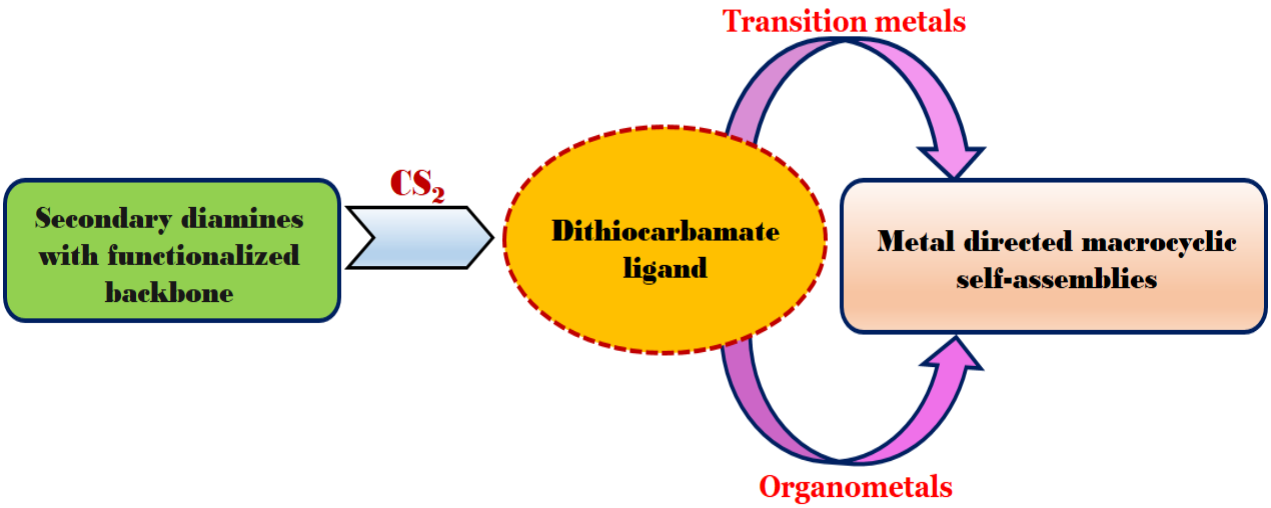
Chapter 1

Introduction: Metal Directed Self-assembly of Dithiocarbamate and their Applications

Abstract



An overview to self-assembly, its wide array of application in numerous aspects of material chemistry and specifically in medicinal chemistry along with the importance of the development of metal directed self-assembled molecular architectures has been contained in this chapter. The exceptional stereoelectronic features of metal ions and dithiocarbamate ligands in metal directed self-assembly directs to the formation of distinct supramolecular frameworks with interesting physico-chemical properties and their application in the biological system has also been highlighted in this section. The objectives of the present work are also mentioned at the end of this chapter.

Chapter 1

1. Self-Assembly

The most significant interdisciplinary areas of chemistry involve the synthesis of wide-range of products through *Self-assembly* with great potential for applications in a range of fields including medicine, energy, materials engineering, and devices. Self-organized structures are formed through various self-assembling processes. Such structures when involve molecules as the basic component it gives rise to *molecular self-assembly* constructing a defined arrangement in absence of any external force. Nobel prize of Lehn, Pedersen, and Cram in the field of supramolecular chemistry has brought up immense development in this major field of chemical research for the past twenty years. The two pillars on which supramolecular chemistry is based on are Self-recognition and self-assembly.[1] The progress of self-assembling of molecules are mainly influenced by various reversible and dynamic steps involved in the synthetic strategies which after series of formation and breakdowns ultimately produces a well-defined assembly [2] One of the key factor governing the formation of any self-assembly is the availability of weak interactions. These interactions determines the flexibility of the assembled molecular framework which basically affects the readjustments of the structure in the course determined by thermodynamic aspects. [3] It mainly involves non-covalent interactions (e.g., hydrogen bonding, van der Waals and coordinative interactions). Large number of factors like reversibility, spatial arrangements, and varied array of interaction strengths provides unmatched hold over syntheses of large and complex structures with diverse functions and properties of the resulting materials that show remarkable application in diverse fields.[1] At present, considerable attention has been received towards coordination-driven supramolecular chemistry as it has been exploited as a proficient methodology for construction of multidimensional framework with previously designed ligands.[4] They are widely used as hosts, molecular sensors and also as catalyst.[5-7] Molecular self-assembly is an indispensable concept of supramolecular chemistry as it delivers an opportunity for fabricating several aggregates of diverse shapes such as helical, spherical,

macrocyclic, ladder, rod-like or sheet like architectures. [8-9] Some examples are displayed in (Figure. 1).

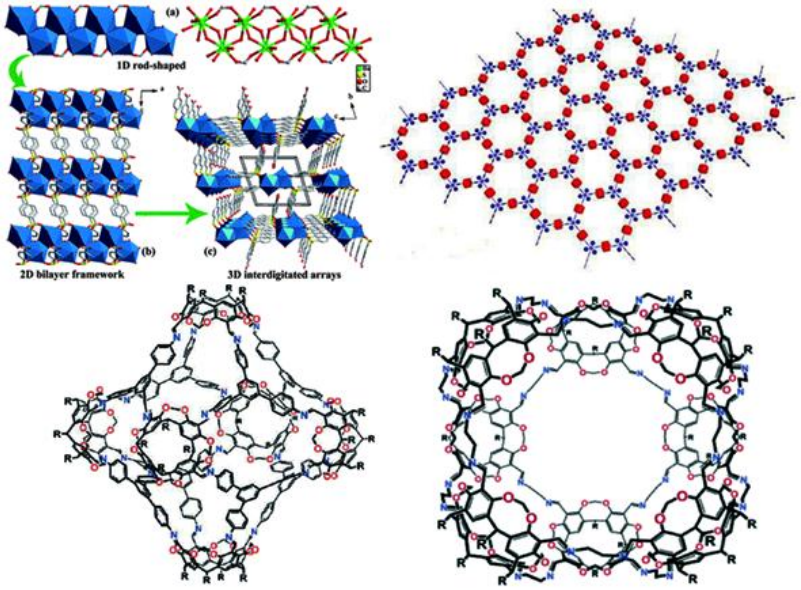


Figure 1. Representation of Self-assemblies giving rise to diverse molecular architectures

Calculated changes induced in the external forces leads to reorientations in the self-assemblies enhancing the potentials of the macrocyclic compounds drug delivery, biosensing and in phase transporting systems.[10] Supramolecular architectures exhibiting diverse cavity size [11-16] are extremely important owing to their potential application in varied arenas of ion sensing,[17-18] catalysis,[19-31] host-guest chemistry,[30-38] transport, separation and storage.[39-42]

Among molecular self-assembly, there are two types: *intra-molecular* and *inter-molecular* self-assemblies. In the biological system folding of protein chains and nucleic acids are illustrations of *intra-molecular* self-assemblies. Individual strands of double helical DNA are brought together by hydrogen bonding which makes it a perfect example of *inter-molecular* self-assembly (Figure 2).[43-44] Such interactions with biomolecules has been studied keeping in mind their helicity which further enforces their role as capable potential therapeutics.[45-47]

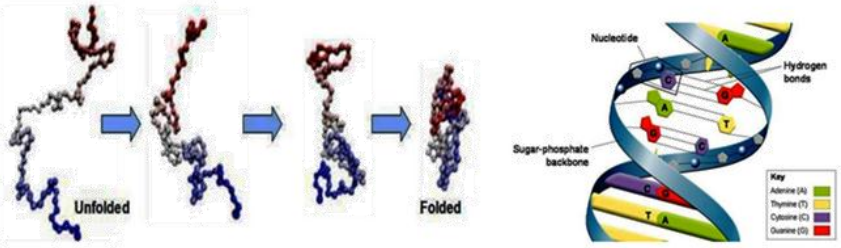


Figure 2. Representation of folding of DNA strands by exhaustive non-covalent interactions resulting in well-organized helical DNA structure

Biological systems involve large number of molecular self-assemblies that are essential for proper functioning of a cell.[48-49] Process involving formation of cell membranes, DNA transcribing and protein folding (Figure 3) are primarily governed by the formations of self-assemblies in nature. Factors like hydrophobic interactions, hydrogen bonding, Van der Waals forces and electrostatic interactions mainly influence the formation of these self-assemblies.

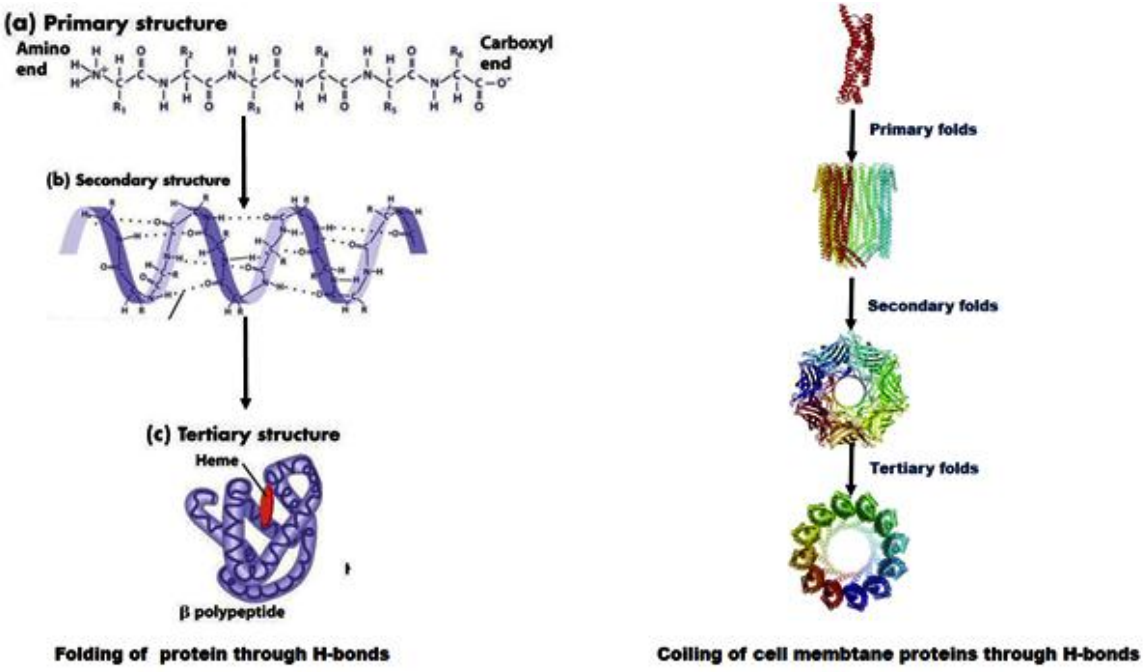


Figure 3. Non-covalent interactions like hydrogen bonds develop the active form of proteins and cell membrane in the biological systems

The incorrect molecular self-assembly could lead to serious problems in an organism (e.g. genetic mutations) and therefore it becomes essential to understand the self-assembly process. The self-assembly of incorrectly folded proteins results into insoluble amyloidal fibres which is responsible for infectious prion-related neurodegenerative diseases. This gives another example illustrating necessity of accuracy in self-assembled structures especially in biological systems. ***The beauty and complexity of self-assembly processes occurring in the nature have inspired synthetic chemists to impersonate such structures at molecular level.*** Once Professor Lehn introduced the concept of supramolecular chemistry,[50] the construction of a biological architectures replicating naturally occurring assemblies has received much attention.

Coordination-driven self-assembly has been evolving as a dynamic research area of chemistry in current years [51-60] Ingenious modification in ligand system and prudent choice of metal ions [8] offers the scope for major modifications in the structural and electronic parameters properties of the self-assembled structures (Figure. 4). As discussed previously, diverse supramolecular architectures like one-, two-, and three-dimensional enormous organic /inorganic hybrid frameworks such as molecular bowl, rod, filament, rack, ladder, brick wall, cylinder, box, square grid, honeycomb, diamondoid, helical, are attained by using the principles of metal-directed self-assembly.

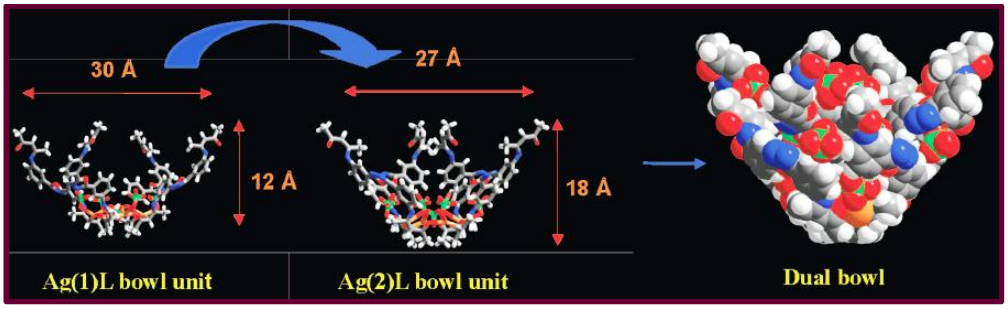


Figure 4(a). Coordination chemistry used in construction of diverse molecular architectures.

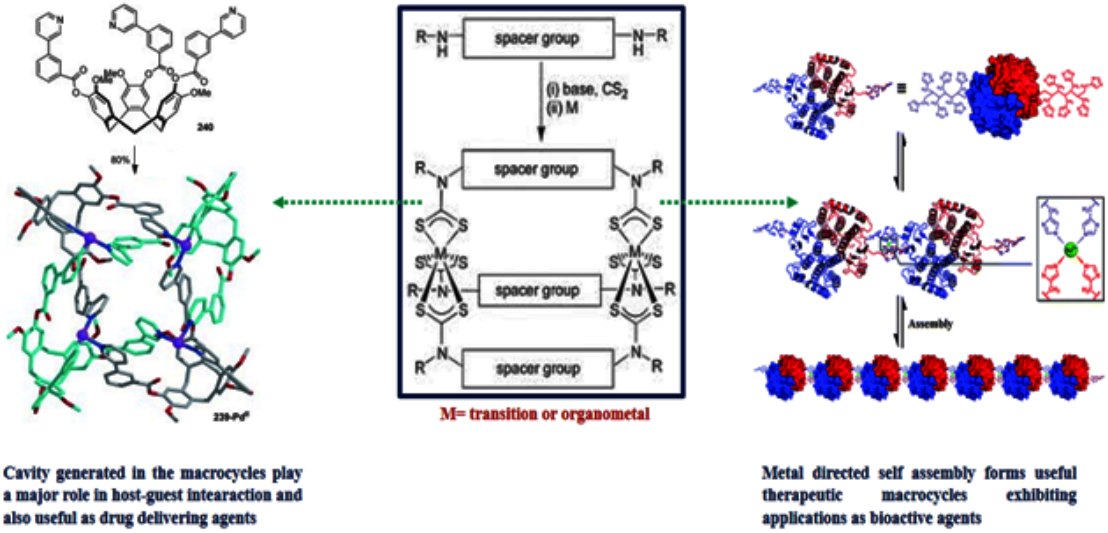


Figure. 4. (b) Application of metal directed self-assemblies in various fields of material and medicinal chemistry.

Thus in this manner, ***coordination chemistry*** magnificently brings out distinct structures with interesting physicochemical properties.[61-62] Metal-directed self-assembly allows for careful selection of metal ions that provide a wide array of binding strengths, coordination geometries and redox behaviours as vital factors for building of self-assembly. Metal-directed self-assembly is advantageous over the traditional methods applied for synthesis of molecular supramolecular frameworks as it comprises of only a few basic subunits brought together in a few steps of the synthetic procedure. [13, 14, 6, 63-67]

1.1 Dithiocarbamate Ligands

Over 150 years ago dithiocarbamates were possibly prepared for the first time, however it was not correctly formulated then. In the prevailing century a mystifying array of different dithiocarbamates have been prepared. This miscellany arises just by altering the substituents on the nitrogen which leads it to the forefront of transition metal chemistry. [68]

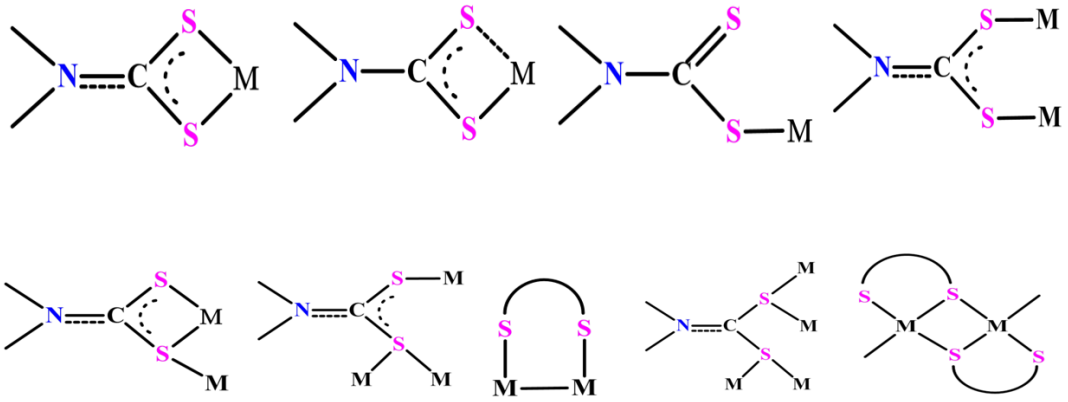


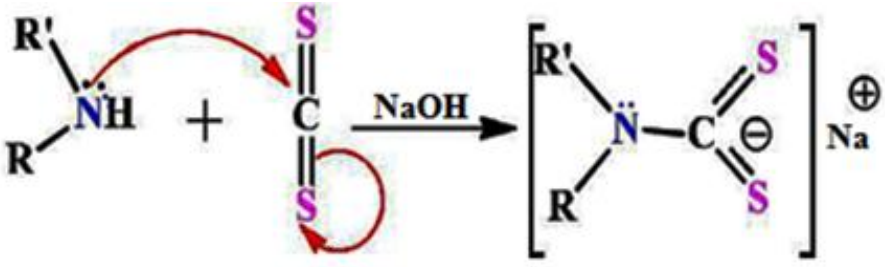
Figure. 5. Vast number of binding modes of 1,1-dithio ligands

The coordination chemistry of 1,1-dithio ligands, particularly dithiocarbamate ligand has been comprehensively documented, [69-71] Dithiocarbamates (DTCs) fits in the class of compounds recognized as the 1,1-dithiolates. [72-74] The amine-1-carbodithioic acid, commonly called as Dithiocarbamate (DTC) is a functional group of organic chemistry comparable to thiocarbamate wherein both oxygen atoms are replaced by sulphur atoms. [75] The strong metal binding properties of the dithiocarbamate ligand is directly related to the presence of the two donor sulphur atoms. The dithiocarbamate (DTC) ligands binds selectively and strongly to many metal ions. (Figure. 5) [76] Dithiocarbamates are identified to alleviate unusually high oxidation states of metal ions. [77] This proposes that complex geometry could be handled by altering the metal oxidation state. Fascinating stereoelectronic properties like strong binding ability and varied binding modes towards various transition/ non-transition metal ions existing in different oxidation states, which eventually make this class of ligands excellent representative for the development of innovative coordination-driven self-assembled molecular architectures. [24, 78-80]

1.1.1 Synthesis and stability of Dithiocarbamates

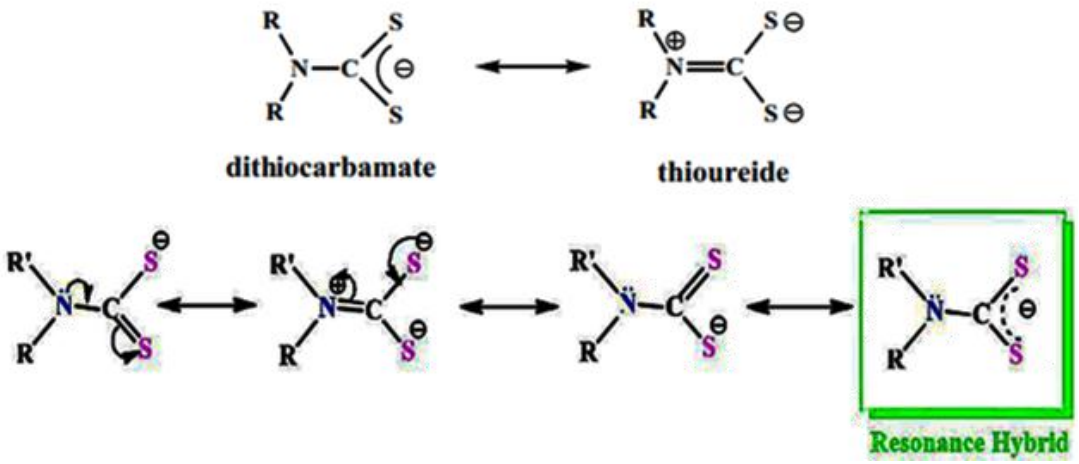
In 1934 the first DTC was reported to be synthesized from a monoamine and carbon disulphide. [81] DTCs are prepared via exothermic reaction between carbon disulfide and primary/secondary amines in the presence of sodium/potassium hydroxide or excess amine. [82] Free dithiocarbamic acids (R_2NCS_2H) are extremely unstable and

the ligands are consequently isolated as their alkali metal salts. (Scheme. 1) A slight yellow tinge to the medium develops during the course of reaction and the successive chemistry is carried out *in-situ*. [68] The solubility of these sodium salts is extensive in water and ethanol but relatively poor in non-polar solvents. Most of the crystals of these DTC salts that were isolated were observed to be hydrated. [75] In case of when transition metal salt is not soluble in water, dithiocarbamates are also prepared in simple organic solvents like dichloromethane, methanol or THF and further mixing with appropriate solution of the metal salt largely provides a very simple and proficient reaction manifold. [68]



Scheme. 1. General synthesis of dithiocarbamates

Dithiocarbamate ligand have an exceptional ability to bind with low as well as high-valent metal ions. This property is mainly due to the formation of dithiocarbamate and thioureide tautomers. The sp^3 hybridized nitrogen has a lone pair of electron with it giving pyramidal arrangement of substituent groups, whereas, planar thioureide (sp^2) shows delocalized lone pair on double-bond characterized carbon-nitrogen bond and the sulfur atoms. (Scheme. 2) The dithiocarbamate form is most capable of binding to low-valent metal atoms thus acting as a soft donor ligand. However, the thioureide tautomer shows high-valent metal binding making it a hard donor ligand due to additional negative charge localized on sulfur.[68] The occurrence of various resonating structures (Scheme 2) provide additional stabilility to the dithiocarbamate moiety.



Scheme. 2. Resonance between dithiocarbamate and thioureide tautomers

1.1.2 Metal directed Self-assembly of Dithiocarbamates

Dithiocarbamates have large number of coordination modes. Dithiocarbamates are flexible ligands recognised to coordinate to metals in diverse forms and their ligation forms are presented below (Figure. 6).The formation of nearly equal metal-sulphur bonds makes DTC an excellent chelate ligand. However, there are examples of metal dithiocarbamate complexes with unequal metal-sulphur bonds. The dtc moiety of dithiocarbamate lignads are known to bind with large number of metal ions present in their low oxidation state as well as in high oxidation states. Although, good number of transition metal dithiocarbamate complexes bearing simple alkyl/aryl N-substituents is known, however functionalization of ligand backbone is still in the early stage of investigations. Because of ready availability starting materials, a plethora of organic amines can be designed and synthesised which can be subsequently utilized in the development of corresponding dithiocarbamate ligands.

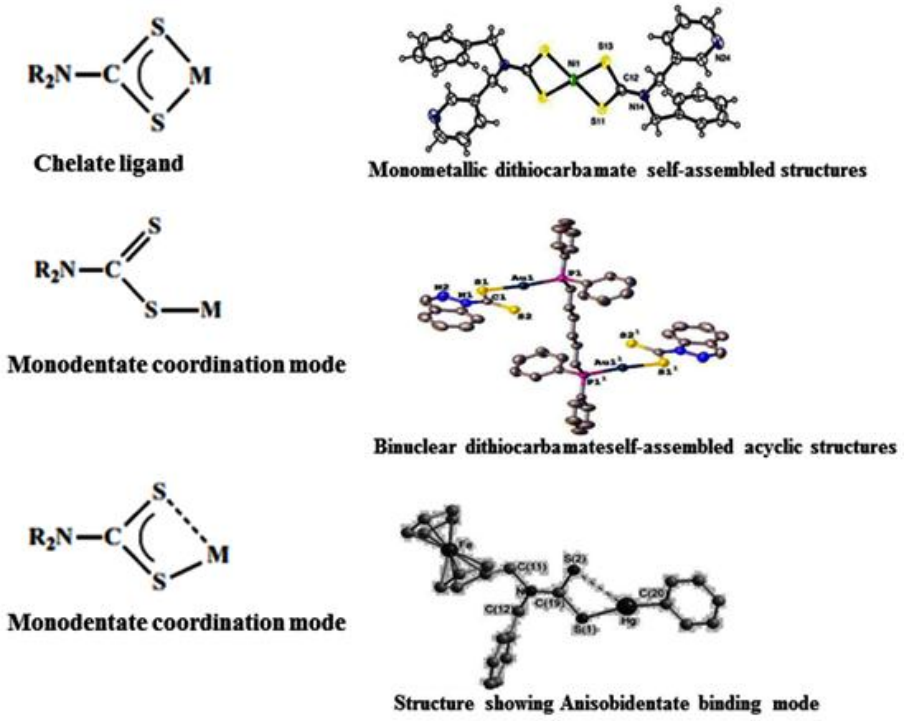
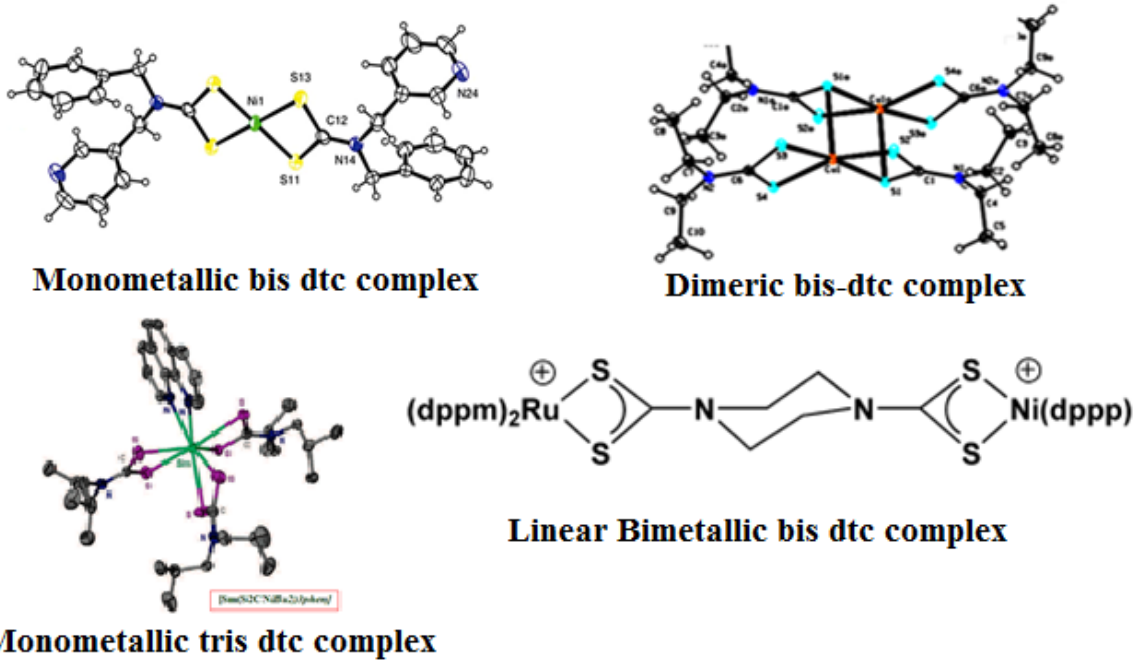


Figure 6. Monodentate and bidentate modes of dithiocarbamate and thioureide tautomers.

By thoughtful choice of the ligand and the metal ion, a wide variety of molecular structures can be derived as exemplified below in Figure 7:



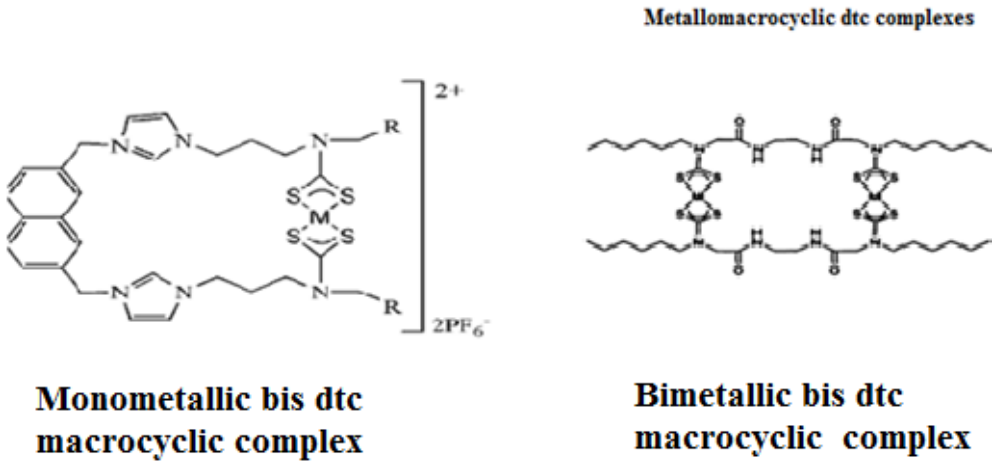


Figure 7. Diverse molecular structures obtained by metal-directed self-assembly of dithiocarbamates

The entropy gain leads to the adoption of chelate binding modes which is highly favoured thermodynamically. Large number of factors decide the possible coordination modes. For example in case of monodentate coordination mode, the steric and electronic environment of the metal-bound ligands play a major role in allowing the availability of the second sulphur coordination along with loss of a ligand which is extremely important for coordination with high activation barrier. Another important factor is the electronic demand of the bound metal centre. Unavailability of vacant orbital and the existing energy for accepting the lone pair on the second sulphur atom also contributes to a great extent. [68]

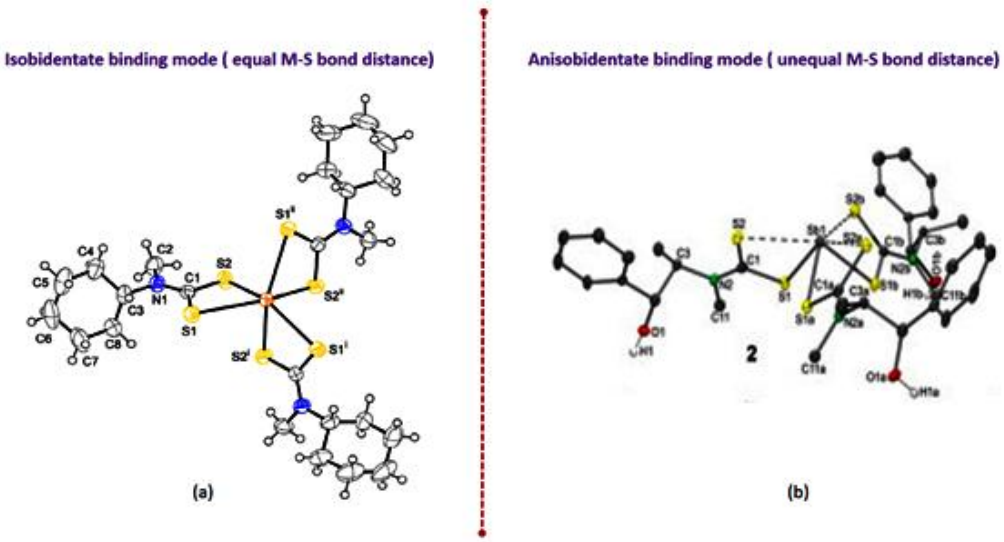


Figure. 8. Isobidentate and anisobidentate binding modes of dithiocarbamate

Based on the stereoelectronic requirements, dithocarbamate ligands exhibit numerous forms of denticity. It has been observed that dithocarbamate ligands show bidentate binding which can be isobidentate or anisobidentate in nature (Figure. 8).

1.1.3 Application of Dithiocarbamates

The coordination compounds of unsaturated sulphur donor chelating ligands, dithiocarbamates, and their related molecules have developed intense interest among chemists, biologists, physicists and theoreticians due to their remarkable chemical properties and vast array of applications.[87-90] Insights in the investigations of the molecular features and structural arrangements of these metal chelates reveals its applicability in diverse fields like medicine, [91] organic synthesis, [70] material science and biology. [92-94] They are successfully used as floatation agents, fungicides, [92] vulcanisation accelerators, [95] radiation protectors, [94] pesticides, [93] photostabilisers [96] of polymers and antioxidants.**[11]** The strong binding properties of DTCs with number of transition metal ions result in number of stable coloured complexes. This is beneficial in quantitative determination of various metal ions by spectroscopy. However its applicability in other procedures such as fluorimetry, gravimetry, neutron activation analysis (NAA), turbidimetry, chromatography and titrimetry are not extensively studied. [82] Dithiocarbamates with a robust chelating capacity toward inorganic species have widely been used in the agricultural industry [97-98] for more than 80 years now as successful pesticides and fungicides. [99] A few of widely used fungicides are Thiram, [100] Ziram. [99] combination of maneb and zineb gives Mancozeb [101] which is a non-systemic agricultural fungicide with multi-sites. (Figure. 9) DTCs have materialized as an as a significant pharmacophore and as an extremely important moiety in the field of medicinal chemistry. Several important biological properties have been discovered and have been assigned to popularly known DTC containing drug such as alcohol abuse drug (disulfiram), antileishmanial, anticancer, antimycobacterial, monoacylglycerol lipase inhibitor (MAGL and platelet aggregation inhibitor) [102]

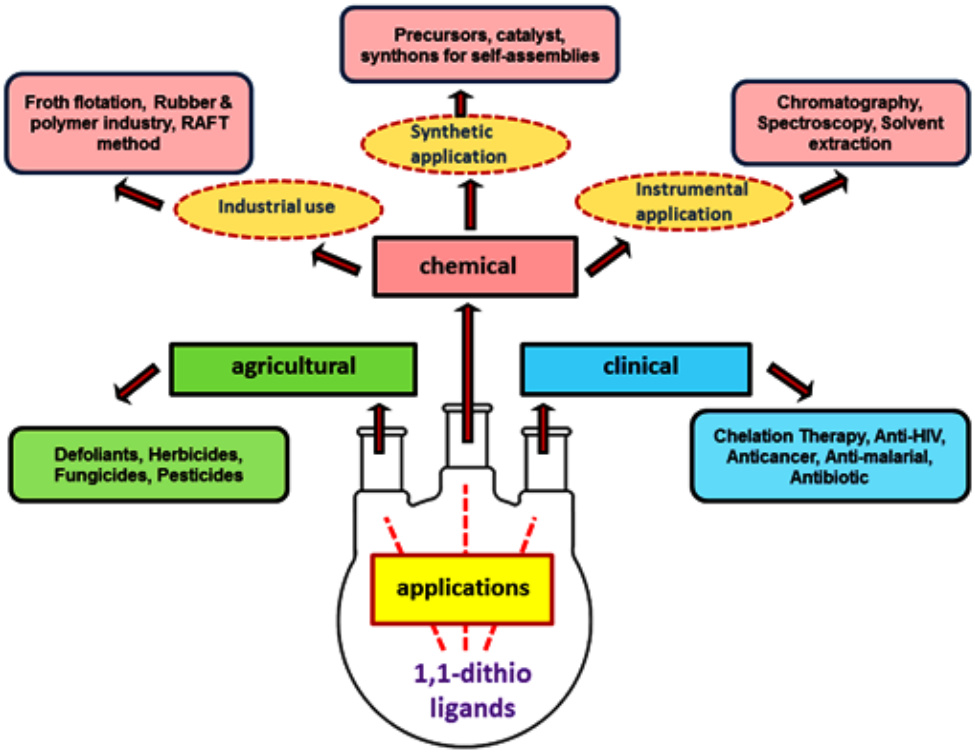


Figure. 9. Pictorial representation for a broad spectrum applicability of compounds complexes derived from 1,1-dithio ligands.

Moreover, A. R. Hendrickons and R. L. Martin *et. al.* have investigated the electrochemical responses of dithiocarbamates of Cu(I), Cu(II), Cu(III) and Co(III) metal ions.[103] Potassium ion recognition by a facile dithiocarbamate assembly of benzo-15-crown-5–gold nanoparticles has been highlighted only recently.[104] A facile one-pot preparation of cyanamide from dithiocarbamate using molecular iodine has been reported by Jayashree Nath *et al.*[105] Multiple nitrene insertions into the copper–sulfur bonds of dithiocarbamate ligands and synthesis and molecular structure of the tetraamido complex $[Cu\{\eta^2\text{-}RNSC(NMe_2)SNR\}_2]$ (R = $SO_2C_6H_4Me$-p) have been documented by Hogarth and his coworkers.[106] Professor Paul D. Beer and co-workers.[8, 17, 24, 35, 37-39] have reported a number of dinuclear dithiocarbamate macrocycles complexes and their utility as ditopic receptors for a variety of guest molecules (Figure 10) have been explored in recent past.

The flexibility of the architecture and exhaustive weak interactions present in macrocyclic self-assembly make the system sensitive to external perturbations, which add merit to their potential applicability in supramolecular chemistry, especially 'host-guest reactivity' study towards variety of guests species like cationic, anionic,

neutral guests and ion-pair recognition. In host-guest reactivity, host–guest binding stoichiometry (1 : 1 or 2 : 1) are predominantly dependent upon the size compatibility of the hosts-guests (Figure 10) and electronic aspects. For instance, due to the small macrocyclic cavity size, receptor only forms 2 : 1 host–guest complexes, whereas larger for macrocycles leads to 1 : 1 indicating the formation of intramolecular inclusion complexes. (Figure 10) However, if macrocyclic cavity is compatible ditopic hosts prefers formation of intramolecular inclusion complexes with ditopic guests. Such material can be used as purifier in ppm level and trapping wide variety of molecules apparently due to presence of cavity.

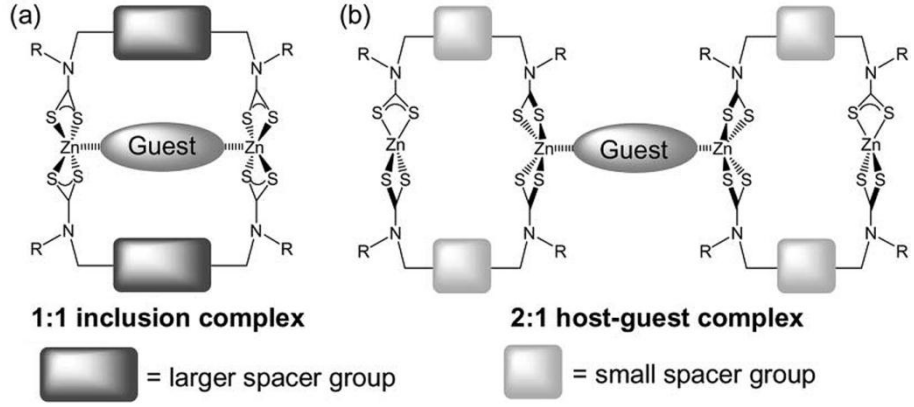


Figure 10: Host-guest complex formation in 1 : 1 or 2 : 1 ratio based on the size compatibility of the hosts-guest species.

Thus, dithiocarbamates are one of the most outstanding groups out of the many existing array of organic-inorganic chemical species.[107] A variety of DTCs have been discovered for their broad spectrum of pharmacological activities. Cao *et al.* [108] studied the antiproliferative activities of certain DTC containing compounds against certain human cancer cell lines like A549 (lung cancer), MCF-7 (breast adenocarcinoma), HeLa (cervical carcinoma), HT29 and HCT-116 (colorectal cancer). Extensive research has been done successfully to demonstrate its other biological outcomes (Figure. 11) such as an effective Antimycobacterial, [109] Anti-HIV, [110] Spermicidal agents. [111] It has been observed that the molecules containing sulfur atom plays a substantial role in biological processes and interacts proficiently with biomolecules.[112] Presence of 1, 1-dithio moieties in organic compounds display imperative biological effects, antioxidant activity, [113] and reticence of cardiac hypertrophy. [114]

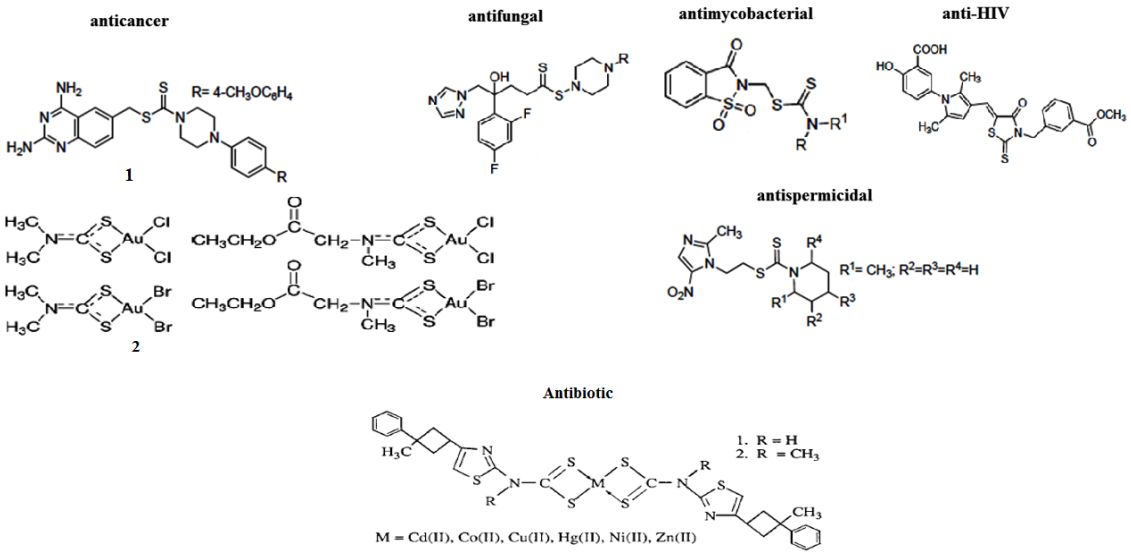


Figure. 11. Examples of dithiocarbamates depicting medicinal significance

In spite of all the foremost innovations in many areas of medicinal chemistry in the recent times especially in the intense development of antitumor drugs, the effective treatment of cancer remains a major challenge in the 21st century. Innovation of new agents having the capability to obstruct propagation of tumour cells selectively without causing toxicity is difficult, which perimeters the use of traditional cancer chemotherapy. For this, in order to synthesize effective drugs with desired properties medicinal inorganic chemistry offers additional opportunities through diverse coordination numbers, thermodynamic-kinetic characteristics, geometries, redox states, and intrinsic properties of the metal ion and ligand itself for large variety of reactivities to be exploited. [115-117] The modern methodologies focus on complexes with tumor targeting properties, thus maximizing the power on cancer cells and curtailing the incidence of adverse side-effects, and on complexes with biologically-active ligands [118-119] as briefly summarized in (Figure. 12) below.

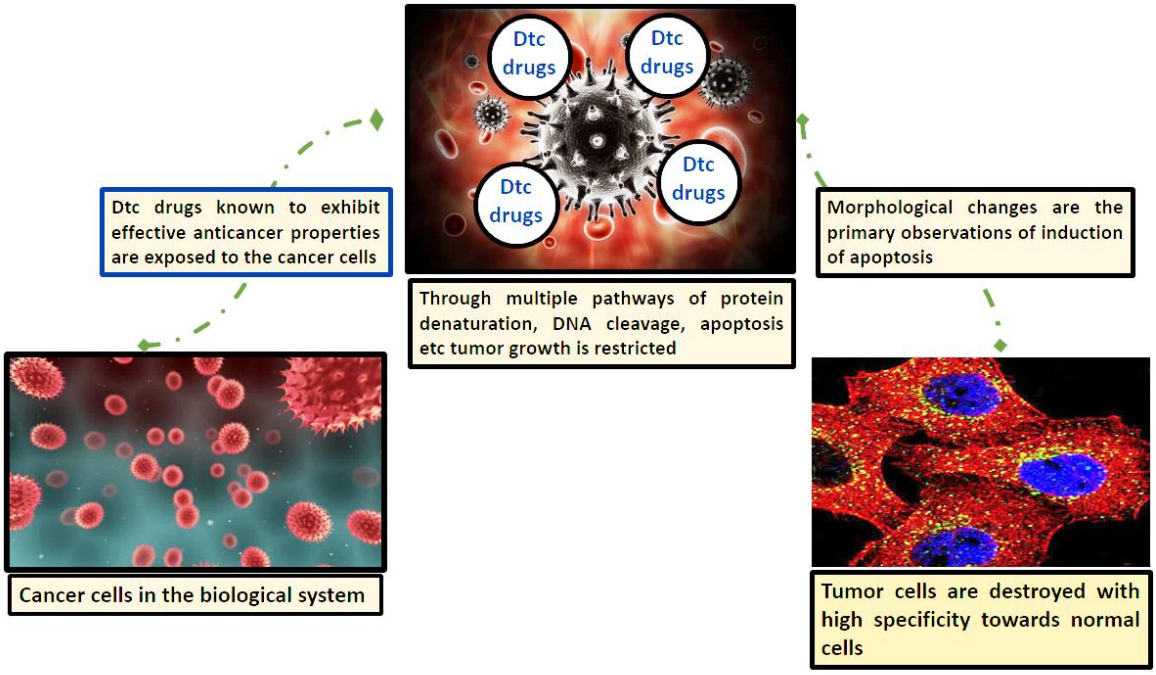


Figure. 12. Few of the changes occurring due to the interaction of the dithiocarbamate drugs with the biomolecules

Dithiocarbamates have the capacity to stabilize transition metals in a varied oxidation states. [120] The cytotoxicity of platinum based medications are curbed by the enzymeethiol complex formed by nucleophilic attack of sulphur atoms related to dithiocarbamate ligands which attacks and removes the platinum moiety. Dithiocarbamates have the potential to to safeguard the normal tissues without compromising the cytostatic activity of parent drugs.[121] In fact, the sulfur donor ligand plays a significant part in the transportation and introduction of the pharmacophore to the targets along with fortification of pharmacophore against untimely exchanges with biomolecules.[112] The successful use of dithiocarbamate as effective medication is illustrated by the wide use diethyldithiocarbamate anion for treatment of Wilson's disease, [122] and also for improved nephrotoxicity in platinum-based chemotherapy.[121] The skin cells responsible for melanin synthesis are called melanocytes. Melanoma is the cancer associated with these cells and are also known to be resistant to chemotherapic procedures. For this pDTC (pyrrolidine dithiocarbamate) are widely used as potential melanoma drugs. Based on the observation by Rosenberg on the inhibitory effect of cisplatin on the mitotic cell division in E-coli bacteria [123-124] cisplatin was approved as an effective anticancer drug for the

treatment of testicular and ovarian tumors. [125-126] Cisplatin, oxalylplatin, nedaplatin carboplatin and lobaplatin are presently used platinum based anticancer drugs. [127-128] Inspite of the success of platinum containing antitumor drugs its use is majorly hindered due to acquired cell resistance on prolonged administration and deadly side effects such as nausea liver and kidney failure along with bonemarrow toxicity. [129] Thus, the focus was shifted exclusively on the study of non-platinum metal-based agents which show varied target sites like proteins and enzymes other than just DNA damage (Figure. 13) in order to bring down the side effects significantly. [130]

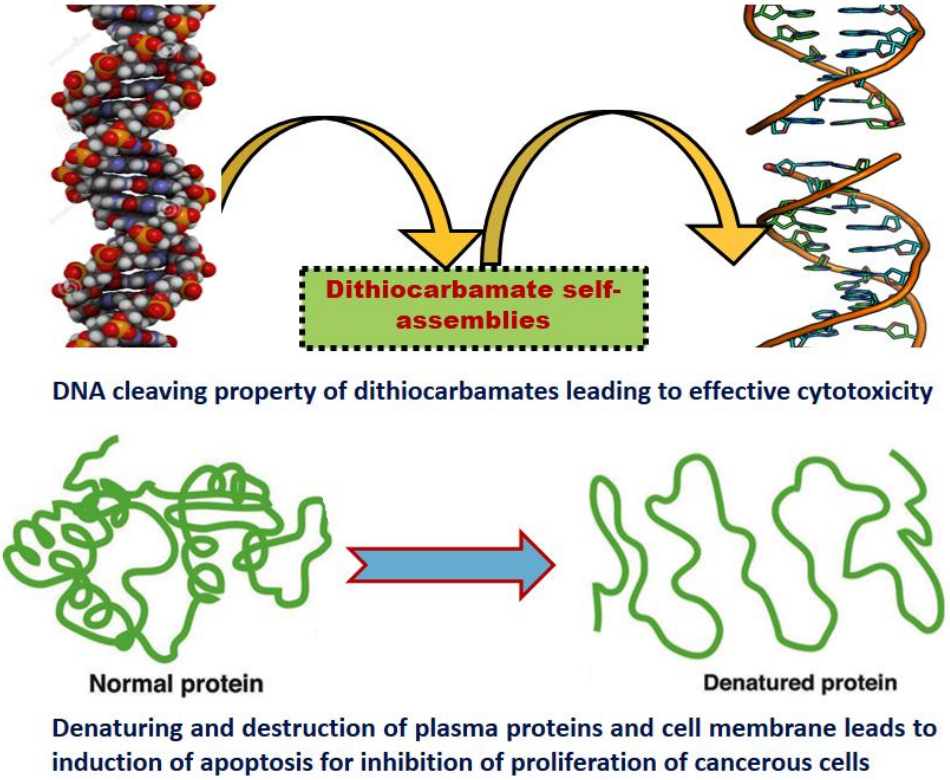


Figure. 13. Few of the changes occurring due to the interaction of the dithiocarbamate drugs with the biomolecules

Based on the interesting preclinical and clinical results of metal complexes of dithiocarbamate as antitumor drugs severe side-effects and resistance development in platinum-based cancer treatment [131] the focus on the research was directed towards the development of innovative metallodrugs with a pharmacological profile different from that of the clinically-established platinum medications. However of them, only gold [132-135] and copper dithiocarbamate complexes were studied over past few decades for their anti-cancer activity.[84,136-138] Gold(I) thiolates [139-142] are known to possess

anticancer properties which is supported by the work of Tiekink and co-workers on triorganophosphinogold-(I) dithiocarbamates of general formula [$(R_3P)Au(S_2CNR_2)$] as highly effective antitumor drug, [140-141] while other transition metal dithiocarbamate complexes were relatively underexplored. In the face of these valued characteristics and successful applicability of macrocyclic dithiocarbamate complexes in the field of supramolecular chemistry, chiefly in host guest reactivity study, [33-39] this structural class (binuclear M^{II}dithiocarbamate macrocyclic complexes) is startlingly not yet exploited in medicinal chemistry especially in effective anticancer therapy.

The positive outcomes of metal directed self-assembly can be applied for effective synthesis of macrocycles which otherwise are perceived to be difficult to synthesize. The major setbacks observed in syntheses of supramolecular structures like lack of appropriate sythons, low yields and major changes in the synthetic methodology in order to counterbalance the loss of entopy [143] makes the macrocyclization step extremely challenging. Hence it becomes inevitable to reconnoitre new facets of metal complexes in the direction of synthesis of macrocyclic scaffolds (organic and coordination complex), which otherwise are considered to be difficult to synthesize by standard conventional procedures.

1. 2 Objectives of the present work

Taking into consideration of all these features of metal directed self-assembly, versatile properties and the exceptional cytotoxic potentials of dithiocarbamate moiety, the entire focus of the work has been directed towards the development of number of metal-directed self-assembled macrocyclic structures using exclusively dithiocarbamate ligands. The objectives of the current study are briefly stated below.

- To design and synthesize novel organic secondary diamine precursors appropriate for the development of macrocyclic bimetallic bis-dithiocarbamate macrocyclic complexes.
- To synthesize bis-dithiocarbamate ligands *in situ* from secondary diamines and carbon disulphide in the presence of a base.
- To explore the possible reactivity of 1,1-dithio ligands (prepared *in situ*) towards transition metal ions as well as organometallic building blocks such as diphenyltin^{IV}- in the development of novel binuclear dithiocarbamate macrocyclic complexes.
- To characterize newly synthesized compounds by relevant spectroscopic techniques such as ESI-MS, IR, NMR, UV visible and thermogravimetric analysis.
- To execute DFT calculations to reinforce the experimental outcomes.
- To examine the impact of structural modifications upon the cytotoxic potentials of the newly synthesized compounds against human cancer cell lines *viz.* HEP G2 and C6 cell lines and their specificity for cancer cells over normal cell line WRL-68.

1.3 References

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