu\{S_2CN(CH_2CH_2OH)R\}_2$ for $R = (CH_2)_3N=C(H)C_6H_4(2-OCH_2Ph) (L^{17})$ against a range of bacteria (*L. monocytogenes*, *B. cereus*, *S. sanguinis*, *C. freundii*, *S. Typhimurium*, and *P. aeruginosa*) and fungi (*A. flavus*, *A. niger*, *A. parasiticus*, *P. citrinum*, and *C. senegalensis*) [57]. Overall, the complexes exerted greater activity against fungi while having no significant effect on the bacterial strains, indicating the complexes were selective towards pathogenic fungi. Among the fungal strains, *A. flavus*, *A. niger*, and *P. citrinum* were more susceptible to the trial complexes as compared to *A. parasiticus* and *C. senegalensis*. Later, Ferreira et al. extended the study to include other metal ions, namely $M(L^x)_2$, for $x = 15$ and 16 , and for $M(II) = Ni, Pd,$ and Pt [36]. The different metals induced distinct antifungal responses

against *A. flavus*, *A. niger*, and *A. parasiticus*. The Pd(L^x)₂ complexes were the most active against *A. flavus* while *A. niger* was more sensitive towards the Ni(L^x)₂ congeners. By contrast, Pt(L¹⁶)₂ was the most active against *A. parasiticus* despite its activity being nearly 10-fold lower when L¹⁵ was employed.

Despite most studies showing the presence of metal ions improves the biocidal activities exhibited by the dithiocarbamates when administered alone, the inverse is true for the case of morpholine dithiocarbamates, M(L¹⁸)₂ for M(II) = Ni and Cu [58]. Thus, K(L¹⁸) displayed better antibacterial efficacy on the growth of Gram-positive (*S. aureus*, *B. cereus*, and *L.monocytogenes*) and Gram-negative (*S. flexneri*) bacteria compared to the metal complexes. No definitive trend in activities between dithiocarbamates and their metal complexes was observed for the series M(L^{19–21})₂ for M(II) = Mn, Fe, Co, Ni, Cu, and Zn, tested by Yilmaz et al. [48]. The complexes showed varied responses towards the microorganisms tested (*E. coli*, *P. aeruginosa*, *S. Typhimurium*, *B. pumilus*, *S. aureus*, *C. albicans*, and *A. niger*). Generally, the dithiocarbamates showed better sensitivity towards Gram-positive bacteria (*B. pumilus* and *S. aureus*), yeast (*C. albicans*), and a mold (*A. niger*) while the complexes exhibited comparative or better activities against Gram-negative bacteria (*E. coli*, *P. aeruginosa*, and *S. Typhimurium*). The above indicates that the inclusion of metal ions does not necessarily improve the bioactivity of the compound.

In 2015, Verma and Singh reported the antimicrobial activities of dithiocarbamate derivatives of naphthoquinone (L²²) and their transition metal complexes M(L²²)_y for y = 3 and M(III) = Mn and Co, and for y = 2, and M(II) = Ni, Cu, and Zn [59]. All complexes showed moderate activities against the tested bacteria and fungi with M(L²²)₂ displaying promising activity towards *S. aureus* (MIC 10 µg/mL cf. ciprofloxacin 15 µg/mL) and *A. niger* (MIC 50 µg/mL cf. fluconazole 40 µg/mL).

Maurya et al. studied the efficacy of zinc(II) compounds bearing benzyl derived dithiocarbamates; Zn(L^{23–26})₂, with the L²⁵ compound having the most prominent killing potential against all the tested bacterial strains, that is, clinical and control strains of *S. aureus* and *E. coli* [60]. Sathiyaraj et al. on the other hand explored the effect of dissymmetric dithiocarbamates L^{27–30}, featuring furyl groups, in Zn(L^{27–30})₂ compounds against bacteria (*V. cholerae*, *B. subtilis*, *K. pneumoniae*, *E. coli*, and *S. aureus*) and two fungi (*A. niger* and *C. albicans*) by disc diffusion methods [61]. The synthesized compounds showed less activity towards *B. subtilis*, *E. coli*, and *S. aureus* but slightly better effects on *V. cholerae* and *K. pneumoniae* while showing moderate activities towards the two fungi.

Ferrocene, Cp₂Fe (CpH is cyclopentadiene) is of great interest as an active pharmaceutical ingredient (API) in no small part owing to its redox chemistry, ability to generate reactive oxygen species (ROS), and its ability to induce oxidation in various species such as DNA and proteins [62,63]. Furthermore, ferrocene can impart increased cell permeability and lipophilicity. Verma and Singh prepared a series of nine transition metal complexes with ferrocene functionalized dithiocarbamates [64]. Among the complexes tested, Ni(L³¹)₂ (MIC = 10 µg/mL against *S. aureus*) and Ni(L³²)₂ (MIC = 10 µg/mL against *C. albicans*) as well as Cu(L³³)₂ (MIC = 10 µg/mL against *S. aureus*) exhibited the most promising antimicrobial activities.

Manav et al. [65] and Shasheen et al. [66] evaluated the antibacterial properties of platinum(IV) and palladium(II) complexes, respectively. None of the three Pt(L^{18,34,35})₂Cl₂ species showed significant antibacterial properties [65]. By contrast, the Pd(L^{10,34,36–39})₂ complexes exhibited moderate to comparable activity in comparison with the standard imipenem [66]. In a wider study, with six variations of H, Me, Cl, and i-Pr substituents distributed among two phenyl rings, that is, M(L^{40–45})₂, for M(II) = Ni and Cu, showed moderate to good, broad range antibacterial activities against Gram-negative (*S. Typhimurium*, *P. aeruginosa*, *E. coli*, and *K. pneumoniae*) and Gram-positive (*S. aureus*) bacteria; however, only a weak effect on methicillin-resistant *S. aureus* (MRSA) was reported by Oladipo and colleagues [67]. Generally, complexes with chloro-substituted and symmetrically-substituted dithiocarbamates ligands displayed better activities.

Thus far, the focus of the discussion has been upon homoleptic transition metal dithiocarbamates. A broader chemistry is evident in their heteroleptic complexes, often involving the incorporation of neutral phosphane and bipyridine-type molecules. While some studies suggest the antimicrobial activity of these heteroleptic complexes is reduced upon the addition of triphenylphosphane [68] and 1,10-phenanthroline (phen) [69,70], the opposite was observed when 2,2'-bipyridine (bipy) was incorporated in $\text{Zn}(\text{L}^{46})_2(\text{bipy})$ which was the most effective complex towards Gram-negative pathogenic bacterial strains (*E. coli*, *S. Typhi*, and *V. cholerae*) [71]. It was proposed that 2,2'-bipyridine enhanced the membrane transport into the bacterium. This compound also displayed a good inhibitory effect against the fungus *T. mentagrophyte* while $\text{Zn}(\text{L}^{46})_2$ showed greater activities against the fungi *M. gypseum* and *T. rubrum*. In another study, the presence of 2,2'-bipyridine in $\text{Zn}(\text{L}^{47})(\text{bipy})\text{Cl}$ was also found to enhance the efficacy against five human bacterial pathogens namely, *S. Typhi*, *S. flexneri*, *S. aureus*, *A. hydrophila*, and *E. faecalis*, compared to $\text{Zn}(\text{L}^{48})_2(\text{pyridine or 4-picoline})$ [72].

Kalia et al. also studied the effect of mixed ligand complexes by evaluating $\text{M}(\text{L}^{37})_2(\text{phen})$ and $[\text{M}(\text{L}^{37})(\text{phen})_2]\text{Cl}$, for $\text{M}(\text{II}) = \text{Mn, Co, and Zn}$, against *C. albicans*, *E. coli*, *P. aeruginosa*, *S. aureus*, and *E. faecalis* [45]. The test complexes were highly effective against *C. albicans* among the microbial species evaluated. A related complex, $\text{Co}(\text{L}^{10})_2(\text{phen})$, showed better antifungal activity towards *C. albicans* compared to *A. flavus* and *A. niger* [73]. Both $\text{Co}(\text{L}^{10})_2(\text{phen})$ and its derived nanoparticles also showed significant antibacterial activities against *E. coli*, *B. subtilis*, *S. aureus*, and *K. pneumoniae* with the nanoparticles exerting a greater antibacterial effect.

The recent report on a series of complexes formulated as $\text{M}(\text{L}^{10})_2(\text{bipy or phen})$ and $\text{M}(\text{L}^{10})_2(\text{pyridyl-3-amine})_2$, for $\text{M}(\text{II}) = \text{Pd and Zn}$, as well as $\text{trans}(\text{PPh}_3)_2\text{Pd}(\text{L}^{10})$ (benzothiazolate or saccharinate) and the evaluation of their antimicrobial properties revealed the phosphane complexes to be the most active against bacteria (*E. coli*, *S. aureus*, and *S. pyogenes*) and fungi (*C. albicans* and *A. niger*) [74]. The authors suggested that in addition to the enhanced activity attributed to the presence of metals and the heteroaromatics, that is, benzothiazolate and saccharinate, the complexes with greater size (molecular weight) were found to exert better antimicrobial responses due to their greater permeability through the microbial cell wall [74]. In another study, El-said and colleagues reported a series of nickel(II) complexes of multifunctional, dianionic dithiocarbamates, that is, dithiocarbamates derived from amino acids, $\text{Ni}(\text{L}^{49-53})(\text{phen})_2$, as well as a dinuclear copper(II) complex formulated as $[\text{Cu}_2(\text{L}^{51})\text{Br}_2(\text{phen})_2(\text{H}_2\text{O})_2]$; these complexes were shown to be active towards bacteria (*B. cereus*, *E. coli*, and *P. aeruginosa*) and fungi (*A. niger* and *T. roseum*) [75].

Rani et al. reported a series of nickel(II) complexes of a dissymmetric dithiocarbamate ligand containing both furyl and thienyl functionalities, namely L^{54} [76]. The screening of the complexes, $\text{Ni}(\text{L}^{54})_2$, $(\text{PPh}_3)\text{Ni}(\text{L}^{54})(\text{NCS})$, and salt $[(\text{PPh}_3)_2\text{Ni}(\text{L}^{54})]\text{ClO}_4$ showed the presence of triphenylphosphine did not induce a significant effect upon their antibacterial activity against *S. aureus*, *E. coli*, *P. aeruginosa*, and *K. pneumoniae*; the three complexes exhibited promising effects against *S. aureus* and *K. pneumoniae*. Among the bacteria species, *E. coli* was the least sensitive towards all the complexes tested.

A series of heteroleptic palladium(II) dithiocarbamates of general formula $(\text{R}_3\text{P})\text{Pd}(\text{L}^{36,55-61})\text{Cl}$, for a broad range of monodentate phosphanes, such as Ph_3P , Cy_3P , (*n*-propyl) Ph_2P , and $(\text{C}_5\text{H}_4\text{N}-2)\text{Ph}_2\text{P}$, were screened against two Gram-negative (*E. coli* and *K. pneumoniae*) and three Gram-positive bacterial strains (*S. epidermidis*, *S. aureus*, and *B. subtilis*) [77,78]. Moderate antibacterial activities were evidenced as well as a few conclusions deduced in terms of a structure-activity relationship: (i) the length of the alkyl group of the dithiocarbamate ligands plays an important role in the antibacterial activity with longer chains being more potent, (ii) bulky substituents increase the lipophilicity and therefore, aid the permeability through the cell membrane of the bacterium, and (iii) electron-withdrawing substituents induce poorer antibacterial responses.

Odola and Woods reported a series of mixed ligand nickel(II) dithiocarbamate complexes bearing a monoanionic Schiff base ligand, ethylsalicylaldimine (EtSal), of general formula $\text{Ni}(\text{L}^n)(\text{EtSal})$, for $n = 6, 34, 39$, and $62\text{--}64$ [79], and $n = 3, 8, 10, 18$, and $65\text{--}67$ [80], and evaluated their antimicrobial activities against six bacterial strains (*S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa*, *P. mirabilis*, and *K. pneumoniae*) and four fungi (*C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. pseudotropicalis*). The common feature of these complexes was their selective activity against *P. mirabilis* and inactivity towards *S. aureus* and *C. glabrata*. In related work, Asuquo et al. reported studies of $\text{Ni}(\text{L}^{6,34,39,56,62\text{--}64,68})(\text{PhSal})$, where PhSal = phenylsalicylaldimine, and tested them against three Gram-negative bacteria (*E. coli*, *P. aeruginosa*, and *S. Typhi*) and two Gram-positive bacteria (*S. aureus* and *B. subtilis*) [81]. Generally, all complexes were active against the bacteria except for $\text{Ni}(\text{L}^{56})(\text{PhSal})$ which was inactive against *S. aureus* while $\text{Ni}(\text{L}^{39})(\text{PhSal})$ and $\text{Ni}(\text{L}^{56})(\text{PhSal})$ were inactive against *E. coli*.

Sovilj et al. showed the incorporation of metal ions improved the antibacterial activities in series of dinuclear copper(II) $[\text{Cu}_2(\text{L}^{10,18,69\text{--}71})\text{tpmc}](\text{ClO}_4)_3$ [82] and $[\text{Mo}(\text{=O})_2(\text{L}^{10,18,69\text{--}71})_2]$ [83] complexes, where tpmc = N,N',N'',N'''-tetrakis(2-pyridylmethyl)-1,4,8,11-terazacyclotetradecane. A similar observation was made in an evaluation of the antibacterial activities of three mononuclear, cyclometallated iridium(III) complexes formulated as $[\text{Ir}(\text{L}^{18,70,72})(2\text{-phenylpyridine})_2]$ against *E. coli*, *V. cholerae*, *S. pneumoniae*, and *B. cereus* by agar disc diffusion [84]. The study showed $[\text{Ir}(\text{L}^{10})(2\text{-phenylpyridine})_2]$ to be the most active and suggested the enhanced activities could be attributed to the increased lipophilic character of the metal complexes which facilitated penetration into the bacterial cell membrane.

Ajibade et al. and Ekennia et al. evaluated the antimicrobial properties of ternary complexes with a variety of transition metals formulated as $\text{M}(\text{L}^{55,56})(\text{sulfadiazine})$ for $\text{M}(\text{II}) = \text{Co}, \text{Cu}, \text{Pd}, \text{and Pt}$ [85], and the complexes $[\text{M}(\text{L}^{55})(\text{benzoylacetone})(\text{H}_2\text{O})_2].n\text{H}_2\text{O}$ and $[\text{M}(\text{L}^{55})(\text{benzoylacetone})].n\text{H}_2\text{O}$ for $\text{M} = \text{Zn}, \text{Cu}, \text{Mn}, \text{and Co}$ [86]. In the first series [85], the cobalt(II) complex showed greater antibacterial activities whereas of the others [86], the zinc(II) compound exhibited overall better antimicrobial activities against Gram-positive bacteria (*S. aureus* and *S. pneumoniae*), Gram-negative bacterium (*E. coli*), and two fungal organisms (*A. niger* and *A. candida*).

Kim et al. developed a polymer matrix for the controlled release of drugs by preparing metal-drug complexes derived from chemically modified chitosan [87]. Briefly, the chitosan species with pendant dithiocarbamate residues ($-\text{CS}_2^{(-)}$), DTCC, was treated with heavy element tetracycline (Tc) complexes to afford DTCC-M-Tc conjugates with $\text{M}(\text{II}) = \text{Ca}, \text{Mg}, \text{Cu}, \text{and Zn}$. The resulting species demonstrated prolonged antibacterial activity (28 to 44 days) against *E. coli* with the exception of the copper(II) example.

While copper(I) and copper(II) species have featured prominently in the above overview, attention now turns to gold and silver. Gold-based drugs are known to have significant medicinal properties with the phosphane-gold(I) thiolate antiarthritic drug, Auranofin[®], being a prominent example [88]; studies of the antibacterial potential of gold compounds are well established [89]. The potential of phosphane-gold(I) dithiocarbamates, that is, $\text{R}_3\text{PAu}(\text{L}^{14})$, for $\text{R} = \text{Ph}$ and Cy , and $\text{Et}_3\text{PAu}(\text{L}^{56,65})$ was explored [38]. From the antibacterial study conducted against a panel of 24 Gram-positive and Gram-negative bacteria, it was found that compounds bearing bulkier phosphane ligands showed specific activity towards Gram-positive bacteria while those with triethyl phosphane displayed a broader range of activity against the tested bacteria [38]. In a related study on a series of $\{\text{Cy}_3\text{PAG}(\text{L}^{11,14,56,65})\}_2$ complexes showed the dinuclear silver(I) species to exhibit selective activity towards Gram-positive bacteria [90]. Against susceptible bacteria, preliminary time-kill assays revealed many of the gold(I) and silver(I) compounds to exhibit both time and concentration-dependent pharmacokinetics [38,90]. The dinuclear silver compounds lead nicely into the final series of multinuclear complexes to be reviewed in this section, which again proved the axiom that the presence of a transition metal element enhanced potency.

Bipodal dianionic dithiocarbamates, that is, $(^-)S_2CN(H)R(H)NCS_2(^-)$, for R = zero, CH_2CH_2 , and C_6H_4 , give rise to dinuclear metal(II) complexes of the general formula $[M(S_2CN(H)R(H)NCS_2)]_2$, with M = Ni, Cu, Zn, and Cd, demonstrating enhanced activity as compared to the ligand alone towards *B. subtilis*, *S. pyogenes*, *E. coli*, *K. pneumoniae*, *A. niger*, and *S. cerevisiae* [91]. On the other hand, the presence of dithiocarbamate dianions in a series of dinuclear transition metal(II) dithiocarbamate based metallamacrocycles of general formula, $[M(S_2CN(H)(C_6H_4)N=C(Ph)-C(Ph)=NC_6H_4(H)NCS_2)]_2$, with M(II) = Co, Ni, and Cu [92], exhibited improved efficacy against *S. aureus* and *E. coli* compared with the free ligand; these complexes were inactive against *P. aeruginosa*. The final series of complexes provide a convenient segue to the next section, as they contain both transition metal, M(II), and tin(IV) centers. In $Sn(thiocarbohydrazide)_2[M(L^{56})_2]_2$, pairs of tin-coordinating nitrogen atoms link transition metals, already coordinated by two L^{56} anions [93]. Thus, trinuclear species with M(II) = Mn, Fe, Co, Ni, and Cu, were screened against bacterial strains *E. coli* and *S. Typhi*. Here, the dithiocarbamate complexes exerted better efficacy compared to $Sn(tch)_2$ with the complex with M = Co being the most potent [93].

3.3. Main Group Element Dithiocarbamates

The study of the antimicrobial potential of main group element dithiocarbamates is dominated by investigations of tin compounds as well as those of antimony and bismuth. Probably the most well-studied are organotin dithiocarbamates, especially diorgano- and triorgano-tin(IV) species.

Shahzadi et al. and Zia-ur-Rehman et al. reported the antimicrobial activities of $Ph_3Sn(L^{70})$ [42] and $Me_2Sn(L^{70})_2$ [46], respectively. In both cases, it was shown that the incorporation of tin(IV) enhanced the antibacterial (*E. coli*, *B. subtilis*, *S. flexneri*, *S. aureus*, and *S. Typhi*) and antifungal (*T. longifusus*, *F. solani*, and *C. glabrata*) activities compared to the ligand alone, Table 1. In 2008, Menezes et al. revealed that for a series of $R_xSn(L^{56,65})_{4-x}$, with x = 1, 2, and 3; R = Cl, n-Bu, Ph, and Cy, the presence of a tin-bound phenyl substituent resulted in lower MIC values towards *S. aureus* [94]. Other important findings worth highlighting from this study include: (i) trisubstituted tin(IV) compounds showed better antibacterial potency, (ii) the L^{56} compounds showed better antibacterial activity with greater inhibition zones, and (iii) the antibacterial potency of the tin(IV) compounds differ when evaluated in solution or pseudo solid medium (agar); the results obtained from the disc diffusion method and MIC values cannot be well correlated possibly due to the limited mobility of the complexes in the agar.

The importance of lipophilicity was also mentioned by Awang et al. [95–97] in their study of compounds in a series of $R_xSn(L^{34,35})_{4-x}$ compounds, with x = 2 and 3, R = Me, n-Bu, and Ph. The compounds were tested against *S. aureus*, *S. Typhimurium*, *P. aeruginosa*, *B. subtilis*, *Klebsiella* sp., *A. baumannii*, *E. raffinosus*, and *E. aerogenes*—increased lipophilicity of the compounds generally enhanced the antibacterial activity; the R = n-Bu compounds were inactive.

The issue of lipophilicity was also addressed in the work published by Adeyemi et al. [98–100] in their reports upon the antimicrobial potential of $RSn(L^6)_2Cl$ with R = n-Bu and Ph; $(n-Bu)Sn(L^{73})_2Cl$ and $R_2Sn(L^{73})_2$ with R = Me, n-Bu, and Ph; $Sn(L^{74})_2Cl_2$ and $R_2Sn(L^{74})_2$ with R = Me, n-Bu, and Ph. The authors observed increased lipophilicity in the diphenyltin derivatives correlated with greater activities in comparison with the other derivatives. Furthermore, these organotin complexes showed better activity towards bacterial species than the fungi tested, with Gram-negative bacteria being more susceptible than the Gram-positive organisms. Another series of $R_2Sn(L^{10})Cl$, with R = Me, Et, n-Bu, Ph, and CH_2Ph , also showed promising antibacterial activities against *E. coli*, *B. subtilis*, *S. flexneri*, *S. aureus*, *P. aeruginosa*, and *S. Typhi* but exhibited reduced activities compared to the standard drugs Miconazole and Amphotericin B against the six strains of fungi screened (*T. longifusus*, *C. albicans*, *A. flavus*, *M. canis*, *F. solani*, and *C. glabrata*) [101].

Several studies indicate triorganotin(IV) species generally show better bioactivities compared to their diorganotin(IV) counterparts [43,102–104]. Zia-ur-Rehman et al. [43]

prepared a series of organotin(IV) complexes bearing 4-benzylpiperidine-1-carbodithioate that is, $R_3Sn(L^{72})$, with $R = Me, n-Bu, Ph,$ and Cy , $R_2Sn(L^{72})Cl$ and $R_2Sn(L^{72})_2$, with $R = Me, Et,$ and $n-Bu$, and evaluated their activities against bacteria species (*E. coli*, *S. Typhi*, *P. aeruginosa*, *S. aureus*, and *Streptococcus* sp.) and fungi (*A. niger*, *A. flavus*, *H. solani*, *A. solani*, and *Fusarium* sp.). The triorganotin(IV) derivatives displayed good antibacterial activities with the exception against *S. aureus* where none of the compounds was able to inhibit its growth. Additionally, the triorganotin(IV) derivatives generally had better antifungal activities than the diorganotin(IV) derivatives against *A. niger* and *A. flavus* but showed weaker sensitivities towards the other three fungi strains. Furthermore, the diorganotin(IV) chloride compounds were more active compared to their counterparts without chloride; it was proposed that the presence of chloride facilitated hydrolysis.

In 2012, Shaheen et al. reported the screening of a series of organotin(IV) compounds: $R_3Sn(L^{75})$, with $R = Me, n-Bu,$ and Ph , $R_2Sn(L^{75})Cl$, with $R = Me, n-Bu, Ph,$ and Et , as well as $Et_2Sn(L^{75})_2$. The antibacterial study conducted against *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *E. coli* revealed a similar trend as observed above where the triorganotin(IV) compounds are more active than the diorganotin(IV) derivatives [102].

Among the three organotin(IV) compounds $Ph_3Sn(L^{76})$ and $R_2Sn(L^{76})_2$, with $R = Me$ and $n-Bu$, those with bulkier substituents showed the greatest antibacterial activities [103]. Furthermore, $Ph_3Sn(L^{76})$ showed maximum potency against *S. aureus* and *B. cereus*, possibly owing to the enhanced lipophilicity [103]. Similarly, enhanced activities were observed for triorganotin(IV) compounds in two series of homobimetallic $R_3Sn(L^{77})SnR_3$ species, with $R = n-Bu$ and Ph , and $R_2(Cl)Sn(L^{77})Sn(Cl)R_2$, with $R = Me$ and $n-Bu$, compounds where L^{77} also carries a thiolate-sulfur atom available for coordination [104]. The triorganotin(IV) congeners displayed better antimicrobial potency towards the eight microbials tested (*S. aureus*, *E. coli*, *B. subtilis*, *P. multocida*, *A. niger*, *A. flavus*, *R. solani*, and *A. alternata*). Antimicrobial studies on $Ph_3Sn(L^{71,77})$, $Ph_2Sn(L^{71})Cl$, $R_2Sn(L^{71})_2$ with $R = n-Bu$ and Ph , and $Ph_2Sn(L^{77})_2$ [105] indicated all compounds were effective against *E. coli* with $Ph_3Sn(L^{71})$ being the most effective and $Ph_3Sn(L^{77})$ being the least. This shows that in determining antibacterial activity both the tin and dithiocarbamate bound substituents must be taken into consideration.

Attention is now directed to the other major class of main group dithiocarbamates, namely those of the Group 15 elements; a review appeared recently covering aspects of the antibacterial activity exhibited by antimony and bismuth compounds [106]. Chauhan et al. prepared two series of ternary dithiocarbamate complexes comprising dithiophosphate ligands, namely, $M(L^{55,56})_2(S_2POYO)$ for $M = arsenic(III)$ [107] and bismuth(III) [35] for $Y = -CH_2C(Et)_2CH_2-$, $-CH_2C(Me)_2CH_2-$, $-CH(Me)CH(Me)-$, and $-C(Me)_2C(Me)_2-$. Coordination of $L^{55,56}$ with bismuth(III) enhanced the biological properties as compared to the ligands alone, Table 1. Furthermore, the compounds were more sensitive towards Gram-positive bacteria. Overall, the compounds with L^{55} showed better inhibition towards the bacterial strains tested (*S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa*) compared to those with L^{56} . Chauhan et al. also studied the antimicrobial properties of arsenic(III) and antimony(III) dithiocarbamates against four bacterial strains (*S. aureus*, *B. subtilis*, *E. coli*, and *P. aeruginosa*) and two fungal species (*A. niger* and *T. reesie*) [108–110]. The investigated mono-nuclear compounds were $[Sb(L^{18,55})_2]X$ for $X = O(O=C)Me$, $O(O=C)Ph$, $O(S=C)Me$, SCH_2COOH , $O(O=)CC_6H_4(OH)$, $S(n-Pr)$, and OPh [109,110]; $[M(L^{18,55})_2]_2X$, for $M(III) = As$ and Sb , $X = -SCH_2CH_2S-$ [108,109], and $M(L^{55,56,65})_2[S(S)P(Y)_2]$ for $M(III) = As$ and Sb ; $Y = OPh$ and Ph [110]. The evaluation of the antimicrobial activities showed that complexation enhanced the biological properties and the compounds showed comparable or better activities than the standard drugs, chloramphenicol and terbinafine.

On the other hand, the study conducted by Tamilvanan et al. on three bismuth(III) furfuryl-substituted dithiocarbamate compounds, $Bi(L^{79-81})_3$ against *V. chlorerae*, *B. subtilis*, *K. pneumoniae*, *E. coli*, and *S. aureus* showed they exhibited selective activities towards *V. chlorerae* and *K. pneumoniae* with the n-butyl compound, $Bi(L^{80})_3$, being less active than the others [111].

Organoantimony(III) and organoantimony(V) dithiocarbamates have also been investigated for antimicrobial activity. Thus, Sharma et al. prepared series of compounds of general formula $\text{PhSb}(\text{L}^{18,37,65,70})\text{Cl}$ and $\text{PhSb}(\text{L}^{18,37,65,70})_2$ [112]. Their antimicrobial properties were screened against two Gram-negative bacteria (*E. coli* and *P. aeruginosa*) and two fungal strains (*A. flavus* and *A. niger*); the results indicated the incorporation of antimony enhanced the inhibitory effect compared to the free ligand owing to the increased lipophilic character of the metal chelate that aids the permeation of the compounds through the lipid layer of cell membranes [112]. Later, Beniwal et al. further investigated the antimicrobial activities of antimony(III) dithiocarbamates also containing substituted oxime molecules, that is, $\text{PhSb}[\text{R}(\text{R}')\text{C}=\text{NO}](\text{L}^{10})$ [113] and $\text{Sb}[\text{R}(\text{R}')\text{C}=\text{NO}]_2(\text{L}^{10})$ [114], and some antimony(V) species, $\text{Ph}_3\text{Sb}[\text{R}(\text{R}')\text{C}=\text{NO}](\text{L}^{18})$ [115], for $\text{R} = \text{Me}$, $\text{R}' = \text{Ph}$, $\text{C}_6\text{H}_4\text{Me-4}$, $\text{C}_6\text{H}_4\text{Cl-4}$, and $\text{C}_6\text{H}_4\text{Br-4}$; $\text{R} = \text{H}$ and $\text{R}' = \text{C}_6\text{H}_4\text{OH-4}$; and $\text{CR}(\text{R}') = \text{C}_5\text{H}_{10}$, against Gram-positive (*B. subtilis*) and Gram-negative (*E. coli*) bacterial strains. Overall, the antimony compounds showed enhanced activity as compared to the free dithiocarbamate and oxime ligands. The $\text{PhSb}[\text{R}(\text{R}')\text{C}=\text{NO}](\text{L}^{10})$ compounds showed greater antibacterial effects towards *B. subtilis* while $\text{PhSb}[(\text{C}_6\text{H}_4\text{OH-4})\text{HC}=\text{NO}](\text{L}^{10})$ exhibited marked activities against both bacteria. On the other hand, $[(\text{C}_6\text{H}_4\text{Me-4})\text{C}(\text{Me})=\text{NO}]_2\text{Sb}[\text{S}_2\text{CN}(\text{L}^{10})]$ was the most active among the series in [114] while in the case of $\text{Ph}_3\text{Sb}[\text{R}(\text{R}')\text{C}=\text{NO}](\text{L}^{18})$ [115], when $\text{R} = \text{Me}$, $\text{R}' = \text{C}_6\text{H}_4\text{Cl-4}$; and $\text{R} = \text{H}$, $\text{R}' = \text{C}_6\text{H}_4\text{OH-4}$, the compounds showed greater antibacterial activity towards *B. subtilis*.

A broader range of main group elements was investigated in a study of $\text{M}(\text{L}^{82})_3$, where $\text{M}(\text{III}) = \text{Ga}$, In , As , Sb , and Bi , which were subjected to antibacterial assays against ten American Type Culture Collection (ATCC) bacterial strains and ten multiresistant clinical isolated strains, including four extended-spectrum β -lactamase producing *E. coli* strains, one methicillin resistant *S. epidermidis* strain, three methicillin-resistant *S. haemolyticus* strains, and one methicillin-resistant *S. simulans* strain [37]. Overall the indium(III) species demonstrated the greatest antibacterial activities against the evaluated bacterial strains, a result correlated with computational studies that showed $\text{In}(\text{L}^{82})_3$ possessed better stability than the other congeners thus promoted its transport to the biological target site in the bacterial cell.

4. Possible Mechanisms of Action

As mentioned in the introduction, dithiocarbamates such as Zineb[®] have been used as agricultural fungicides in various countries since the 1940s but their possible mode(s) of action and molecular targets remained elusive until the last decade. Dithiocarbamates are strong chelating agents, and this feature seems to play a crucial role in their antimicrobial activity. To date, evidence shows that 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.

4.1. Carbonic Anhydrase Inhibitors

Carbonic anhydrases (E.C. 4.2.1.1) are a group of metalloenzymes that catalyze the conversion of carbon dioxide to bicarbonates and protons. This group of metalloenzymes is made up of genetically distinct protein families, namely, the α -, β -, γ -, δ -, ζ -, η -, and θ -families, which are distinguished by their molecular structures and folds. These metalloenzymes are widespread and were identified in organisms across all three life domains: Eukarya, Bacteria, and Archaea [116]. Like carbon dioxide, bicarbonate, and protons play important roles in various physiological processes, the use of carbonic anhydrase inhibitors was demonstrated to have multiple therapeutic applications, including antiglaucoma, anti-obesity, anticonvulsant, and antimicrobial [117]. Various classes of carbonic anhydrase inhibitors have been identified to date, including carboxylic acids, phenols, polyamines, diols, borols, boronic acids, coumarins, and sulfonamides [118]. The potential of dithiocarbamates as a carbonic anhydrase inhibitor in the context of antimicrobial agents was

established and reviewed [119,120]. In the following Sections 4.1.1–4.1.3), the carbonic anhydrase inhibitor roles of dithiocarbamates in bacteria, fungi, and protozoa will be reviewed.

4.1.1. Bacteria

Bacteria encode three families of carbonic anhydrases, namely α -, β -, and γ -. The α - and β -carbonic anhydrases use zinc(II) as the catalytic metal in their active sites while γ -carbonic anhydrases use iron(II) centers, and possibly bound zinc(II) or cobalt(II) centers as catalytic metals [121]. Evidence suggests dithiocarbamates act as carbonic anhydrase inhibitors in two human pathogenic bacteria, namely *L. pneumophila* and *M. tuberculosis*.

L. pneumophila, a Gram-negative bacterium that causes Legionnaires' disease, is an intracellular pathogen that evolves to evade phagocytosis of human macrophage cells by surviving within phagosomes of macrophages. Generally, once a pathogen is engulfed by a macrophage, a phagosome will form around the pathogen, followed by a change in the pH within the phagosome as part of the processes of killing and digesting the pathogen. *L. pneumophila* evolved to maintain a neutral pH in phagosomes avoiding the acidic conditions that occur naturally in phagosomes [122]. It is thought that the pH regulation by *L. pneumophila* is associated with the activity of a carbonic anhydrase enzyme that generates protons and bicarbonate via the hydration of any available CO_2 [123]. An earlier study investigated the carbonic anhydrase inhibition activity of various molecules, including diethyldithiocarbamate among other species such as sulfamide, phenylboronic acid, and phenylarsonic acids on two of the β -class carbonic anhydrases from *L. pneumophila*, lpCA1, and lpCA2. Data showed that diethyldithiocarbamate was a much stronger inhibitor for lpCA1 and lpCA2 compared to the known carbonic anhydrase inhibitor, sulfamide [124].

In a separate study, Bryne and coworkers reported the potent antibacterial activity of diethyldithiocarbamate, pyrrolidine dithiocarbamate and Disulfiram[®] on persister cells of *M. tuberculosis*, dormant bacterial cells that do not respond to antibiotic treatment. At this point, the mechanism of action of these compounds was not known but the authors suggested that the antibacterial activity may be related to their metal-chelating abilities [125]. It was not until 2013, when Maresca et al. showed that a wide range of 27 dithiocarbamate derivatives were able to inhibit the activity of carbonic anhydrases, mtCA1 and mtCA3, from *M. tuberculosis*, indicating the antibacterial activity of these molecules is due to their inhibition of carbonic anhydrase [126]. From this study, a structure-activity relationship revealed that dithiocarbamates obtained from primary amines exhibited good inhibitory activity while those derived from secondary amines are comparatively less effective. Overall, it was observed that the increase in aliphatic chain and/or cyclization contributed to enhanced inhibitory activity, with dihydroxyethyl dithiocarbamate, $[\text{S}_2\text{CN}(\text{CH}_2\text{CH}_2\text{OH})_2]^-$, morpholine dithiocarbamate, $[\text{S}_2\text{CN}(\text{CH}_2\text{CH}_2)_2\text{O}]^-$, and (S)-proline dithiocarbamate, $[(\text{S})\text{-NaS}_2\text{CNC}_4\text{H}_7\text{CO}_2\text{-2Na}]$, being the most effective inhibitors.

In a recent report, a panel of seven dithiocarbamates was tested against β -carbonic anhydrase 3 of *M. tuberculosis*. Of the seven compounds, sodium morpholine dithiocarbamate appeared to inhibit the carbonic anhydrase enzyme effectively and exhibited low toxicity effects on zebrafish larvae [127]. The potent carbonic anhydrase inhibition activity of dithiocarbamates on *M. tuberculosis* brings hope to the scientific community as this deadly pathogen was recorded to kill 1.5 million people in 2014 alone. Compounding the issue, many *M. tuberculosis* strains have evolved into Multi Drug-Resistant (MDR) and Extensively Drug-Resistant (XDR) tuberculosis pathogens that are challenging to treat using existing antibiotics [128].

4.1.2. Fungi

Similar to bacteria, fungal species encode for both α - and β -carbonic anhydrases [119]. The known antifungal activity of dithiocarbamate molecules and their metal complexes were reviewed above. The overwhelming majority of those studies focused upon the

testing for antifungal potential without elucidating the possible mechanisms of the putative antifungal agents.

A limited number of studies demonstrated the carbonic anhydrase inhibitory role of dithiocarbamates. In 2012, Monti et al. reported N-mono- and N,N-disubstituted dithiocarbamates generally inhibited the activity of three β -carbonic anhydrases, namely Can2, CaNce103, and CgNce103 from three opportunistic yeast species, *C. neoformans*, *C. albicans*, and *C. glabrata*, respectively [129]. In a more recent report, the β -carbonic anhydrase inhibitory role of dithiocarbamates was also proven in baker's yeast *S. cerevisiae* [130]. The carbonic anhydrase inhibition capability of dithiocarbamates on α -carbonic anhydrase has not been described thus far.

4.1.3. Protozoa

To date, a limited number of studies have demonstrated the antiprotozoal potential of dithiocarbamate derivatives and metal dithiocarbamates. As discussed in Section 3.1, pyrrolidine dithiocarbamate was able to kill extracellular *T. gondii*, the causative agent of toxoplasmosis, but not intracellular *T. gondii*. The authors claimed the killing effect of pyrrolidine dithiocarbamate was related to oxidation in cells [27]. In a separate study, three sodium salts of piperazine bis(dithiocarbamate) esters, that is, $(^-)S_2CN(CH_2CH_2)_2NCS_2R$ for R = n-Bu, CH₂Ph, and CH₂CH₂N(CH₂)₅, were reported to have effects against *T. vaginalis*, even though these are weaker compared to the chemotherapeutic agent, metronidazole [46]. Despite interesting data on the antiprotozoan activity of these compounds, the mode of action remains unexplored. However, in the following year, Pal and coworkers investigated the inhibition activity of three metal dithiocarbamates, Zineb[®] and closely related species Propineb[®], $\{Zn(S_2CN(H)CH(Me)CH_2N(H)CS_2)\}_n$, and Maneb[®], $\{Mn(S_2CN(H)CH_2CH_2N(H)CS_2)\}_n$, on *L. major* promastigotes [131]. Using both real-time polymerase chain reaction (RT-PCR) and carbonic anhydrase assays, their data confirmed these metal dithiocarbamates inhibited carbonic anhydrase expression and its activity at submicromolar concentrations. Their study also reported the ability of these metal dithiocarbamates to reduce the intracellular burden of the protozoa without exhibiting cytotoxic effects on human mammalian cell lines, that is, macrophage 774A.1 and fibroblast NIH 3T3 [131] cells. *L. major* is one of the causative agents for vector-borne disease leishmaniasis that occurs commonly in tropical and subtropical regions. Despite being the ninth-largest disease burden among infectious diseases, limited drug options are available to treat this disease [132]. The carbonic anhydrase inhibition activity of dithiocarbamates on this parasite provides a foundation for further investigations of the potential of metal dithiocarbamates in combating leishmaniasis globally.

4.2. Metallo-Beta-Lactamase Inhibitors

Beta-lactam antibiotics that target bacterial peptidoglycan structure are one of the largest groups of commercially available antibiotics, and include penicillin, cephalosporins, monobactams, and carbapenems [133]. The unregulated use of these antibiotics has led to the emergence of beta-lactam-resistant bacteria. One of the resistance mechanisms involves the production of beta-lactamases, enzymes that hydrolyze the beta-lactam rings present in many antibiotics. Of the four classes of beta-lactamases, metallo-beta-lactamases (MBLs), Class B Ambler beta-lactamases, are produced by a group of multidrug-resistant Gram-negative bacteria, including *Enterobacter* spp., *K. pneumoniae*, and *P. aeruginosa*, members of the key nosocomial ESKAPE pathogens [134,135]. MBLs confer resistance to carbapenems, such as imipenem and meropenem, employed as the last resort antibiotics for extended-spectrum beta-lactamase (ESBL) producing drug-resistant bacteria [136]. The most common metallo-beta-lactamase families include the New Delhi metallo-beta-lactamase 1 (NDM-1), Verona integron encoded metallo-beta-lactamase (VIM) and imipenem resistant pseudomonas (IMP) [137]. MBLs contain zinc(II) in their catalytic sites which enable nucleophilic attack at the beta-lactam via a polarized water molecule. Unlike other serine-

containing beta-lactamases (Classes A, C, and D), the activity of MBLs is not susceptible to beta-lactam inhibitors such as clavulanic acid, sulbactam, and tazobactam [138].

As part of the attempt to address carbapenem resistance, the development of carbapenemase inhibitors, particularly MBL inhibitors, emerges as a feasible approach. The investigation of drugs containing thiols such as captopril, thiorphan, dimercaprol, and tiopronin, restored the efficacy of imipenem in resistant bacteria, proving the potential of thiol-containing drugs as MBL inhibitors [139]. A separate study in the same year reported the potential of combining two metal chelating agents, namely 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), in restoring the efficacy of carbapenems, such as imipenem and meropenem, in *E. cloacae* and *K. pneumoniae*, with the former showing superior antibacterial activity in combination with carbapenems [140]. Following the success of thiols, particularly in combination with NOTA, Zhang et al. synthesized a series of cyclic dithiocarbamate analogs of NOTA and examined their potential as MBL inhibitors and successfully proved that trisodium 1,4,7-triazonane-1,4,7-tris(carboxylodithioate) was most active in restoring the activity of meropenem in clinical carbapenem-resistant *K. pneumoniae* and *E. coli* isolates carrying the blaNDM-1 gene [141]; this compound was shown to have low cytotoxicity towards a mammalian cell line. Later, the same group identified two more dithiocarbamate compounds, sodium piperidine dithiocarbamate and sodium pyrrolidine dithiocarbamate which were able to reverse the resistant phenotype against meropenem in clinical isolates harboring blaNDM-1 and IMP-4 [142]. When in combination with these dithiocarbamates, the effectiveness of meropenem was increased up to 2560 times in the tested bacterial strains. The potential of dithiocarbamates as MBL inhibitors was also proved in two separate recent reports [143,144]. In the most recent of these articles, Chen et al. demonstrated that Disulfiram[®] was a promising NDM-1 inhibitor that works by covalently binding to NDM-1 by forming a S–S bond with the cysteine 208 residue in the enzyme using an in silico approach. Disulfiram[®] successfully restored the antibiotic activity of imipenem, a carbapenem, against drug-resistant *K. pneumoniae* and *P. aeruginosa* [143].

These advances in the development of novel dithiocarbamate MBL inhibitors in a few key ESKAPE pathogens are clearly an exciting development. The enhancing of the efficacy of existing antibiotics, via the use of new inhibitors, that are approved by the FDA [145], may be a cornerstone in the identification of effective antibiotics in the post-antibiotic era.

5. Overview

While long known [18,146], there is an increasing appreciation of the potential of metal-based drugs in the treatment of various diseases [19–22,147], including as antimicrobial agents. The potential of heavy elements, incorporating both transition metals and main group elements, dithiocarbamates as antimicrobial agents, in particular against bacteria, was demonstrated in a relatively large number of studies. The range of dithiocarbamate ligands that may be synthesized is vast [148] and offers opportunities for tailoring properties relevant to the development of therapeutics, such as solubility, lipophilicity, etc. In keeping with this idea, in the present survey, 82 different dithiocarbamate ligands were found complexed to a heavy element. In the same way, a wide variety of transition metals, but usually belonging to the first row, and main group elements feature in this survey. While the reader is alerted to the salient outcomes of many of these studies, several serious shortcomings are apparent and need to be acknowledged. First and foremost is the lack of systematic study, whereby many different elements were coupled with a larger number of different dithiocarbamate ligands. Is there a standout metal that ought to be studied as a priority? Is there a dithiocarbamate ligand or even class of dithiocarbamate ligands deserving of special attention? In other words, there seems little progress towards a guiding structure-activity relationship. In the same fashion, militating against a structure-activity relationship is that there is also a very wide variety of potential co-ligands that can be employed to generate ternary, quaternary, etc. compounds and there is no coherent panel of microorganisms under investigation. Drug-resistant bacteria, particularly ESKAPE (*E. faecium*, *S. aureus*,

K. pneumoniae, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* sp.) pathogens which are capable of causing severe nosocomial infections, should be given more attention in the development of new antimicrobial agents. Despite its relevance and impact on human health, none of the surveyed articles tested dithiocarbamate based compounds and derivatives on *E. faecium*. However, the majority of the articles investigated antibacterial activity of dithiocarbamate derivatives on *S. aureus* and *P. aeruginosa*. Additional work is warranted as there may be a special combination of metal and dithiocarbamate (and other) ligands that is specifically active against a given microorganism.

6. Conclusions

In summary, the evaluation of metal dithiocarbamates has presented evidence for their potential use as antimicrobial agents; this potential is enhanced compared to the dithiocarbamate ligands themselves. Opportunities arise to fine-tune crucial biological indicators such as lipophilicity by varying the heavy element center (transition metal, main group element . . .), the dithiocarbamate ligand (substituents, denticity . . .) and even co-ligands (phosphane, pyridine . . .). Systematic studies leading to structure-activity relationships are highly desirable, as are investigations into possible mechanisms of action. There is increasing evidence to indicate dithiocarbamates inhibit the activity of a group of essential metalloenzymes, that is, carbonic anhydrases. As these enzymes are conserved in different organisms including bacteria, fungi, and protozoa, novel dithiocarbamate compounds may possess significant antimicrobial potential. The ability to restore the efficacy of metallo-beta-lactams in drug-resistant bacteria by dithiocarbamates further supports the imperative to develop effective dithiocarbamate antimicrobial compounds.

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Appendix A

Table A1. A list of bacterial species mentioned in the review and the diseases inflicted by these.

Bacteria	Infections and Diseases
<i>Acinetobacter baumannii</i>	Pneumonia, urinary tract infections, blood-stream infections, wound infections, and meningitis
<i>Aeromonas hydrophila</i>	Soft-tissue infections, diarrhea, bacteremia, and septicemia
<i>Aggregatibacter actinomycetemcomitans</i>	Chronic and localized aggressive periodontitis
<i>Bacillus cereus</i>	Food poisoning, ocular infection, bacteremia, and pneumonia
<i>Bacillus pumilus</i>	Bacteremia and sepsis
<i>Bacillus subtilis</i>	Bacteremia, endocarditis, pneumonia, and septicemia
<i>Citrobacter freundii</i>	Gastroenteritis, neonatal meningitis, septicemia, and urinary tract infections
<i>Enterobacter aerogenes</i>	Iatrogenic bacteremia, septicemia, pneumonia, urinary tract infections, and wound infections
<i>Enterobacter cloacae</i>	Nosocomial bloodstream infections

Table A1. Cont.

Bacteria	Infections and Diseases
<i>Enterococcus faecalis</i>	Foodborne infections, endocarditis, bacteremia, urinary tract infections, intra-abdomen, pelvis, and soft tissue infections
<i>Enterococcus raffinosus</i>	Nosocomial infections, including bacteremia, urinary tract infection, wound, and abscesses
<i>Escherichia coli</i>	Urinary tract infections, diarrhea, sepsis, meningitis, respiratory infections, and pericarditis
<i>Fusobacterium nucleatum</i>	Periodontal disease and colorectal cancer
<i>Klebsiella pneumoniae</i>	Urinary tract infections, pneumonia, septicemia, wound infections, and soft tissue infections
<i>Lactobacillus plantarum</i>	Part of the normal microbiota and a lactic acid bacterium
<i>Legionella pneumophila</i>	Legionnaires' disease and pneumonia
<i>Leuconostoc mesenteroides</i>	Part of the normal microbiota and a lactic acid bacterium
<i>Listeria monocytogenes</i>	Listeriosis—a foodborne infection
<i>Mycobacterium marinum</i>	Chronic skin infections—aquarium granuloma, swimming pool granuloma or fish tank granuloma
<i>Mycobacterium tuberculosis</i>	Tuberculosis
<i>Pasteurella multocida</i>	Bacteremia, cellulitis, endocarditis, lymphadenopathy, meningitis, and osteomyelitis
<i>Porphyromonas gingivalis</i>	Periodontal disease and putative causative agent for rheumatoid arthritis, and neurodegenerative diseases
<i>Proteus mirabilis</i>	Kidney failure, kidney stones, pneumonia, and sepsis
<i>Pseudomonas aeruginosa</i>	Bacteremia, chronic lung infection, acute ulcerative keratitis, and urinary tract infections
<i>Rhodococcus</i> sp.	<i>Rhodococcus equi</i> in the genus causes zoonotic infection and infections in immunosuppressed patients, including those in HIV patients
<i>Salmonella enterica</i> serotype Typhi	Typhoid fever
<i>Salmonella enterica</i> serotype Typhimurium	Salmonellosis
<i>Serratia mercescens</i>	Respiratory tract, the urinary tract, surgical wounds, and soft tissues in hospitalized patients
<i>Shigella flexneri</i>	Shigellosis (diarrhea, severe abdominal pain, cramping, septicemia, pneumonia, and haemolytic uremic syndrome)
<i>Staphylococcus aureus</i>	Skin (Scalded skin syndrome, skin abscesses) soft tissue, bone (osteomyelitis), joint and central intravenous line infections, endocarditis, staphylococcal meningitis, septic arthritis, and toxic shock syndrome
<i>Staphylococcus epidermidis</i>	Prosthetic valve endocarditis (PVE) infections, intracardiac abscesses, bacteremia, and neonatal sepsis
<i>Staphylococcus haemolyticus</i>	Meningitis, endocarditis, prosthetic joint infections, and bacteremia in immunocompromised individuals
<i>Staphylococcus sciuri</i>	Subcutaneous abscesses, dermatitis, and surgical wound infections
<i>Staphylococcus simulans</i>	Skin and soft tissue infections
<i>Streptococcus pneumoniae</i>	Pneumonia and sepsis
<i>Streptococcus pyogenes</i>	Pharyngitis (Strep Throat), cellulitis, Scarlet Fever, Streptococcal Toxic Shock Syndrome, impetigo, acute rheumatic fever, and type II necrotizing fasciitis
<i>Streptococcus sanguinis</i>	Bacterial endocarditis
<i>Vibrio cholerae</i>	Cholera

Table A2. A list of fungal species mentioned in the review and the diseases inflicted by these.

Fungi	Infections and Diseases
<i>Alaternaria solani</i>	Septic arthritis, osteomyelitis, and epiglottitis
<i>Alternaria alternata</i>	Rhinosinusitis
<i>Aspergillus carbonarius</i>	Human kidney diseases such as chronic interstitial nephropathy and renal diseases
<i>Aspergillus flavus</i>	Chronic granulomatous sinusitis, keratitis, cutaneous aspergillosis, wound infections, and osteomyelitis
<i>Aspergillus fumigatus</i>	Abscesses, pleural empyema, cholangitis, thrombophlebitis, and haemolytic uraemic syndrome
<i>Aspergillus niger</i>	Respiratory infections associated with pneumonia in immunocompromised individuals
<i>Aspergillus parasiticus</i>	Produces aflatoxins known as carcinogens for liver cancer
<i>Candida albicans</i> (formerly known as <i>Miconia albicans</i>)	Candidiasis, including vaginal candidiasis, and candidemia
<i>Candida auris</i>	Invasive candidiasis in immunocompromised patients
<i>Candida glabrata</i>	Superficial candidiasis, including vulvovaginitis, oral thrush, and candidemia
<i>Candida parapsilosis</i>	Candidal arthritis and candidemia
<i>Candida pseudotropicalis</i>	Fungemia and invasive diseases in spleen and kidney in immunocompromised individuals
<i>Candida tropicalis</i>	Candidemia
<i>Cryptococcus neoformans</i>	Cryptococcosis and cryptococcal meningitis
<i>Curvularia senegalensis</i>	A plant pathogen, but an etiologic agent of allergic sinusitis, keratitis, and endophthalmitis in immunocompetent and immunosuppressed patients
<i>Fusarium solani</i>	Keratitis, onychomycosis, endophthalmitis, and skin and musculoskeletal infections
<i>Fusarium oxysporium</i>	Urinary tract infection, diarrhea, sepsis, meningitis, respiratory infections, pericarditis, and septicemia of poultry
<i>Helminthosporium solani</i>	A plant pathogen that causes silver scurf in potatoes
<i>Microsporium canis</i>	Zoophilic dermatophytosis but occasionally causes human skin infections
<i>Microsporium gypseum</i>	Dermatophytosis
<i>Penicillium citrinum</i>	Mycotic keratitis, urinary tract infection, and pneumonia in immunocompromised individuals
<i>Rhizoctonia solani</i>	A plant pathogen that causes damping-off on cultivated plants including potato, legumes, and vegetables
<i>Saccharomyces cerevisiae</i>	Part of the normal microbiota but has been shown to cause fungemia in critically ill patients
<i>Sporothrix schenckii</i>	Sporotrichosis, also known as rose garden disease
<i>Trichoderma reesii</i>	A soil fungus that rarely causes human diseases
<i>Trichoderma viride</i>	Pulmonary mycoma in immunocompromised individuals
<i>Trichophyton longifusus</i>	Dermatophytosis
<i>Trichophyton mentagrophytes</i>	Dermatophytosis
<i>Trichophyton rubrum</i>	Dermatophytosis
<i>Trichothecium roseum</i>	A plant pathogen that causes pink rot on apples and white stains on grapes

Table A3. A list of parasites species mentioned in the review and the diseases inflicted by these.

Parasites	Infections and Diseases
<i>Leishmania major</i>	Leishmaniasis
<i>Toxoplasma gondii</i>	Toxoplasmosis
<i>Trichomonas vaginalis</i>	Trichomoniasis

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