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MINI REVIEW

Metal Complexes of Dithiocarbamate Derivatives and its Biological Activity

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The recent applications of various substituted metal complexes of dithiocarbamate derivatives based drugs and have clearly shown that the biological approaches for this new generation of dithiocarbamate would be a symbol of implementing and development of better medical agents socially. In this brief review, the synthesis and biological activities of dithiocarbamate complexes are discussed. Dithiocarbamate is known to contain ($R_2NCS_2^-$ or $RNHCS_2^-$) containing fragments act simply as counter ions. The dithiocarbamate group (Rdtc-) of ligands has been discovered to perform usually as uninegative bidentate ligands coordination *via* each of sulfur atoms with many metal ions. The metal complexes with these ligands have been extensively investigated and are of interest in many fields such as flotation agents and as antifungal agents. Due to the chelating feature they are utilized as scavengers in water-waste processing.

Keywords: Dithiocarbamate, Metal complexes, Biological studies.

INTRODUCTION

In chelate complexes the metal ion performs a coordination with two or more donor atoms of the same ligand. The chelate impact means preferring metal ions in order to create complexes with chelating ligand instead of non-chelating ones in which the two types of ligands are capable of forming bonds of similar strength. The impact of the chelate is influenced by the effects of enthalpy and entropy [1]. Metal complexes of oxygen, sulfur and nitrogen-chelating ligands gained consideration owing to their curiously explanatory [2], biological [3] and physico-chemical [4], properties, articulated biological activities and for their utility as models of metalloenzyme dynamic sites [5]. In coordination of metals, sulfur and nitrogen atoms play a key part at the dynamic destinations of various metallobimolecules [6]. The intrigued in sulfur given chelating operators have developed exceptionally rapidly [7].

Coordination chemistry is centered on potential applications of macrocylic thio Schiff bases and their metal complexes [8]. Dithiocarbamates are very common compounds binding strongly and selectively to a wide range of metal ions, therefore, in the past decade self-assembly which is controlled by the coordination of metal dithiocarbamate has emerged in a form of a beneficial supramolecular method for preparing macrocycles, cages, catenanes and nanoparticles. The majority of the applications are implemented on the basis of complexation characteristics of dithiocarbamate ligands with ions of metal, particularly with transition metal ions [9]. Dithiocarbamate ligands readily produce chelating compounds with all metal ions *via* its two donor atoms of sulfur. Dithiocarbamate compound can stabilize high oxidation state metal ions in complexes of metal because of the strong O-bond property of those ligands. Even though the atoms of sulfur of dithiocarbamate ligands include O-donor and N-back donation properties of identical magnitude order, those ligands possess certain features in the fact that there's an extra *n*-electron that flows from nitrogen to sulfur through a planar delocalized π orbital system [10] (Fig. 1). The coordination chemistry of dithiocarbamate ligand may coordinate to the metals in three different ways, *i.e.*, as bidenate, ansiobidnate and monodenate (Fig. 2).

Many metallic elements play a crucial role in the living system. Without appropriate metal ion, a biochemical reaction catalyzed by a particular metalloenzyme would process very slowly. Transition metal ions are components of biological process from oxygen arrangement to hypoxia detecting. This

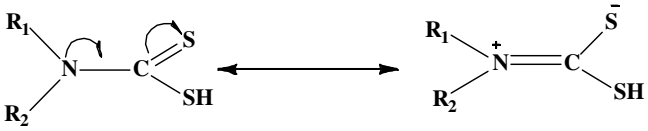


Fig. 1. Flow of the electron from nitrogen to sulfur

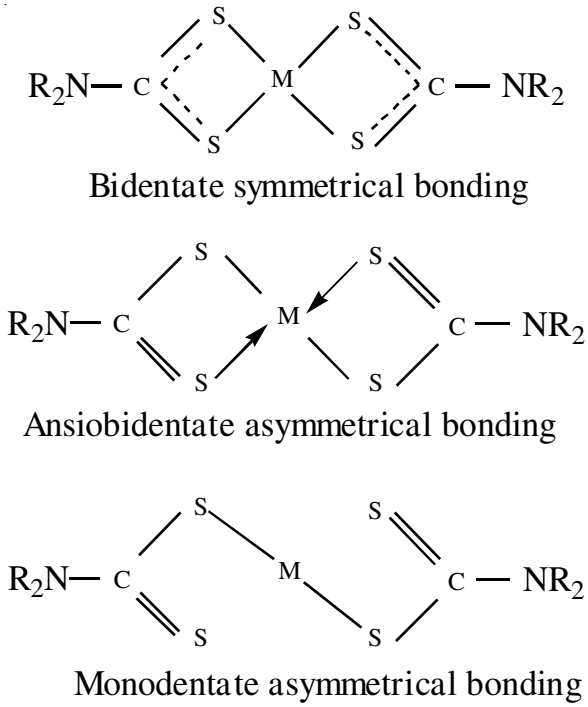
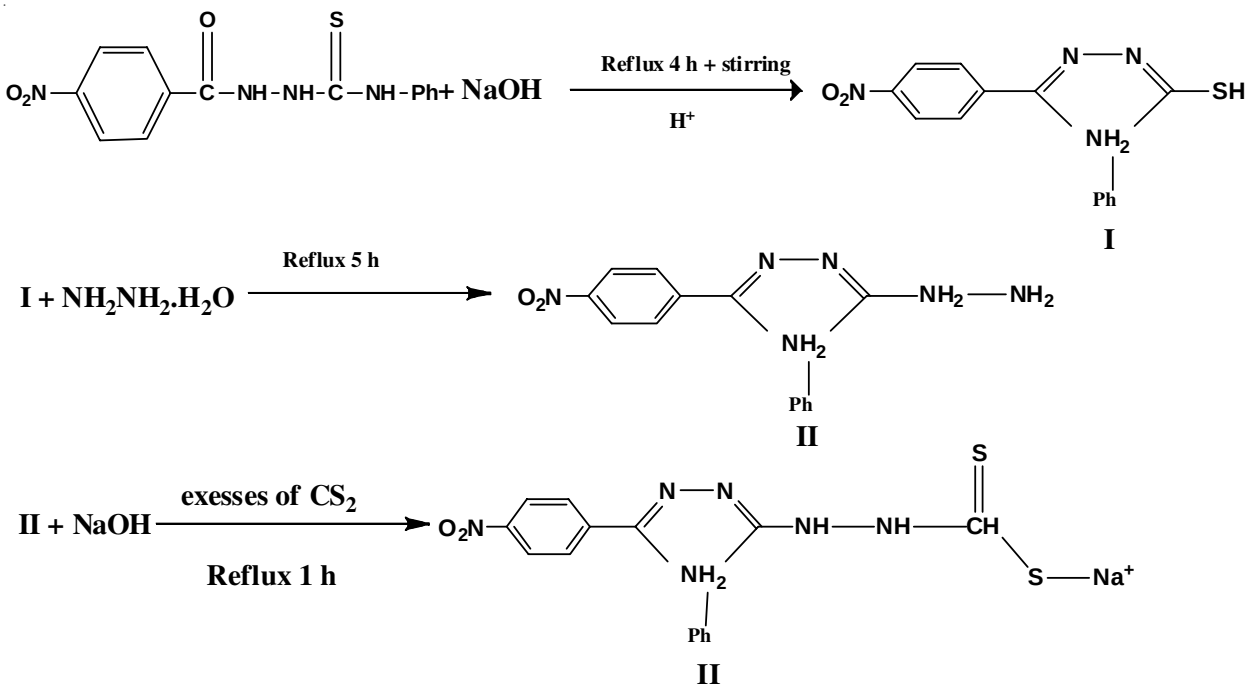


Fig. 2. Characteristics of the nature of binding of the dithiocarbamato moiety

has been embroiled in numerous infections counting microbial contamination, cancer and neurodegenerative disorders [11,12]. Metal ions are normally displayed in organic systems. In fact, metals such as, calcium, copper, zinc, magnesium, sodium or potassium are well-known fundamental components of human body homeostasis. Be that as it may, past these components, numerous more are too present in traces. Hence, indeed though a few of them are by and large considered as toxic, metals such as selenium or molybdenum display benefit impacts even at low concentration [13,14]. Additionally, not as it were the component or its sum interior the cell should be considered in science, but to the coordination environment of the metals is pivotal to decide the adjust between useful and harmful effects. As a case, "free" copper ions are nearly truant within the cytosol and are exceedingly poisonous. Copper is carried through the cytoplasm by chaperones such as Atox1 and delivered to its actual destination such as mitochondria where it is joined into metalloenzymes. One case of such enzyme is cytochrome c oxidase, which contains a Fe/Cu center in its active location for the transformation of O_2 to H_2O [15]. This highlights the significance of the coordination chemistry of metals in biological systems.

Metal complexes derived from dithiocarbamates: Alias *et al*. [16] synthesized series of (TRZ.DTC) ligand (**Scheme-I**) and their Pd(III), Cu(II), Ni(II), Cr(II) and Cd(II) complexes (Fig. 3). The structural geometries of prepared complexes were characterized and also suggested in a gas phase by using a Hyperchem-8 program. The elemental analysis indicates that the complexes have octahedral structure except for cadmium(II) which has tetrahedral geometry, whereas copper(II) has a dimeric structure. The palladium complexes evaluated *in vitro* against Rhabdomyosarcoma cell line and compared this effect with control positive cisplatin. The efficiency of these new compounds on the RD cell line may be attributed to blocking the protein synthesis of cells.

Similarly, a new set dithiocarbamate ligand of Na[5-(*p*-nitrophenyl)-/4-phenyl-1,2,4-triazole-3-dithiocarbamato hydrazide] (TRZ·DTC) has been synthesis by Hashim *et al.* [17] from the reaction of 1-phenyl-4-(*p*-nitro-benzoyl)thio-



Scheme-I: Symthesis of sodium "[5-(pnitrophenyl)-/4-phenyl-1,2,4-triazole-3-dithiocarbamato hydrazide]"

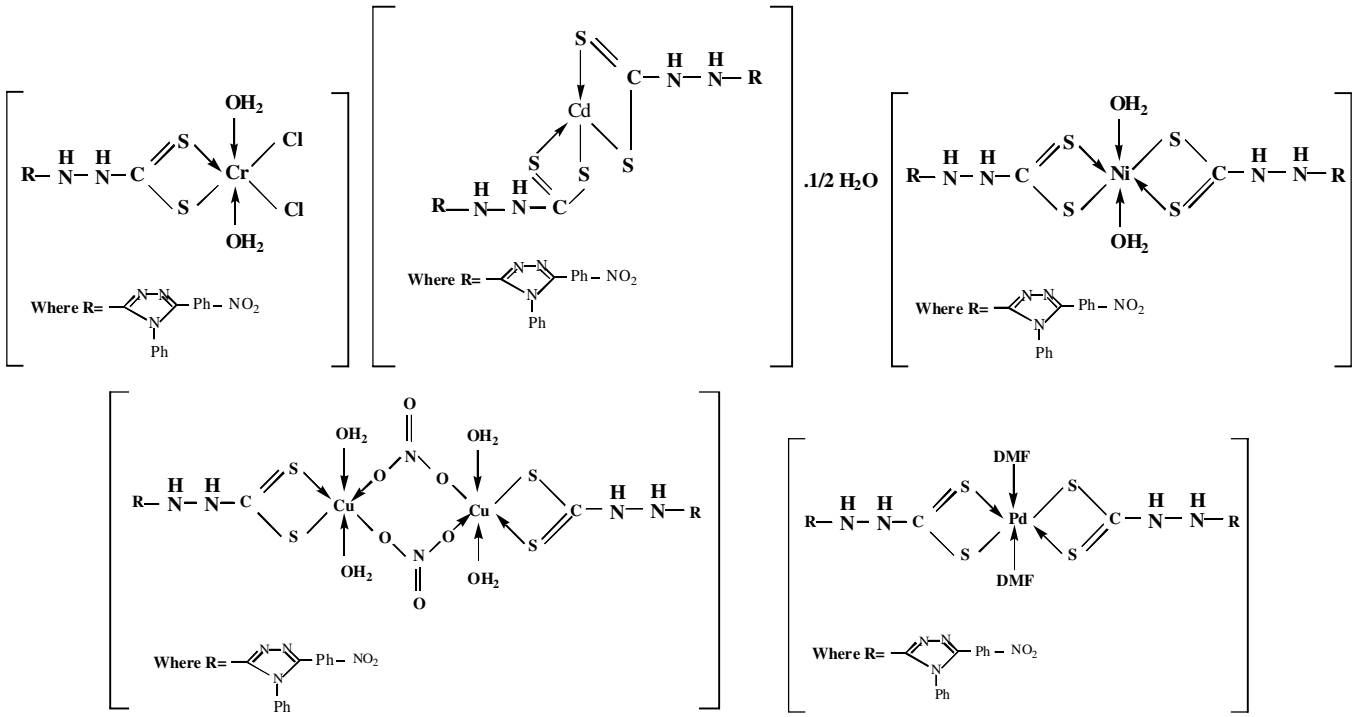


Fig. 3. Proposed structure of metal (TRZ.DTC) complexes

semicarbazide with hydrazine hydrate and prepared its Pt(IV), Au(III), Rh(III), cobalt(II) and V(IV) complexes (Fig. 4). The prepared ligand and their some complexes were examined for their biological action. The *in vitro* cytotoxicity behaviour against RD cell line. The bioassay results demonstrated that the synthetic compounds displayed good inhibition activity on selected cell lines compared with the standard drug.

Ingle *et al*. [18] have synthesized and characterized copper (II), nickel(II), cobalt(II), cadmium(II) and mercury(II) complex of ammonium phenyl dithiocarbamates (Fig. 5). The *in vitro* biological activity of ligand and their metal chelates is screened against bacterial species *E. coli*, *S. aureus*, *P. vulgaris* and *P. aeruginosain*.

Nabipour [19] reported the Co(II) and Co(II) complexes with 1,10-phenanthroline, pentamethylene dithiocarbamate sodium salt (**Scheme-II**). The complexes were characterized by XRD and SEM. The biological activities of synthesized compounds were studied against, *K. pneumonia*, *E. coli* and *S. aureus*, and *B. subtilis*, for *in vitro* antifungal activity against, *C. albicans*, *A. flavus* and *A. niger*.

Complexes of Cu(II) and Mn(II) with 2-amino-2-methyl 1-propanol dithiocarbamate (**Scheme-III**) were synthesized,

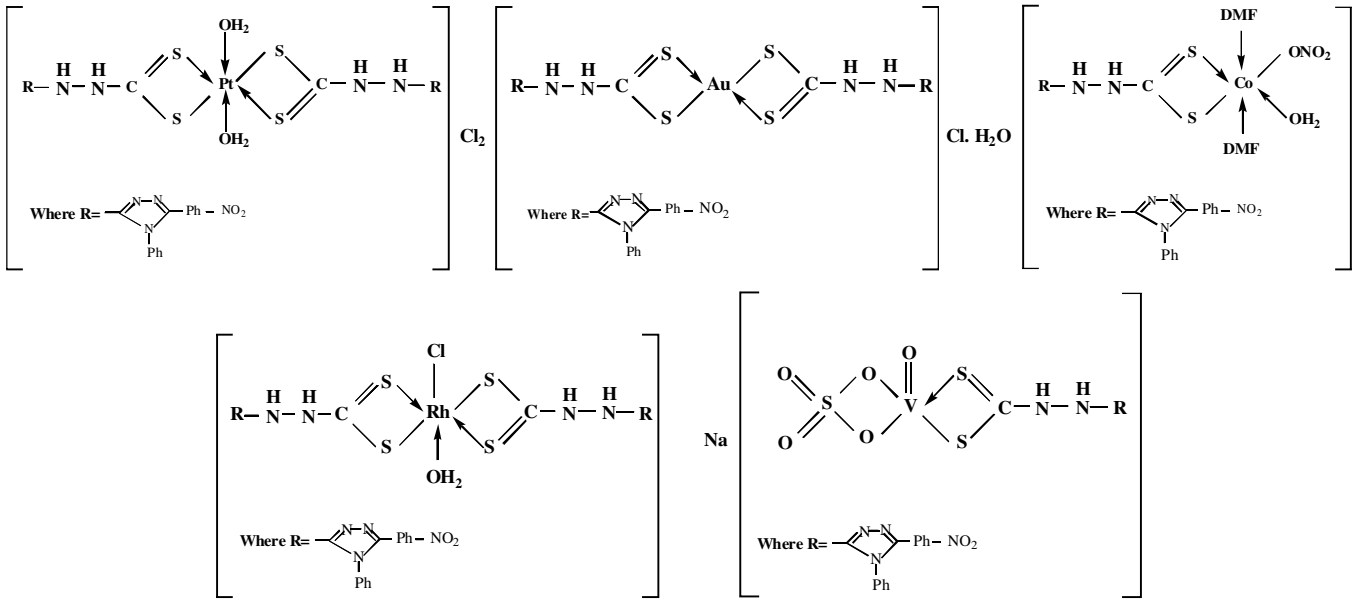
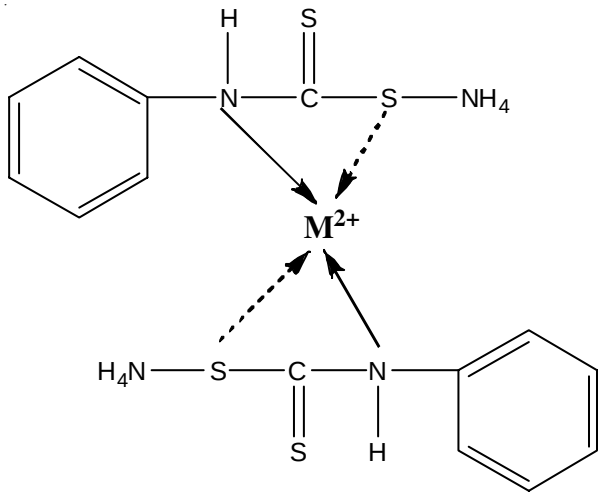
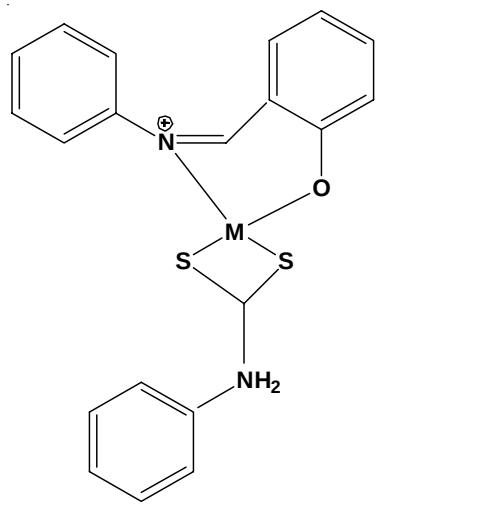


Fig. 4. Structure for synthesized complexes



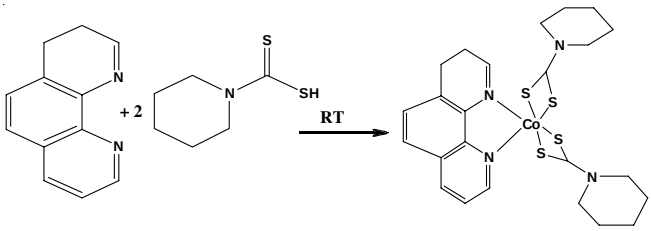
M^{2+} = Cu, Ni, Co, Cd, Hg

Fig. 5. Structure for synthesized complexes

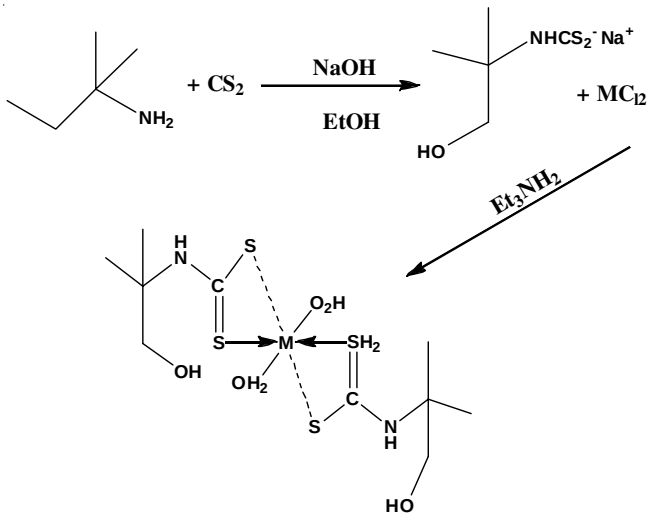


M = Cu(II), Pb(II), Ni(II), Mn (II), Zn (II) Fe (II), Co (II) and Cd (II)

Fig. 6. Structure of synthesized complexes



Scheme-II: Synthesis of (pipdtc)2(1,10-phen) ligand and the structure of proposed metal complexes



M = Cu^{2+} and Mn^{2+}

Scheme-III: Synthesis of (AMPDTC) ligand and their metal complexes

and characterized by Jayaraju *et al*. [20]. The complexes have the composition $[Cu(AMPDTC)_2)Cl_2]$ and $[Mn (AMPDTC)Cl_2]$, and has shown selective activity towards some of the test micro-organisms [20].

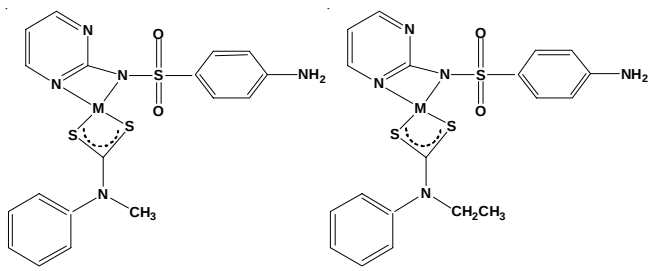
The ligand aniline-N-phenyl dithiocarbamate has been synthesized by Ejelonu *et al*. [21]. It is suggested that the mixed ligand coordinate to metal ion through the two sulfur atoms of N-phenyl dithiocarbamate and through nitrogen and oxygen atoms of alanine Schiff base (Fig. 6). All the synthesized compounds were tested for *in vitro* activities against 10 different microorganisms.The results revealed that all the complexes have shown potent biological activity against tested the microorganisms.

Imadul Islam *et al.* [22] prepared nickel (II) and palladium (II) complexes with pyrrolidine dithiocarbamate (PDTC). The prepared complexes were characterized using spectroscopic methods and found that the ligand coordinate with metal ion through two sulfur atoms . All the synthesized products were evaluated for their antibacterial activity against Gram-negative bacteria (*E. coli*, *V. cholerae*, *S. pneumonia*) and Gram-positive bacteria (*B. cereus*).

Sharma *et al*. [23] synthesized a series of morpholine dithiocarbamato and their Cu(II), Ni(II) and VO(IV) complexes and evaluated their antifungal studies. The antifungal activity of the prepared complexes exhibited a linear relationship with the concentration.

Ajibade *et al.* [24] have prepared four coordinate complexes of M(II) of 4-amino-N-(2-pyrimidinyl)benzenesulfonamide (sulfadiazine) with some *N*-alkyl-*N*-phenyl dithiocarbamate (Fig. 7). The structure geometries of these complexes have been investigated by elemental analysis, conductivity measurements, FT-IR and UV-visible spectra. The spectroscopic studies indicate that Cu(II), Pd(II) and Pt(II) complexes have square planar structure, whereas Co(II) complexes have a tetrahedral structure. The complexes have been evaluated for antibacterial activity against *S. aureus*, *S. faecalis*, *B. cereus*, *B. pumilus*, *E. coli*, *P. aeruginosa*, *P. vulgaris* and *K. pneumonia*.

A new mixed ligand of cobalt (II) formed by interaction of $CoCl_2$ with piperazine dithiocarbamate (pipdtc) and amino



M = Co, Cu, Pd and Pt

Fig. 7. Proposed structures of the complexes

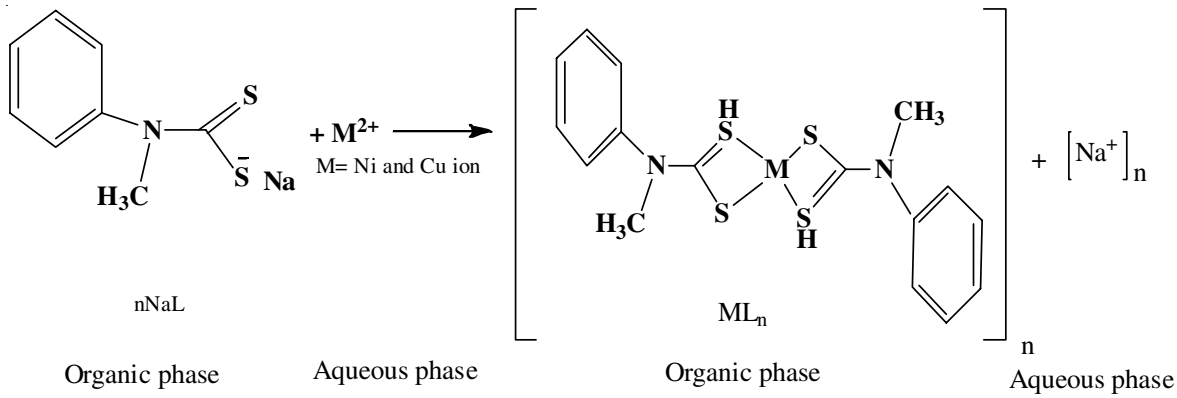
acids (aaH) such as alanine (alaH), phenyl alanine (phealaH), tyrosine (tyrH), methionine (metH) and glycine (glyH) were reported [25]. These complexes have been characterized by spectroscopic, magnetic susceptibility studies, elemental and thermal analysis. The low molar conductance values indicate that the non-electrolytic nature of these complexes. Electronic spectra coupled with magnetic susceptibility values indicated the presence of an octahedral environment around the central metal ion. The SEM image of cobalt(II) complexes implies that the spherical shape of complexes and size roughly less than 500 nm. The anticancer activity of complex with formula $[Co_2(pipdtc)(ala)_2(H_2O)_4]$ and $[Co_2(pipdtc)(phenala)_2(H_2O)_4]$ showed a promising results further supported by the DNA studies. The antioxidant properties of complexes show the gradation due to the presence of different amino acids and hence it could be proved that the presence of a second ligand affects the properties of complex. The selectivity index as high as 32 and 64, which indicates the fact that these compounds could be used as good anticancer agents [25].

Ekennia *et al*. [26] prepared a novel N-methyl-N-phenyl dithiocarbamate and its Ni(II), Co(II), Cu(II) and Mn(II) complexes (**Schemes IV** and **V**). The structures of ligand and their metal complexes had been resolved, the ligand acts as a bidentate and coordinated with metal *via* sulfur atoms of dithiocarbamate and through the nitrogen atom of pyridine. The ligand and their complexes were investigated for *in vitro* antifungal namely (*A. niger*, *C. albicans* and *A. flavus*). The results showed the Co(II) complex exhibited the best antifungal activity among the test compounds.

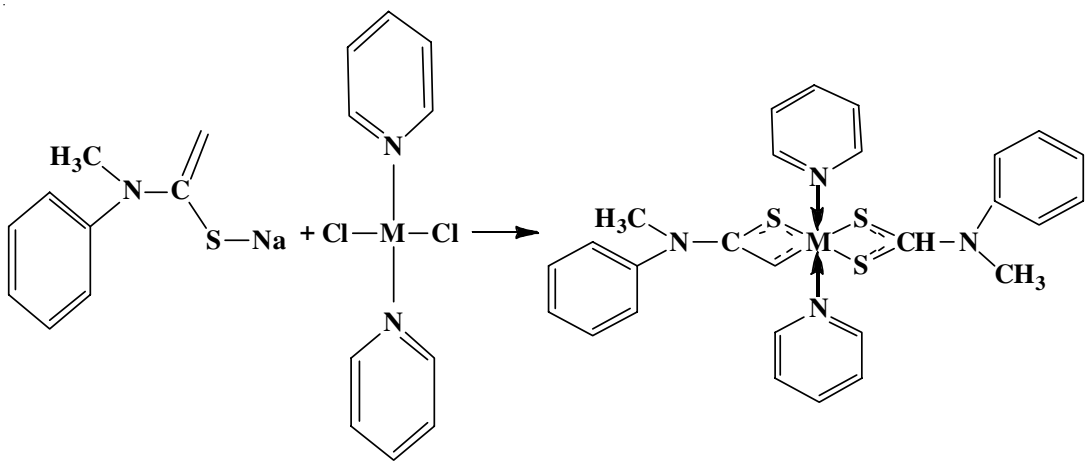
Sainorudin *et al*. [27] studied the synthesis and biological activity of di-2-ethylhexyldithiocarbamate and N-methyl-butyldithiocarbamate and their novel set of organotin (IV) complexes. The structure of the ligands and their complexes were investigated by various spectroscopic analysis methods. The organotin(IV) complexes were investigated for *in vitro* antimicrobial activity for bacterial strain compared with the positive control (penicillin) and negative control (streptomycin). The results also demonstrated that the synthesized complexes have higher biological effectiveness compared with positive and negative control.

In view of antibacterial and antifungal activity of organotin(IV) complexes of 1*H*-1,2,4-triazole-3-thiol (**Scheme-VI**), Parveen *et al.* [28] synthesized and found the homobimetallic derivatives more active antimicrobial agents when compared with mononuclear organotin(IV) compounds and free ligand.

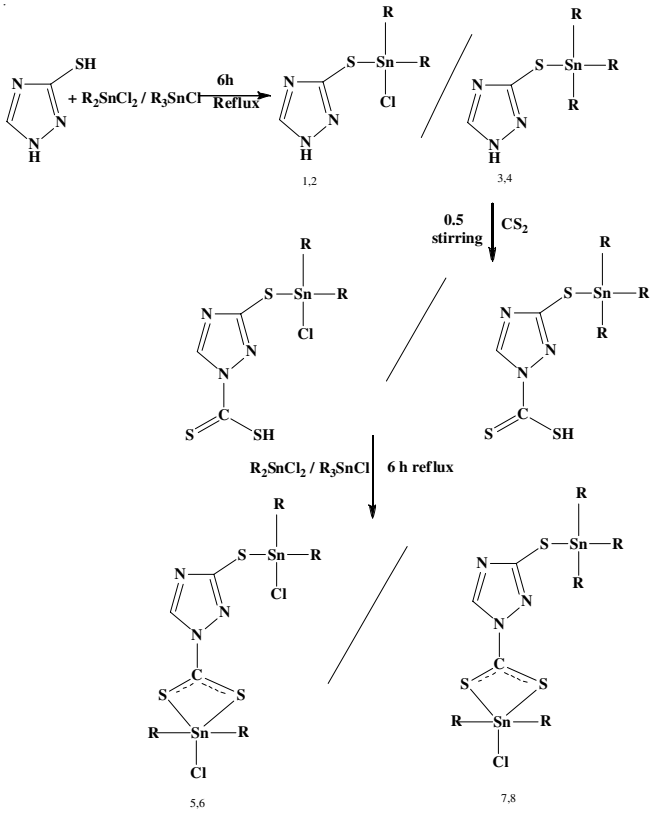
DNA binding and cytotoxicity activity of a novel ligand 2,2′-bipyridine with ethyldithiocarbamate and their Pt(II) and Pd(II) complexes (Fig. 8) are reported. The DNA interaction modes of the complexes are investigated using circular dichroism, ultraviolet difference and fluorescence spectroscopies. The *in vitro* cytotoxic results estimated that Pd(II) complex had more growth inhibitory activity against K562 relative to Pt(II) complex and both are more cytotoxic than cisplatin.



Scheme-IV: Synthesis procedure



Scheme-V: Synthesis of ligand and complexes



Scheme-VI: Synthesis of the homobimetallic complexes

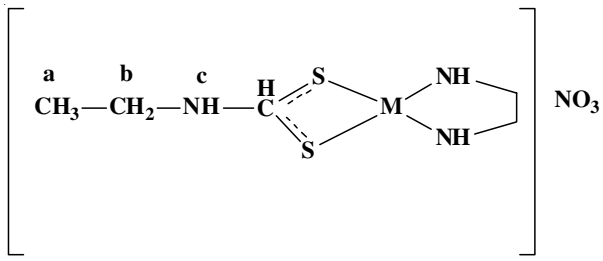


Fig. 8. Proposed structures of [Pt(bpy)(Et-dtc)]NO_3 or [Pd(bpy)(Etdtc)]NO_3

Detailed interaction studies of both complexes with calf thymus DNA were carried out. They cooperatively bind to DNA and unexpectedly denature the DNA at very low concentrations [29].

In order to study the cytotoxicity effect of compound containing thiocarbamate, Alias *et al.* [30] synthesized new mixed ligand obtained from [5-(*p*-nitrophenyl)-4′-phenyl-1,2,4-triazole-3-dithiocarbamato hydrazide] (TRZ·DTC) as primary ligand and 2,2′-bipyridyl (bipy) as a co-ligand and their Ni(II) and Co(II) complexes. The complexes of ligand had been characterized and the structure identification carried out on the basis of different spectroscopic methods. The spectral data suggested that the Ni(II) complex had five-coordinate square pyramidal geometry, while Co(II) complex have six-coordinated octahedral geometry in the solid state (Fig. 9). The *in vitro* cytotoxicity behaviour screened on human HepG2 cell line using cisplatin drug as a control positive. The synthetic complexes especially nickel(II) complex displayed more *in vitro* antioxidant potential than standard drug.

Mohamad *et al.* [31] reported the synthesis and antibacterial activity of new complexes of dimethyltin(IV) and diphenyltin(IV) with *bis*(2-methoxyethyl)dithiocarbamate ligand.

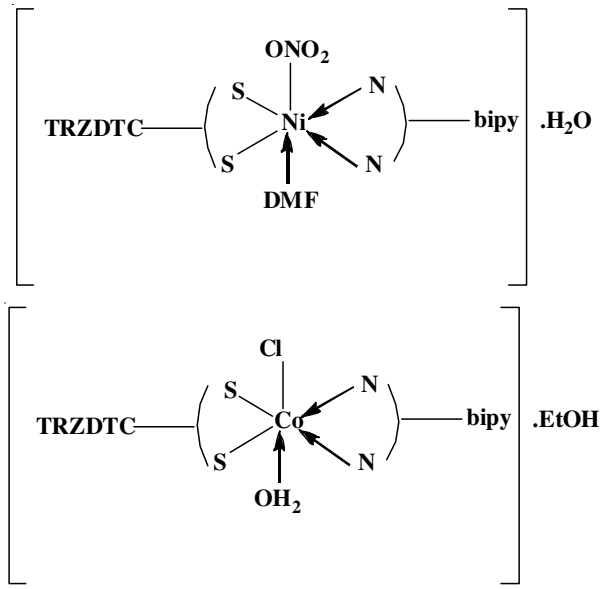


Fig. 9. Suggested structure of Ni^{2+} and Co^{2+} complexes of (TRZ·DTC)(bipy)

The IR spectra of diorganotin(IV) complexes of dimethyltin(IV) and diphenyltin(IV) with *bis*(2-methoxyethyl)dithiocarbamate ligand (Fig. 10) showed that an intense band in the region 1,482 and 1489 cm^{-1}, thus indicated the presence of chelated dithiocarbamates. Besides the stretching bands C-N and C-S, the ν(Sn-S) coordination is supported by the presence of a new medium to weak absorptions in the area 425-386 cm^{-1} [31]. Antibacterial activity of these complexes showed that both complexes are inhibited towards *P. aeruginosa* and *S. aureus*. However, diphenyltin(IV) *bis*(2-methoxyethyl)dithiocarbamate was more active and more promising as an antibacterial agent.

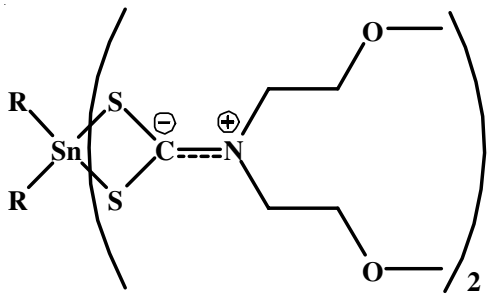


Fig. 10. Structure of diorganotin(IV) complexes

Mathew *et al.* [32] reported a few mixed ligand complexes of the general formula [M(mordtc)(1,10-phen)] where M = Ni(II), Co(II), Cu(II), Zn(II) and mordtc = morpholine dithiocarbamate]. The biological activity test results showed that mixed ligand complex have significant anti-bacterial activity against bacteria. However Zn(II) complex might be effective as an antibacterial agent, which may be attributed due to partial sharing of its positive charge with donor group and possible electron delocalization occured in morpholine dithiocarbamate ring.

Venugopal and Sreeramulu [33] reported the sytheses of Au(III) and Ru(III) complexes of 2-amino-1,2,4-triazole dithiocarbamate and 2-amino-4-hydroxy-6-methyl-pyrimidine dithiocarbamate. The structures and anticancer activities of complexes

were elucidated by different type of structural techniques. It was found that Au(III) and Ru(III) complexes have shown excellent activity against bacteria and cancer viruses [33].

Ekennia *et al*. [26] synthesized *bis*(*N*-methyl-*N*-phenyl dithiocarbamate) and its metal complexes, having the general formula $[M\{S_2CN(MePh)\}_2]$ (where M = Cu, Co and Ni) (Fig. 11). The *in vitro* antibacterial activity of the complexes was investigated against strains of gram-negative *Escherichia coli*, *Klebsiella oxytoea* and *Pseudomonas aureginosa*, and Gram-positive *Bacillus cereus*, *Staphylococcus aureus* and *Protues mirabilis*. The antibacterial activity of the complexes compared favourably with that of streptomycin and augmentine against *S. aureus* and *B. cereus*. The cobalt(II) complex had the better antibacterial activity against the test compounds with inhibitory zone range of 11-14.5 mm in comparison of Cu(II) and Ni(II) complexes.

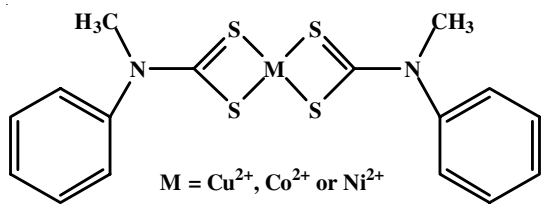


Fig. 11. Structure of synthesized complexes

Similarly, Osoro *et al.* [34] reported the synthesis and characterization of piperazinedithiocarbamate (pipdtc) bridged homobinuclear mixed ligand complexes of Mn(II) containing chelated amino acidato ligands *viz.*, glycine, alanine, phenyl alanine, tyrosine, methionine and cystine. The complexes were screened for antimicrobial activity which showed the promising results against the common bacteria and fungi studied. The complexes were also evaluated for their toxicity towards human breast cancer line MCF-7 and the complexes exhibited low IC_{50} values and high selectivity index values.

Onwudiwe *et al*. [35] reported the synthesis of platinum dithiocarbamate (DTC) complex from the ligand diallyl dithiocarbamate having molecular formula $Pt[S_2CN(C_3H_5)_2]_2$ (Fig. 12). The single-crystal X-ray analysis showed that the complex has a square planar geometry. The diallyl groups of dithiocarbamate ligands are not symmetrical making the complex non-centrosymmetric and the complexes are stacked with intermolecular ring-ring interactions.

Krishnan *et al*. [36] reported the mixed ligand complexes of Co(II), Cu(II) and Zn(II) having composition $[M(morphdtc)_2$ (diamine)] and found that nickel complexes exhibited a wide spectrum of antimicrobial activity against all the bacteria and fungi studied. A striking feature of the anticancer studies is the high selectivity index with a special mention to copper-trien complex, which may be attributed due to as the ring size.

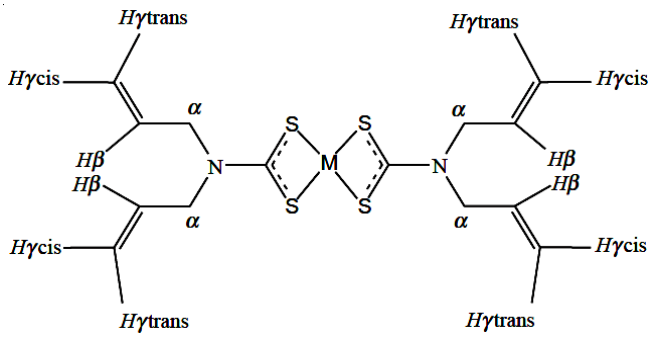
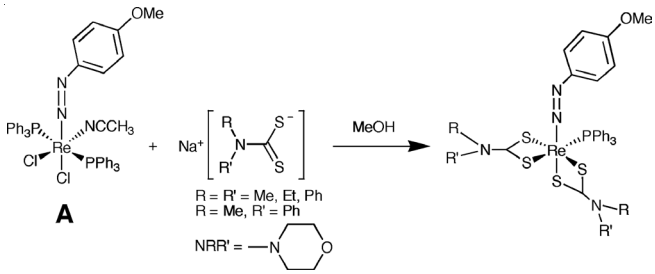


Fig. 12. Schematic diagram of the complex, showing the position of the hydrogen atoms with respect to *-cis* and *-trans* positions

Cowley *et al*. [37] reported the synthesis of rhenium diazenide ternary complexes with dithiocarbamate ligands containing a variety of subsituted groups (**Scheme-VII**) which are found to have potential relevance to the development of new therapeutic radiopharmaceuticals. Ronconi and Fregona [38] designed a number of metal-dithiocarbamato derivatives (Fig. 13) which resemble the main features of cisplatin together with higher activity, improved selectivity and bioavailability and lower side-effects. Among all, gold(III) complexes have shown outstanding *in vitro* and *in vivo* anti-tumour properties and reduced or no systemic and renal toxicity, compared to the reference drug [38].



Scheme-VII: Synthesis of rhenium diazenide ternary complexes with dithiocarbamate ligands

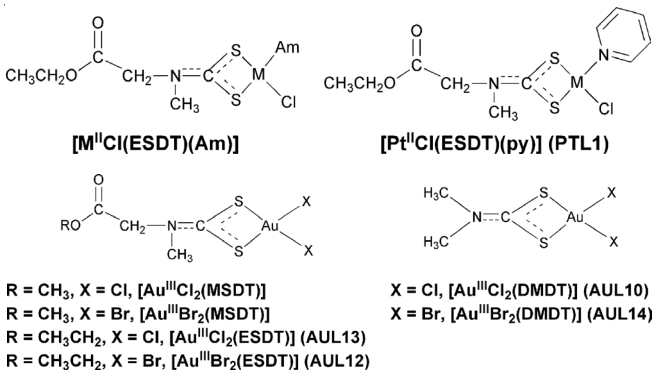
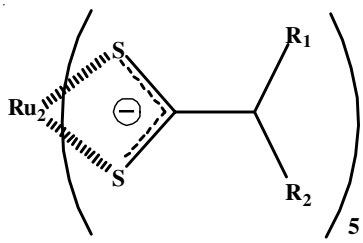


Fig. 13. Selected Pt(II) and Pd(II) dithiocarbamato derivatives: $M^{II} = Pt^{II}, Pd^{II}$; Am = n-propylamine, c-butylamine, pyridine, 2-picoline, 3-picoline, norphenylephrine, synephrine; ESDT = ethylsarcosinedithiocarbamate and selected Au(III)-dithiocarbamato derivatives: X = Cl, Br; DMDT = N,N-dimethyldithiocarbamate; MSDT = methylsarcosinedithiocarbamate; ESDT= ethylsarcosinedithiocarbamate

Complexes of the transition metal ions with dithiocarbamate ligands have been checked for being fungal toxic *in vitro* states [39]. Monitoring of the antifungal activities of the complexes of transition metal with dithiocarbamates, ruthenium dithiocarbamate compounds were synthesized (Fig. 14) and evaluated as well for the antifungal activities against 8 isolates of Aspergillus, that comprises 7 distinct kinds, such as, *Aspergillus clavatus*, *A. flavus*, *A. fumigatus*, *A. niger*, *A. nomius*, *A. tamarii* and *A. terreus* [40]. One of the surveys of small molecule therapeutic elements has shown that most of those therapeutics result from an analogue based method and that their market value comprises two-third of the entire drug sales [41]. On the other



1: $R_1 = R_2 = CH_3$; **2:** $R_1 = R_2 = CH_2CH_3$; **3:** $R_1 = C(CH_3)_3$, $R_2 = H$; **4:** $R_1 = CH(CH_3)_2$, $R_2 = H$; **5:** $R_1 = R_2 = CH(CH_3)_2$

Fig. 14. Structure of the ruthenium complexes

hand, treating the infectious illnesses is still a significant and challenging issue due to combining factors such as emerging infectious illnesses and the raising number of MDR microbial pathogens that have some specific relevance for Gram-positive bacteria [42].

Conclusion

Thus, with these facts and described herein includes the recent applications of various metal complexes of dithiocarbamate derivatives based drugs and clearly shown that the biological approaches for this new generation of dithiocarbamate would be a symbol of implementing and development of better medical agents socially.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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