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Glimpses of Synthesis and Biological Applications of Metal - Dithiocarbamate Derivatives

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Abstract: ***Dithiocarbamates are organosulfur, highly versatile, monoanionic chelating ligands that can form stable complexes with transition metals and most of the main group, lanthanide and actinide elements. Metal- dithiocarbamate derivatives have wide range of applications including medicine. Many metal-dithiocarbamate derivatives have been synthesized and investigated for biological activities. In this review paper synthesis and study of biological activity of some of them, especially as antifungal, antibacterial, and antitumor agents has been discussed.***

Keywords: Dithiocarbamate, antifungal, antibacterial, antitumor, antioxidant, insecticidal

1. Introduction

The chemistry of dithiocarbamates was started from early 20th century. They were first time commercially used as fungicides during World War II [1]. Dithiocarbamates are organosulfur [2] , highly versatile, monoanionic, chelating ligands shown in **Figure 1** [3,4]. On the basis of the primary or secondary amine used in there synthesis, dithiocarbamates are classified as monoalkyl and dialkyl dithiocarbamates [4,5]. Dithiocarbamate ligands form stable complexes with transition metals and most of the main group, lanthanide and actinide elements [4]. They can readily produce chelate compounds with metal ions via its two donor sulfur atoms [6]. Dithiocarbamate ligands may coordinate to the metals as bidentate, ansiobidentate, and monodentate as shown in **Figure 2** [6]. Due to the unique coordination and redox properties, dithiocarbamate complexes are used in several areas, which range from biology and medicine to material sciences and catalysis [7,8].

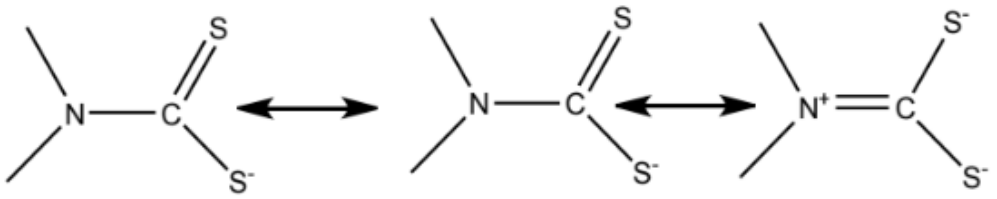


Figure 1. Resonating structures of dithiocarbamate ligand [3].

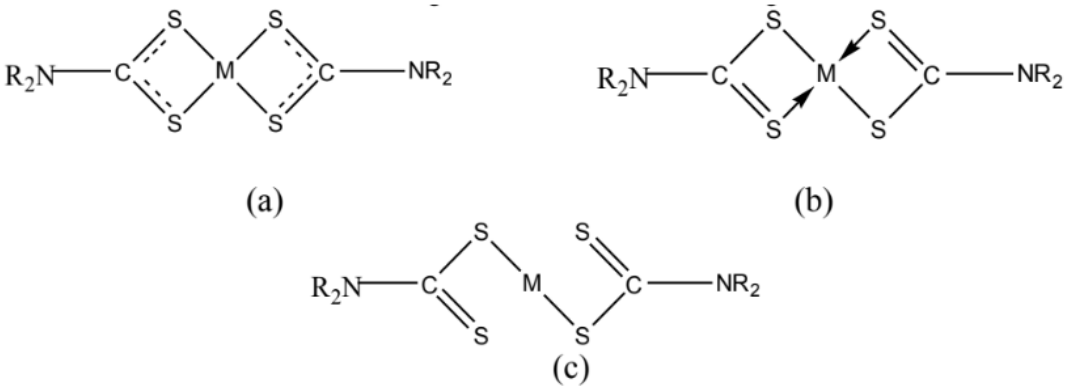
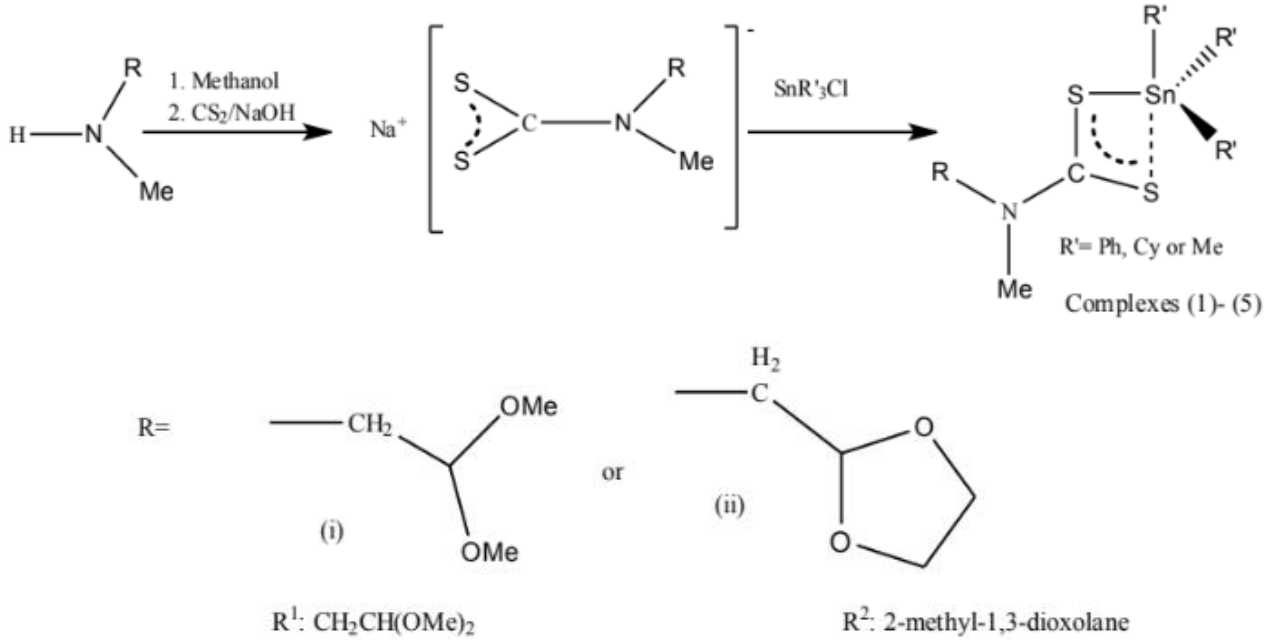


Figure 2: Nature of coordination of dithiocarbamate ligands (a) Bidentate symmetrical bonding (b) Ansiobidentate asymmetrical bonding (c) Monodentate asymmetrical bonding [6].

A variety of applications of dithiocarbamates occurred historically in the field of accelerating vulcanization, pesticides (in agriculture) material science, organic synthesis, photostabilizing polymer, protecting radiators, and medicine [9,10].There applications as antibacterial and antifungal agents and for possible treatment of AIDS have also been reported [11] . Application of dithiocarbamate complexes as anticancer therapeutic agents has been explored for the last two decades and the anticancer activities of some Ru, Au, and Pt dithiocarbamate complexes have been described [12-19]. This paper presents a review of synthesis and biological applications of metal-dithiocarbamate derivatives, especially as antimicrobial, antifungal, and antitumor agents.

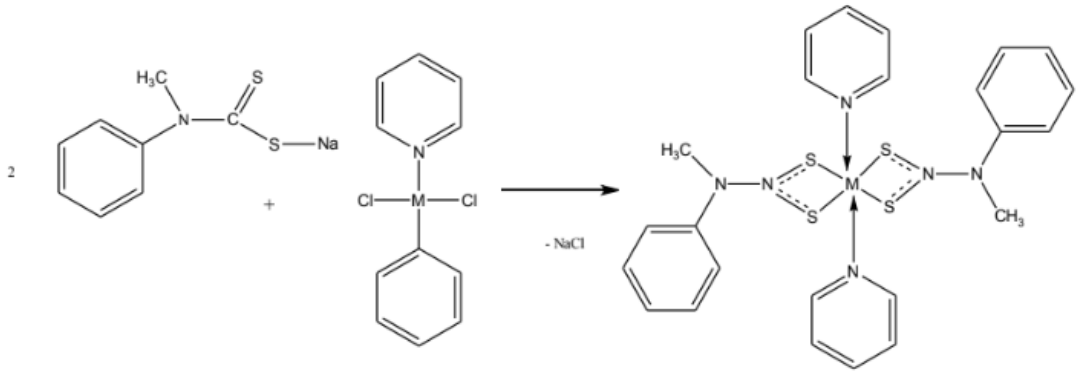
Antifungal Studies: Due to increase in the discovery and rate of widespread and serious invasive fungal infections and reduced effectiveness of available antifungal agents towards

certain infections because of the emergence of drug resistance in microbes, the importance of discovery of alternative drugs has increased [20]. In last two decades, several dithiocarbamate compounds have been synthesized and reported to show better antifungal activity in comparison to already used antifungal agents. Awang et al. synthesized organotin (IV) dithiocarbamate compounds namely dibutyltin (IV) ethylphenyldithiocarbamate (**1**), diphenyltin (IV) ethylphenyldithiocarbamate (**2**), triphenyltin (IV) ethylphenyldithiocarbamate (**3**), dibutyltin (IV) butylphenyldithiocarbamate (**4**), diphenyltin (IV) butylphenyldithiocarbamate (**5**), and triphenyltin (IV) butylphenyldithiocarbamate (**6**) [21]. The compounds were screened against Gram-positive bacteria: Bacillus cereus, Bacillus subtilis, MRSA, Staphylococcus aureus, Streptococcus pneumonia; Gram-negative bacteria: Acinetobacter baumanni, Escherichia coli, Klebsiella sp., Shigella sonnei, Vibrio cholera; and Fungal strain: Aspergillus fumigates, Aspergillus niger, Candida albicans, Saccharomyses cerevisiae by disc diffusion method and microdilution test [21]. Compound **3** and **6** exhibited antibacterial activity towards most of the tested bacterial and fungal strains [21]. The obtained MIC value for compound **3** and **6** against Vibrio cholera and Acinetobacter baumanni, respectively was 39 µg/mL [21]. However, all the compound showed bacteriostatic or fungistatic effect as reported by the authors [21].Ekennia et al. synthesized four novel mixed ligand complex, ZnMDBz, ZnEDBz, NiMDBz, and NiEDBz, where MD= N-methyl-N-phenyldithiocarbamate, ED= N-ethyl-N-phenyldithiocarbamate and Bz= benzoate [22] The synthesized compounds were characterized by elemental analysis, IR and electronic spectroscopy, magnetic and conductivity measurements, and quantum chemical calculations [22]. Results of their screening against different test microbes elucidated moderate to high antimicrobial activity [22]. The methyl substituted complex, ZnMDBz and NiMDBz, exhibited better antimicrobial activity than the rest two [22]. Ferria et al. prepared a series of organotin (IV) dithiocarbamate complexes (**Scheme 1)** [23]. Their structures have been established by IR, ^{1}H, ^{13}C, and ^{119}Sn NMR, and ^{119}Sn Mossbauer spectroscopy, and X-ray crystallography [23]. The antifungal activity of the compounds was investigated in terms of IC_{90} (µ mol/L) and IC_{50} (µ mol/L) [23]. In terms of IC_{50}, compound **1** and **4** exhibited considerable activity at very low inhibition concentration against all test microbes [23].



Scheme 1: Synthesis of complexes $[SnPh_3\{S_2CNR\ (R^1)\}]$ (**1**), $[SnCy_3\{S_2CNR\ (R^1)\}]$ (**2**), $[SnMe_3\{S_2CNR\ (R^2)\}]$ (**3**), $[SnPh_3\{S_2CNR\ (R^2)\}]$ (**4**) and $[SnCy_3\{S_2CNR\ (R^2)\}]$ (**5**) [R = CH_3, R^1 = $CH_2CH\ (OMe)_2$ and R^2 = 2-methyl-1,3-dioxolane] [23].

Ekennia et al. synthesized a series of mixed ligand dithiocarbamate complexes of Ni (II), Co (II), Cu (II), and Mn (II) with general formula $[ML_2\ (py)_2]$, where M= Mn (II), Co (II), Ni (II), and Cu (II), py= pyridine, and L= N-methyl-N-phenyldithiocarbamate (**Scheme 2)** [24]. The synthesized compounds were characterized by elemental analysis, FT-IR and UV spectroscopy, magnetic moment, and thermogravimetric and conductance analysis and investigated for in-vitro antifungal activity against A. niger, C. albicans, and A. flavous [24]. The best antifungal activity among the test compounds was reported for Co (II) complex [24]. Similarly, some other dithiocarbamate- metal derivatives has been synthesized and screened for antifungal activities against various test microbes [25-28] as given in **Table 1**.



Scheme 2: Synthesis procedure of $[ML_2 (py)_2]$ (M=Mn (II), Co (II), Ni (II) and Co (II))[24].

Table 1: Summery of studies of metal-dithiocarbamate derivatives and their biological activity.

Complex	Characterization Techniques	Test Microbes	Result	Reference
ZnMDBz, Zn EDBz, NiMDBz, NiEDBz	Elemental analysis, IR, electronic spectra, magnetic and conductivity measurements, quantum chemical calculations	Fungal strain; Aspergillus niger, Fusarium oxysporium; Bacterial strain: K. oxytoea, P. aeruginosa, E. coli, B. cereus, S. aureus	Complexes showed moderate to high activity. N-methyl-N-phenyldithiocarbamate complexes exhibited better sctivity then N-ethyl-N-phenyldithiocarbamate complexes.	[22]
$Ni[S_2CN (C_6H_5)_2]$, $Zn[S_2CN (C_6H_5)_2]$, $Cu[S_2CN (C_6H_5)_2]$ **(Figure 3a)**	Magnetic susceptibility, elemental analysis, conductivity measurements, mass spectra, NMR, IR, and UV-visible studies	Fungal strain: Aspergillus niger, Aspergilus flavous, Candida Albicans, Acetomyceta; Bacterial strain: Rhodococcus, Actinomyses viscous, Bacillus subtilis, E. coli	All the complexes exhibited better antifungal activities as compared to the standard (fluconazole) and better antibacterial activity than the ligand and the standard (ampicillin).	[25]
$[VO (morphdtc)_2L].H_2O$, Ni $(morphdtc)_2.L$, Cu $(morphdtc)_2.L$, Ni $(morphdtc)_2.L_2$, Cu $(morphdtc)_2.L_2$, (where morphdtc= morpholinedithiocarbamate, L= morpholine or piperidine)	Elemental analysis, molar conductance, magnetic susceptibility, IR, UV-visible, and TGA/DTA techniques	Fusarium oxysporium	The results elucidated a linear relationship of activity with concentration .	[26]
$[Ru_2 (S_2CN (CH_3)_2)_5]$ (1), $[Ru_2 (S_2CN (CH_2CH3)_2)_5]$ (2), $[Ru_2\{S_2CN (C (CH_3)_3) (H)\}_5]$ (3), $[Ru_2\{S_2CN (CH (CH_3)_2) (H)\}_5]$ (4), $[Ru_2\{S_2CN (CH (CH_3)_2)_2\}_5]$ (5) **(Figure 3b)**	^1H and ^{13}C NMR and IR spectroscopy	Aspergillus clavatus, Aspergillus flavous, Aspergillus fumigates, Aspergillus niger, Aspergillus nomius, Aspergillus tamari, Aspergillus terreus	Synthesized compound showed antifungal activity against some of the test microbes except A. nomius and A. terrus. Compound **1** and **2** presented low MIC values (4-8 µg mL^{-1}) against A. clavatus and A. fumigates. Complex 5 exhibited the lowest MIC value towards A. niger.	[27]
$[Sn\{S_2CN (CH_2)_4\}_2Cl_2]$ (**1**), $[Sn\{S_2CN (CH_2)_4\}_2Ph_2]$ (**2**), $[Sn\{S_2CN (CH_2)_4\}Ph_3]$ (**3**), $[Sn\{S_2CN (CH_2)_4\}_2 (n\text{-}Bu)_2]$ (**4**), $[Sn\{S_2CN (CH_2)_4\}Cy_3]$ (**5**)	IR, multinuclear NMR (^1H, ^{13}C and ^{119}Sn) and ^{119}Sn Mossbauer spectroscopy	Human pathogenic fungi Candida albicans	Compounds showed remarkable antifungal activity in the screened concentration, 0.025; 0.050; 0.100; 0.200; 0.400; 0.800; 1.600 and 3.200 mM with inhibition zones≥ 11 mm, intermediate inhibition zones within the range 11-9 mm and resistant ≤ 9 mm. Most of the complexes were moderately active. Compound **1** and **4** exhibited highest activity.	[28]

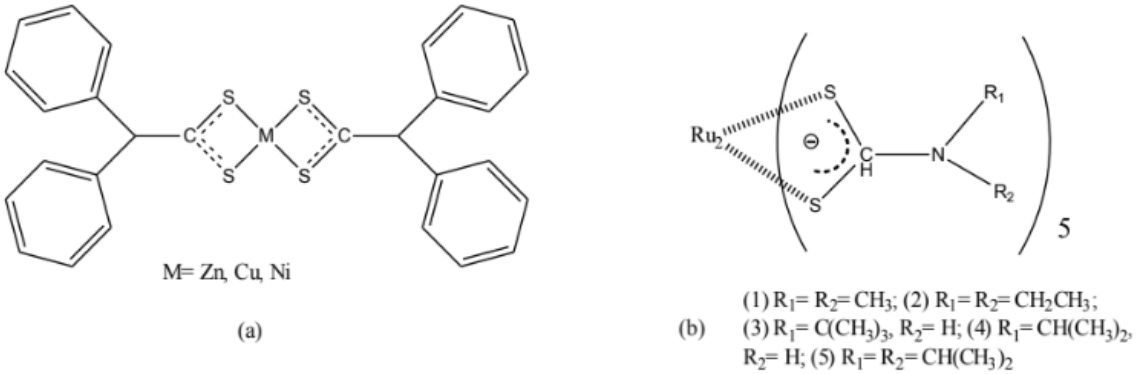


Figure 3: Molecular structure of (a) Ni[S_2CN (C_6H_5)$_2$], Zn[S_2CN (C_6H_5)$_2$] and Cu[S_2CN (C_6H_5)$_2$] [25] (b) [[Ru_2 (S_2CN (CH_3)$_2$)$_5$], [Ru_2 (S_2CN (CH_2CH_3)$_2$)$_5$], [Ru_2{S_2CN (C (CH_3)$_3$) (H)}$_5$], [Ru_2{S_2CN (CH (CH_3)$_2$) (H)}$_5$], and [Ru_2{S2CN (CH (CH_3)$_2$)$_2$}$_5$][27].

Antibacterial Studies

Sim et al. investigated in- vitro antibacterial activity of three phosphinogold (I) dithiocarbamate compounds with general formula [$R_3Pau[S_2CN$ (i-Pr)CH_2CH_2OH}] (where R= Ph (**1**), Cy (**2**), and Et (**3**) respectively) (**Figure 4a**)[29] against 25 strains of Gram-positive and Gram- negative bacteria pathogens: Aeromonas hydrophilla, Acinetobacter baumanni, Bacillus cereus, Bacillus subtilis, Citrobacter freundii, Enterobacter cloacae, Enterobacter aerogenes, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella pneumonia, Listeria monocytogenes, Proteus mirabilis, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella paratyphi A, Salmonella typhimurium, Shigella flexneri, S. aureus, methicillin-resistant S. aureus (MRSA), Staphylococcus saprophyticus, Stenotrpphomonas maltophilia, Streptococcus pyogenes and Vibrio parahaemolyticus, using the disk diffusion method, the determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) and by time-Kill assay [29]. Results showed that compounds **1** and **2** were active against tested Gram- positive bacteria with MIC value in the range 7.81- 125 µg mL^{-1} [29]. Compound **3** exhibited activity against 24 strains with MIC values in the range 0.98- 1000 µg mL^{-1} [29]. Compound **3** showed activity towards methicillin-resistant Staphylococcus aureus (MRSA) and Bascillus sp., as same as standard antibiotic ciprofloxacin [29]. In time-kill studies the investigated compound exhibited bacteriostatic and bactericidal activity towards susceptible strain similar to that determined by MBC and MIC techniques [29]. Similarly, Awang et al. synthesized some organotin (IV) dithiocarbamate compounds with molecular formula $R_mSn[S_2CN$ (CH_3) (C_6H_{11})]$_{4-m}$ (where m= 2, R= CH_3 (**1**); m= 2, R= C_4H_9 (**2**); m= 3, R= C_6H_5 (**3**)) (**Figure 4b**)[30] using in-situ method [30]. The characterization was done by elemental analysis, IR, ^1H and ^{13}C NMR spectroscopy [30]. The antibacterial activity of the synthesized compounds was investigated against Staphylococcus aureus, Salmonella typhimurium, Pseudomonas auruginosa, and Bacillus subtilis [30]. Only compound **3** showed activity against Staphylococcus aureus and Salmonella typhimurium [30]. Awang et al. also synthesized six organotin (IV) dithiocarbamate complexes: methyltin (IV) methylcyclohexyldithiocarbamate (**1**), butyltin (IV) methylcyclohexyldithiocarbamate (**2**), phenyltin (IV) methylcyclohexyldithiocarbamate (**3**), methyltin (IV) ethylcyclohexyldithiocarbamate (**4**), butyltin (IV) ethylcyclohexyldithiocarbamate (**5**), and phenyltin (IV) ethylcyclohexyldithiocarbamate (**6**) [31]. All the six were investigated towards Enterococcus raffinosus, Staphylococcus aureus, Klebsiella sp., Acinetobacter baumanni, Pseudomonas auruginosa, and Enterobacter aerogenes [31]. All the complexes exhibited bacteriostatic effect at the minimum bactericidal concentration [31]. Compound **3** showed antibacterial activity towards most of the bacteria tested with an inhibition range of 10- 15 mm and MIC value of 2.5 mg ml^{-1}, similar to ampicillin [31]. Thus phenyltin (IV) complex possessed the best activity and potential as an antibacterial agent [31]. Some other dithiocarbamate-metal derivatives and study of their biological activities [32-40], available in literature, are summarized in **Table 2**.

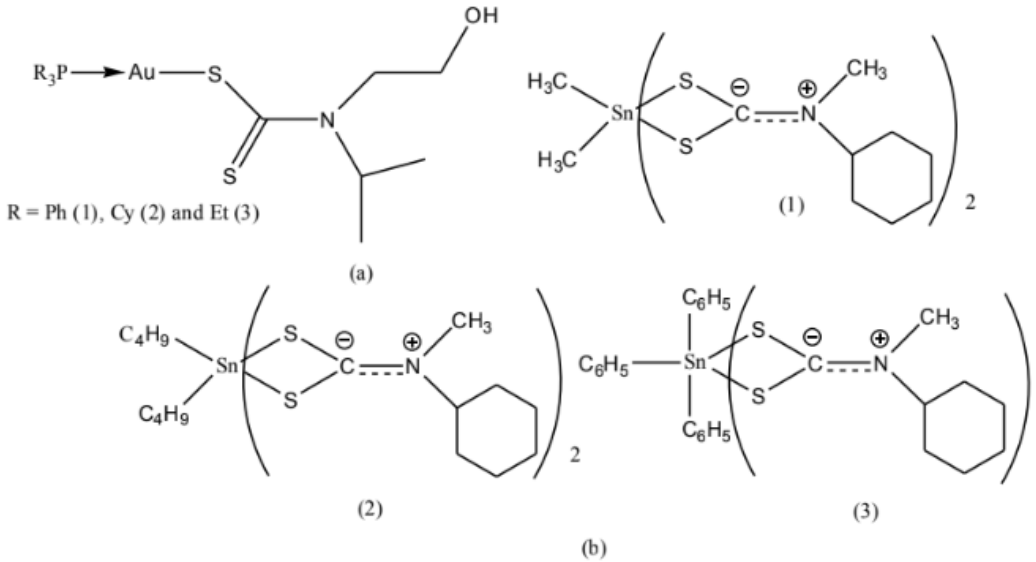
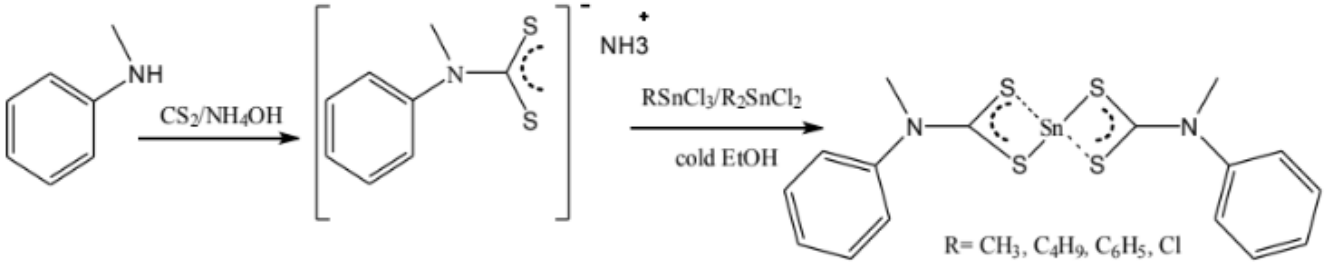


Figure 4: Chemical structure of **(a)** Phosphanegold (I) dithiocarbamate compounds[29] **(b)** organotin (IV) dithiocarbamate compounds[30].

Table 2: Study of Metal-dithiocarbamate derivatives and their antibacterial activity

Complex	Characterization Techniques	Test Microbes	Result	Reference
$Bu_2Sn[C_{16}H_{34}NCS_2]_2$ **(1)**, $Ph_3SnC_{16}H_{34}NCS_2$ **(2)**, $Bu_2Sn[S_2CNC_5H_{12}]_2$ **(3)**, $Ph_3SnS_2CNC_5H_{12}$ **(4)**, (where Bu= butyl, Ph= phenyl)	Determination of melting point, CHNS elemental analysis, FT-IR and UV-visible spectroscopy.	Escherichia coli, Staphylococcus aureus, Salmonella typhi, and Bacillus cereus.	Results showed broad-spectrum activity towards Gram-positive and Gram-negative bacteria for all complexes. Compound **4** showed better antibacterial activity then the other compounds.	[32]
dibutyltin (IV) 1-methylpiperazinedithiocarbamate, dimethyltin (IV) 1-methylpiperazinedithiocarbamate, triphenyltin (IV) 1-methylpiperazinedithiocarbamate, dibutyltin (IV) N-methylcyclohexyldithiocarbamate, dimethyltin (IV) N-methylcyclohexyldithiocarbamate, and triphenyltin (IV) N-methylcyclohexyldithiocarbamate	CHNS elemental analysis, FT-IR, UV-vis, and ^1H and ^{13}C NMR spectroscopy.	Staphylococcus aureus, Bacillus cereus, Salmonella typhi, and Escherichia coli.	The results elucidated the great potential of synthesized complexes as antimicrobial agents except for triphenyl (IV) N-methylcyclohexyldithiocarbamate.	[33]
C_4H_9 (Cl)SnL_2 **(1)**, C_6H_5 (Cl)SnL_2 **(2)**, ($CH_3)_2SnL_2$ **(3)**, ($C_4H_9)_2SnL_2$ **(4)**, ($C_6H_5)_2SnL_2$ **(5)** (where L= N-methyl-N-phenyldithiocarbamate) (**Scheme 3)**	FT-IR, ^1H, ^{13}C, and ^{119}Sn NMR spectroscopy, elemental and thermal analysis (TGA and DTG).	S. aureus, B. cereus, K. pneumonia, P. aeruginosa, E. coli	Compounds exhibited good to moderate activity against test microbes. Compound **5** gave the best antibacterial activity with an inhibition diameter ranging between 10-21mm. The least antibacterial activity was obtained for compound **3** with inhibition diameter ranging between 8-15 mm.	[34]
[M (SD) (me-DTC)], [M (SD) (et-DTC) (where M= Co, Cu, Pd, Pt; SD= sulphadiazine; me-DTC= N-methyl-N-phenyldithiocarbamate; et-DTC= N-ethyl-N-phenyldithiocarbamte)	Elemental analysis, conductivity measurements, FT-IR and UV-visible spectroscopy.	S. aureus, S. faecalis, B. cereus, B. pumilus, E. coli, P. aeruginosa, P. vulgaris, K. pneumonia	The results showed varied antibacterial activities with the highest activity for [Co (SD) (et-DTC)].	[35]
[Cu $(AMPDTC)_2Cl_2$], [Mn $(AMPDTC)_2Cl_2$] (where, AMPDTC= 2-amino-2-methyl-1-propanoldithiocarbamate) (**Figure 5a)**	Elemental analysis, IR, ^1H NMR, ESR spectroscopy and TGA-DTA techniques.	Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa.	The compounds showed selective activity towards some of the test micro- organisms.	[36]
[M (mordtc) (1,10-phe)] (where M= Ni (II), Co (II), Cu (II), Zn (II) and mordtc= morpholine dithiocarbamate)	Electronic and IR spectroscopy and elemental analysis.	Gram-positive bacteria: Streptococcus pneumonia,	All compounds showed significant antibacterial activity against test microbes.	[37]

		Staphylococcus aureus, and Gram-negative bacteria: Klebsiella subtilis, Escherichia coli.		
[Ni $(PDTC)_2$] and [Pd $(PDTC)_2$] (where PDTC= pyrrolidine dithiocarbamate)	Elemental, physiochemical and spectroscopic methods.	Gram-positive bacteria: B. cereus and Gram-negative bacteria: E. coli, V. cholera, S. pneumonia.	Compounds showed higher antibacterial activity compared to the ligand.	[38]
[M{S_2CN $(MePh)\}_2$] (where M= Cu, Co, Ni; Me= methyl; Ph= phenyl) (**Figure 5b)**	FT-IR and electronic spectroscopy, Magnetic moment and conductivity measurement.	Gram-negative bacteria: Escherichia coli, Klebsiella oxytoea, Pseudomonas auruginosa and Gram-positive bacteria: Bacillus cereus, Staphylococcus aureus, Protues mirabilis.	The Co (II) complex showed better antibacterial activity in comparison to Cu (II) and Ni (II) complexes.	[39]
Cu (II), Ni (II), Co (II), Cd (II), and Hg (II) complexes of ammonium phenyl dithiocarbamate (**Figure 6)**	Elemental analysis, ^1H NMR and IR spectroscopy.	E. coli, S. aureus, P. vulgaris, and P. auruginosa.	The synthesized compounds showed prominent activity against all the test microbes.	[40]



Scheme 3: Synthesis of N-methyl-N-phenyl dithiocarbamate and the organotin complexes [34].

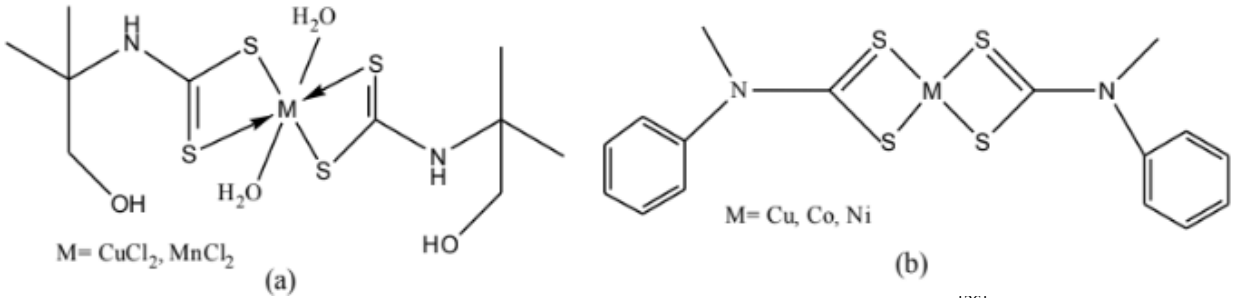


Figure 5: Chemical structure of (a) [Cu $(AMPDTC)_2Cl_2$] and [Mn $(AMPDTC)_2Cl_2$] [36]; (b) N-methyl-N-phenyldithiocarbamate complex of Cu (II), Co (II) and Ni (II) [39].

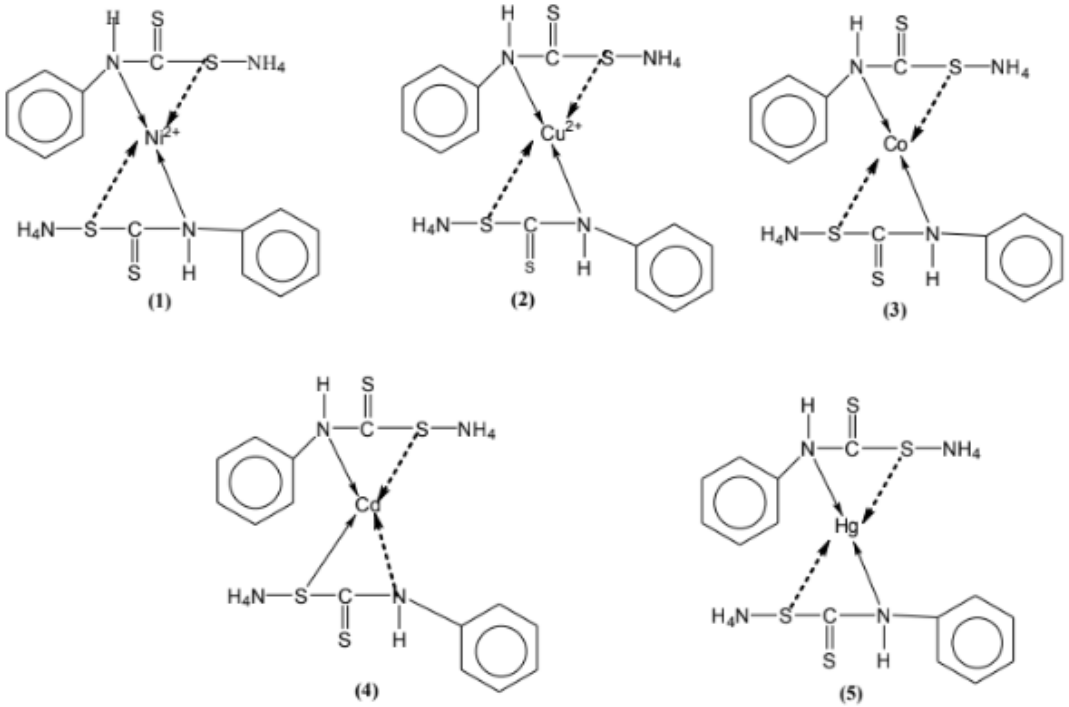


Figure 6: Chemical structures of Cu (II), Ni (II), Co (II), Cd (II) and Hg (II) complexes of ammonium phenyl dithiocarbamate [40].

Antitumor/ Anticancer Studies: In past two decades several dithiocarbamate compounds have been reported for their antitumor activities. It has been proposed that the antitumor activity of dithiocarbamate compounds is due to their ability to complex tumor cellular copper leading to binding and inhibition of the proteasome which in turn inhibits tumor cell- specific apoptosis [41]. Due to the high toxicity of current chemotherapeutic agents, their efficacy in the eradication of tumors is very limited [41]. This led to the synthesis of novel compounds as potent proteasome inhibitors with reduced toxicity and therefore better anticancer agents. Further, dithiocarbamate compounds and their metal derivatives have been reported to modulate key proteins involved in biological processes such as apoptosis, transcription, oxidative stress, and degradation [42]. It was also reported that coordinated dithiocarbamates posses potential chemo protective function and antitumor property [43]. A series of phenyltin (IV) dithiocarbamate compounds with general formula $Ph_{4-n}Sn$ $(S_2CNEt_2)_n$ (where n= 1 to 3) were investigated for cytotoxicity against the L1210 mouse leukemia cell line [44]. The investigated compounds showed a high cytotoxic effect compared to cisplatin and carboplatin [44].

A series of Gold (III) derivatives of N,N-dimethyl dithiocarbamate and ethylsarcosine dithiocarbamate: [Au (DMDT)Cl_2], [Au (ESDT)Cl_2], [Au (ESDT)Br_2], and [Au (DMDT)Br_2] (**Figure 7)**[45] were synthesized and reported to inhibit cisplatin- induced nephrotoxicity [45,46]. The compounds were screened for in-vitro cytotoxicity towards a variety of human tumor cell lines[45,46]. Results elucidated more in-vitro cytotoxicity of compounds compared to cisplatin with 1-4 fold lower IC_{50} value[45,46]. The compounds also showed cytotoxicity against the cisplatin resistant cell lines [45,46]. Similarly, Keter et al. synthesized gold (I) dithiocarbamate complexes with the general formula [AuL (PPh_3)] (**1-3**), [Au_2 $(L)_2$ (dppe)] (**4-6**), [Au_2 $(L)_2$ (dppp)] (**7-9**), and [Au_2 $(L)_2$ (dpph)] (**8-12**) (where, dppe= 1,2-bis (diphenylphosphono)ethane, dppp= 1,3-bis (diphenylphosphino)propane, and dpph= 1,6-bis (diphenylphosphino)hexane; L= pyrazolyldithiocarbamate (L1), 3,5-dimethylpyrazolyldithiocarbamate (L2), or indazolyldithiocarbamate (L3) as shown in **Scheme 4** and **Scheme 5** [47]. The synthesized compounds were characterized by mass spectroscopy, the combination of IR and NMR spectroscopy, and microanalysis and in selected cases by single-crystal X-ray crystallography [47]. Compounds **4-6** were found to be unstable in solution for prolonged periods [47]. Compounds **1-3** and **4-12** have been reported active against human cervical epithelioid carcinoma (HeLa) cells [47]. The results of the screening showed the highest activity for compounds **10** and **11** with IC_{50} values of 0.51 µM and 0.14 µM, respectively [47]. Compounds **10** and **11** showed more selectivity (25.0 and 70.5 times, respectively) toward HeLa cells as compared to normal cells [47]. Novel binuclear diphenyltin (IV) dithiocarbamate macrocyclic compounds (**1-6)** having general formula [$(Ph_2Sn^{IV})_2$-µ^2-bis{κ^{2}S,S-S_2CN (R)$CH_2CONHC_6H_4)_2O$}] were prepared by Kadu et al. (**Scheme 6)** and characterized by elemental analysis, FT-IR, ^{1}H, ^{13}C and ^{119}Sn NMR spectroscopy, TGA-DTA, and TLC techniques [48]. In-vitro cytotoxicity of the synthesized compounds was evaluated against HEP3B (hepatoma) and IMR32 (neuroblastoma) using the (4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide assay [48]. All the compounds showed extreme activity against test cell lines with 16-fold potency compared to cisplatin [48]. Similarly, some other dithiocarbamate-metal derivatives has also been synthesized and screened against various cancer cells [49-55] as given in **Table 3**.

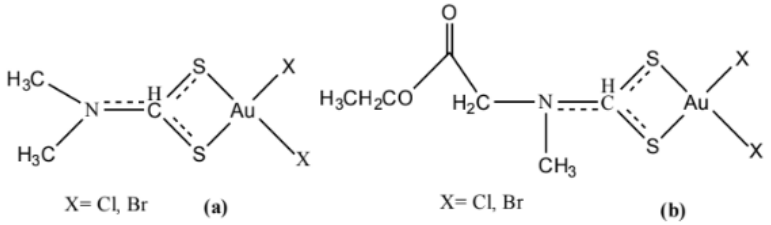
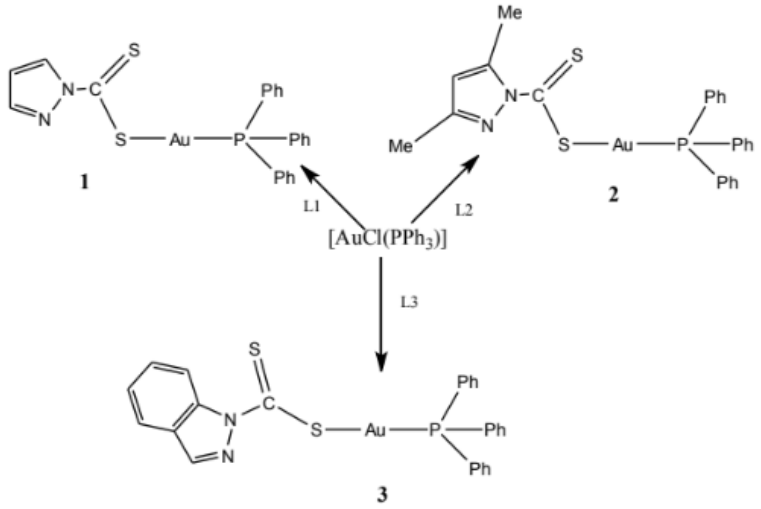
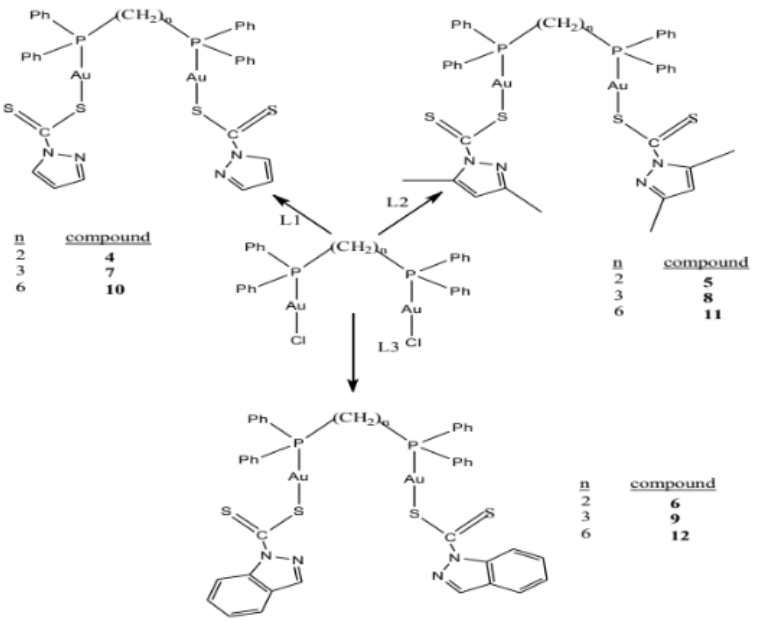


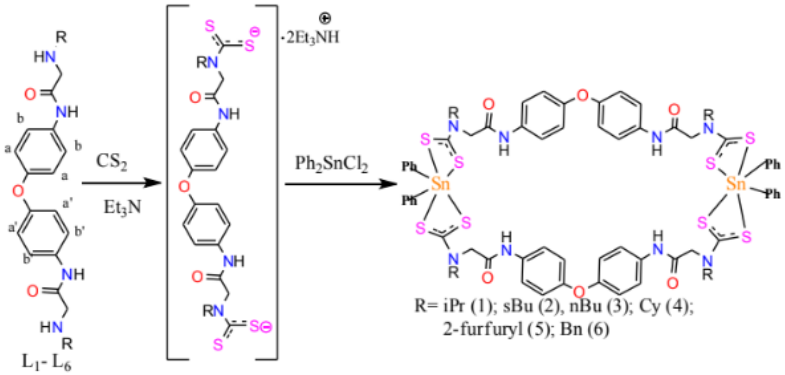
Figure 7: Chemical structure of (a) [Au{DMDT)Cl_2], [Au (DMDT)Br_2]; (b) [Au (ESDT)Cl_2], [Au (ESDT)Br_2] [45]



Scheme 4: Preparation of (Monophospino)gold (1) dithioiocarbamate complex 1-3 [47].



Scheme 5: Preparations of (Diphosphino)alkylgold (1) Dithiocarbamato Complexes **4-12** [47].



Scheme 6: One-pot synthetic protocol for binuclear Ph_2Sn (IV) dithiocarbamate macrocycles **1-6** [48].

Table 3: Metal complexes of dithiocarbamates and their anticancer/antitumor study

Complex	Characterization Technique	Cancer cell lines	Result	Refer ence
[$(t\text{-}Bu)_3PAuS_2CN(C_7H_7)_2$] **(1)**, [$(DPPM)Au_2\{S_2CN(CH_3)_2\}_2$] **(2)**, [$(DPPM)Au_2\{S_2CN(C_2H_5)_2\}_2$] **(3)**, and [$(DPPM)Au_2\{S_2CN(C_7H_7)_2\}_2$] **(4)** (where DPPM= 1,1-bis (diphenylphosphino)methane, $S_2CN(CH_3)_2$= dimethyldithiocarbamate, $S_2CN(C_2H_5)_2$= diethyldithiocarbamate, and $S_2CN(C_7H_7)_2$= dibenzyldithiocarbamate)	CHNS analysis, FT-IR, ^1H, ^{13}C and ^{31}P NMR spectroscopy were used. The molecular structure of compound **1** was determined by X-ray diffraction.	Human A549 lung cancer cells, human HeLa cervix cancer cells and human HCT15 colon cancer cells.	The order of cytotoxicity was (2)> (3)> cisplatin> (1)> (4). Compound **2** and **3** were most effective against HeLa cancer cell line.	[49]
[Ni (TRZ.DTC) (bipy)ONO_2].H_2O and [Co (TRZ.DTC) (bipy) (H_2O)Cl].EtOH (where TRZ.DTC= 5- (p-nitrophenyl)-4'-phenyl-1,2,4-triazole-3-dithiocarbamatohydrazide and bipy= 2,2'-bipyridyl) (**Figure 8)**	Elemental analysis, flame atomic absorption, magnetic susceptibility, and molar conductance measurements, UV-visible and FT-IR spectroscopy.	Human HepG2 cell line.	The compounds showed good inhibition activity, especially Ni (II) complex on selected cell lines comparable with standard drug cisplatin.	[50]
[Au (III)Br_2 (dtc-Sar-Gly-O (tBu))] **(1)** and [Au (III)Br_2 (dtc-Sar-Aib-O (tBu))] **(2)** (where Sar= sarcocine, N-methylglycine, Gly= glycinato, Aib= 2-methylalaninato)) **(Figure 9)**	_____	PC3 and DU145 prostate cancer cells.	Compounds showed higher in- vitro cytotoxicity than the reference drug cisplatin and induce apoptosis, promote mitochondrial membrane permeabilization and stimulate reactive oxygen species generation. Inhibit both selenoenzyme thioredoxin reductase and proteasome activity. Compound **1** efectively reduces tumor growth in prostate tumor- bearing nude mice with minimal systemic toxicity.	[51]
[Au{P ($t\text{-}Bu)_3$} ($S_2CN(CH_3)_2$)] and [Au{P ($t\text{-}Bu)_3$} ($S_2CN(C_2H_5)_2$)] (where Bu= butyl)	FT-IR and NMR spectroscopy, cyclic voltammetry, elemental analysis, and X-ray diffraction.	Human lung cancer (A549), breast cancer (MCF7), and cervical cancer (HeLa) cell lines.	The compounds were highly effective, particularly against HeLa cancer cell lines and have better cytotoxic activity than cisplatin.	[52]
[Au (PR_3) ($S_2CNR'_2$)] (where R= methyl, ethyl, isopropyl and R'= methyl, ethyl)	Elemental analysis, FT-IR and multinuclear NMR spectroscopy.	A549 and HepG2 human cancer cell lines.	The compounds showed 4 to 6-fold potency for A549 and 3 to 5-fold potency for HepG2 cell line than the cisplatin.	[53]
[$AuCl_2$ (pipeDTC)] **(1)**, [Au ($pipeDTC)_2$]Cl **(2)**, [Ru ($pipeDTC)_3$] **(3)** and β-[Ru_2 ($pipeDTC)_5$] **(4)** (where, pipeDTC= piperidine dithiocarbamte)	Elemental analysis, FT-IR and ^1H NMR spectroscopy.	Adenocarcinoma gastric cell line (AGS) and the human colorectal carcinoma cell line (HCT116).	Compound **1-3** displayed IC_{50} values lower than or close to 1μM after 24 h or 72 h of treatment. Compound **4** showed a promising cytotoxic effect of one order of magnitude greater than the standard drug cisplatin.	[54]
[Ru ($PDT)_3$] **(1)**, β-[Ru ($PDT)_5$]Cl **(2)**, [Ru ($CDT)_3$] **(3)** and α-[Ru_2 ($CDT)_5$]Cl **(4)** (where PDT= pyrrolidine dithiocarbamate, CDT= carbazole dithiocarbamate)	FT-IR, NMR, UV-visible, ESI- MS spectroscopy, silica gel and thin layer chromatography, and elemental analysis.	HeLa (cervix adenocarcinoma) and HCT116 (colon carcinoma) human tumor cell line.	Compound **4** showed in-vitro antiproliferative activity which increases when delivered via the PF127 carrier.	[55]

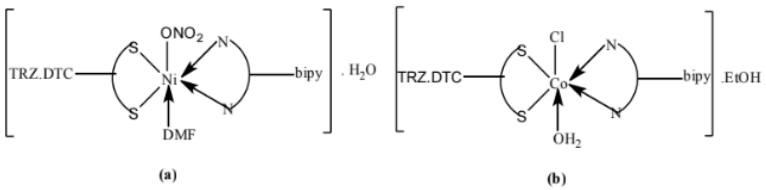


Figure 8: Structural geometries of (a) [Ni (TRZ.DTC) (bipy)ONO_2].H_2O (b) [Co (TRZ.DTC) (bipy)ONO_2].EtOH [50].

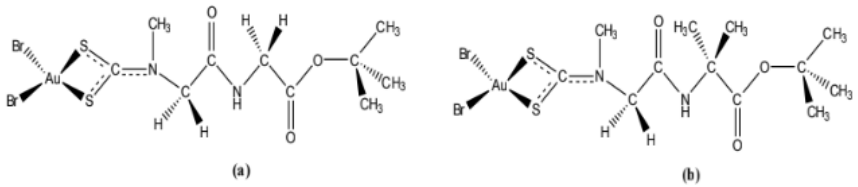


Figure 9: Molecular structure of (a) [Au (III)Br_2 (dtc-Sar-Gly-O (tBu))] (b) [Au (III)Br_2 (dtc-Sar-Aib-O (tBu))] [51].

Other Biological Activities

Dithiocarbamate gold nanoparticles were found to have applications as a plasmonic sensor in biological and environmental media [56]. Kailasa et al. prepared gold nanoparticles with multifunctional groups of 4-hydroxy-6-methyl-3-nitro-2-pyridone-dithiocarbamate derivative and screened for use as a plasmonic sensor for simple and competitive detection of diafenthiuron (insecticide) in water and food sample [56]. The result demonstrated high selectivity of the designed plasmonic sensor towards diafenthiuron with a detection limit of 7.1 nM, which is lower than the permissible limit of diafenthiuron [56]. Eng. et al. prepared triorganotin (IV) dithiocarbamate complexes with general formula $R_3SnS_2CNR'_2$ (where R= Cy, Ph; NR'_2= NEt_2, N (n-Bu)$_2$, N (i-Bu)$_2$, N (i-Pr)$_2$, N $(CH_2)_5$, NH (n-Pr), NH (n-Bu), NH (i-Bu) [57]. The synthesized compounds were characterized by IR, Mössbauer and NMR spectroscopic techniques and screened for insecticidal activity against the second larval instar of the Anopheles stephensi Liston and Aedes aegypyi (L.) mosquitoes [57]. Promising insecticidal activities has been obtained against both species of larvae [57]. Khan et al. reported that the aforementioned Ni (II), Cu (II) and Zn (II) complexes of diphenyldithiocarbamate with general formula $M[S_2CN(C_6H_5)_2(H_2O)_n]$ (where M= Zn, n= 0 (**1**); M= Cu, n= 0 (**2**); M= Ni, n= 2 (**3**)) exhibited remarkable antioxidant potential as compared to standard butylated hydroxytoluene [25] Compound **1** showed IC_{50} of 31.45±0.31 µM while that 44.67±0.45 was showed by the standard [25].

Similarly, the aforementioned complexes of Zn (II) and Ni (II): ZnMDBz, ZnEDBz, NiMDBz and NiEDBz, where MD= N-methyl-N-phenyl dithiocarbamate, ED= N-ethyl-N-phenyl dithiocarbamate and Bz= benzoate, were investigated for anti-inflammatory activity using Bovin serum albumin denaturation assay and antioxidant potential using DPPH assay and ferrous chelating assay [22]. The compounds showed the potential to be anti-inflammatory and antioxidant agents [22]. Ali et al. prepared organotin (IV) dithiocarbamates: $(n\text{-}Bu_2SnCl)_2L$ (**1**), $(Ph_2SnCl)_2L$ (**2**), $(Ph_3Sn)_2L$ (**3**), and $(Bz_3Sn)_2L$ (**4**) (where L= 4,4-trimethylenedipiperidine-1-carbodithioate) [58]. The compounds were investigated by FT-IR, multinuclear NMR (^1H and ^{13}C) and X-ray single- crystal analysis and screened against the pathogenic Leishmania major using Amphotericin B (0.342 µg/mL) as a standard drug [58]. All the compounds showed promising anti-leishmanial activity [58].

2. Conclusion

Study of biological activities of various synthesized metal-dithiocarbamate derivatives clearly shown that metal-dithiocarbamate derivatives can be used as potent medical agents especially as antifungal, antibacterial and antitumor agent. Their other biological applications such as antioxidant, anti- inflammatory, and anti- leishmanial agents also have been reported. Metal- dithiocarbamate derivatives can also be used as plasmonic sensors for detecting insecticides present in water and food samples. They can also have application as insecticidal agent. Above discussion lead the synthesis of novel dithiocarbamate ligands and their metal derivatives and to find out their applications in treatment and prevention of various diseases especially as antivirus agents and antitumor agents.

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