Medicinal Importance of Dithiocarbamate Complexes: Potential Agents in Management of Diabetes

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Abstracts
Recent studies in bioinorganic chemistry and drug design have revealed the role of transition metal complexes as therapeutic compounds and diagnostic agent in medicine. Dithiocarbamates are organosulphur ligands which have the ability to form stable complexes with transition metals, and this chelating ability has been utilized in numerous applications. Their application as anticancer, antimicrobial, medical imaging and anti-inflammatory agents have been reported. According to World Health Organization (WHO) about 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.5 million deaths are directly attributed to diabetes each year. Increasing resistance to available drugs and their associated side-effects have drawn wide attention towards designing alternative therapeutic strategies for control of hyperglycemia and oxidative stress The development of antidiabetic metal complexes replacing insulin injection to regulate sugar levels appears to be promising. The administration of vanadium and zinc in form of inorganic salt to control glucose level in the blood plasma have been achieved. This article reviews the applications of dithiocarbamate and its metal complexes as potential agent in the management of diabetes.
Keywords: *dithiocarbamate, complex, diabetes, medicine*

Introduction

Diabetes mellitus (DM) is an ailment in which the body does not deliver or notice the insulin (hormone) required for regulating glucose in blood or tissues. It is classified into two: insulin dependent and insulin non-dependent. (Shaheen *et al.*, 2016).The insulin-dependent type 1 DM is caused by destruction of insulin producing pancreatic cells. Noninsulin-dependent type 2 DM is associated with aging, obesity, stress, or other environmental factors which are treated by daily injections of insulin or several types of synthetic therapeutic substances respectively. Unfortunately, these methods of treatment have some defects. Injecting insulin several times in a day is painful and elevates the level of patient stress, especially in young people and moreover administration of synthetic therapeutic substances often exhibits some serious side effects (Sukarai, 2002)) in Maanvizhi *et al.*, (2014). Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of microvascular damage like retinopathy, nephropathy and neuropathy. It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications like heart disease, stroke and peripheral vascular disease and diminished quality of life (WHO, 2006). Numerous factors, such as genetics, environment, eating habits, physiological state, hormones and stress are considered to be associated with the development of diabetes mellitus (Sakurai, 2002).

Due to alarming increase in the number of people suffering from diabetes, chemists and pharmacists are continuously searching and synthesizing new potent therapeutics to treat the disease. The use of multiple pathophysiological factors in the treatment and management of disease demands the use of combination therapy in most of the cases. Therefore, there is an increasing need of improved anti-diabetic agents, targeting novel aspects of diabetes. The development of anti-diabetic metal complexes replacing insulin injection to regulate sugar levels appears to be promising. Dithiocarbamate complexes have attracted great interest due to their biological properties as anticancer (Adokoh, 2020 and Vila *et al*., 2022), anti-cocaine addiction (Mukherjee *et al*., 2001), antimalarial (Sofuoglu and Kosten, 2005), antifungal (Mansouri-Torshizi *et al*. 2011), anti-tuberclosis (Kartina *et al.*, 2019) anti-inflammation (Rojas *et al.*, 2002) and antidiabetic (Dugganaboyana *et al.*, 2023 and Mollazadeh *et al*., 2021).

Dithiocarbamate chemistry

Dithiocarbamates (DTC) are organosulphur ligands that possess two sulphur atoms

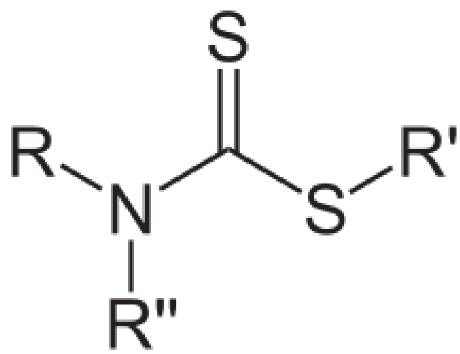


Figure 1: dithiocarbamate

that often act as the binding sites for metal coordination in a monodentate, bidentate, or anisodentate fashion.

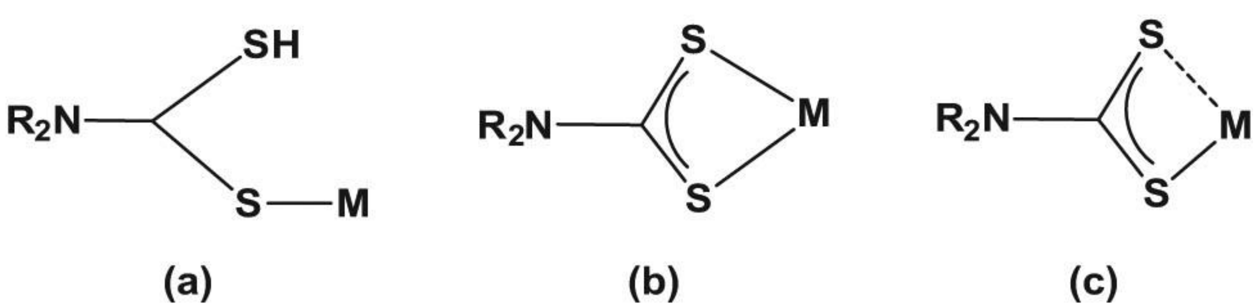


Figure 2: Different coordination modes of dihtiocarbamate complexe (a) monodentate, (b) bidentate and (c) anisobidentate modes

They are versatile group of ligands with a wide range of applications and useful chemical properties, such as the ability to stabilize different oxidation states of metals and coordination geometries (Javed *et al*., 2016).These different coordination modes enhance the possibility for complex formation and make them useful in different areas especially in biomedical fields. Dithiocarbamates can form complexes with octahedral, square planar or tetrahedral geometry depending on the type of metal ion and also the ratio of the metal-to-ligand (Ajiboye *et al.*, 2022). The ability of DTC to coordinate to metals by providing electrons and stabilizing the complex makes it a favorable candidate. The presence of donor atoms (sulphur) in DTC makes them possess good antimicrobial properties. As a result of the presence of two sulfur atoms within its molecule, that are available for complexation, dithiocarbamate ligands show strong metal binding capacity; and this has proven to be useful in enzyme inhibition that ultimately affects biological systems. The ability of sulphur atoms to reduce the polarity of the binding metal through delocalization of electrons over the entire chelate ring enables them to form stable compounds (Adeyemi and Onwudiwe, 2020). Dithiocarbamates compounds and its metal complexes have the aptitude of modulating key proteins involved in biological processes such as apoptosis, transcription, oxidative stress and degradation (Buac *et al.*, 2012). Dithiocarbamate compounds have received increasing attention in the last few decades due to the ease of preparation, ability to stabilize different metals in the periodic table (even at a varying oxidation states), and adopting a wide range of structural geometry upon coordination to a metal (Al-Obaidy *et al*., 2020)

Dithiocarbamates are compounds formed from the reaction of either a primary or secondary amines with cold carbon(IV) sulfide in basic media or alcoholic solution. The basic medium can either be a weak base (ammonia solution) or strong bases (sodium hydroxide and potassium hydroxide). Bases are incorporated to conserve the amines (Odularu and Ajibade, 2019). The chemistry and the biological activity of metal dithiocarbamate complexes are the con- sequence of both the individual properties of the central metal and dithiocarbamate ligand (Saiyed, Adeyemi, and Onwudiwe, 2021)

$$\mathbf{RNH_2 + CS_2 + XOH \rightarrow RHNCS_2X + H_2O}$$

$$\mathbf{R_2NH + CS_2 + XOH \rightarrow R_2NCS_2X + H_2O}$$

Where X = $NH4^+$, Na or K

Application of dithiocarbamate in medicine

With the discovery of platinum metallodrug: cisplatin in 1978 as antitumor drug that was approved clinically, effort to investigate and develop more metallodrugs as anticancer, antidiabetes, anti-inflammatory, antimalarial and antimicrobial continues tremendously. Many compounds have been prepared based on well-conceived ideas of improving their efficacy and have been subsequently screened with many successfully passing clinical trials. The effort is focused on achieving more specific, selective and bioavailable drugs than cisplatin that has many side effects such as weakening of bone marrow and tumor resistance.

Dithiocarbamates (DTCs) compounds and its metal complexes have the aptitude of modulating key proteins involved in biological processes such as apoptosis, transcription, oxidative stress and degradation (Buac *et al.*, 2012). Dithiocarbamate have found wide applications in the field of medicine. It has been revealed that dithiocarbamate linked to biologically active heterocycles have exhibited diverse pharmacological profiles including anticancer, antibacterial, antifungal, antitubercular, anti-Alzheimer activities and many more (Dattatray, Sakla and Shankaraiah 2020).These derivatives exert their action through targeting various enzymes. Recent studies have shown application of DTC as anticancer and in treatment of HIV, anti-inflammatory, for medical imaging. The medical application could be attributed to their ability to form metal chelate and high reactivity of DTC anion to other moieties such as thiols (Ajiboye *et al.,* 2022). Javed *et al*., (2016) synthesized some tin-dithiocarbamate complexes which show significant activity against various bacterial and fungal strains. The synthesized complexes were also found to be effective antioxidants. All the complexes have been assayed for antileishmanial activity *in vitro* and found some promising results. Thalidomide dithiocarbamate was evaluated for wound healing to confirm its usage as the anti-angiogenic agent (El-Aarag *et al*., 2014). Dithiocarbamate ligands and complexes have also been studied for magnetic resonance imaging and other radiopharmaceutical imaging (Berry *et al.,* 2012). Gold nanoparticles functionalized with biomimetic amino acid dithiocarbamate were used as nanoprobe for cell imaging as a result of their negligible toxicity to human cells (Adokoh, 2020). Dithiocarbamate have also been investigated for antiparasitic property against protozoans such as *t. cruzi*. Enhanced activity was observed when compared to a standard drug (benznidazole drug). The antiparasitic activity of dithiocarbamate is probably attributed to their ability to chelate metals (Winum and Supuran, 2015)

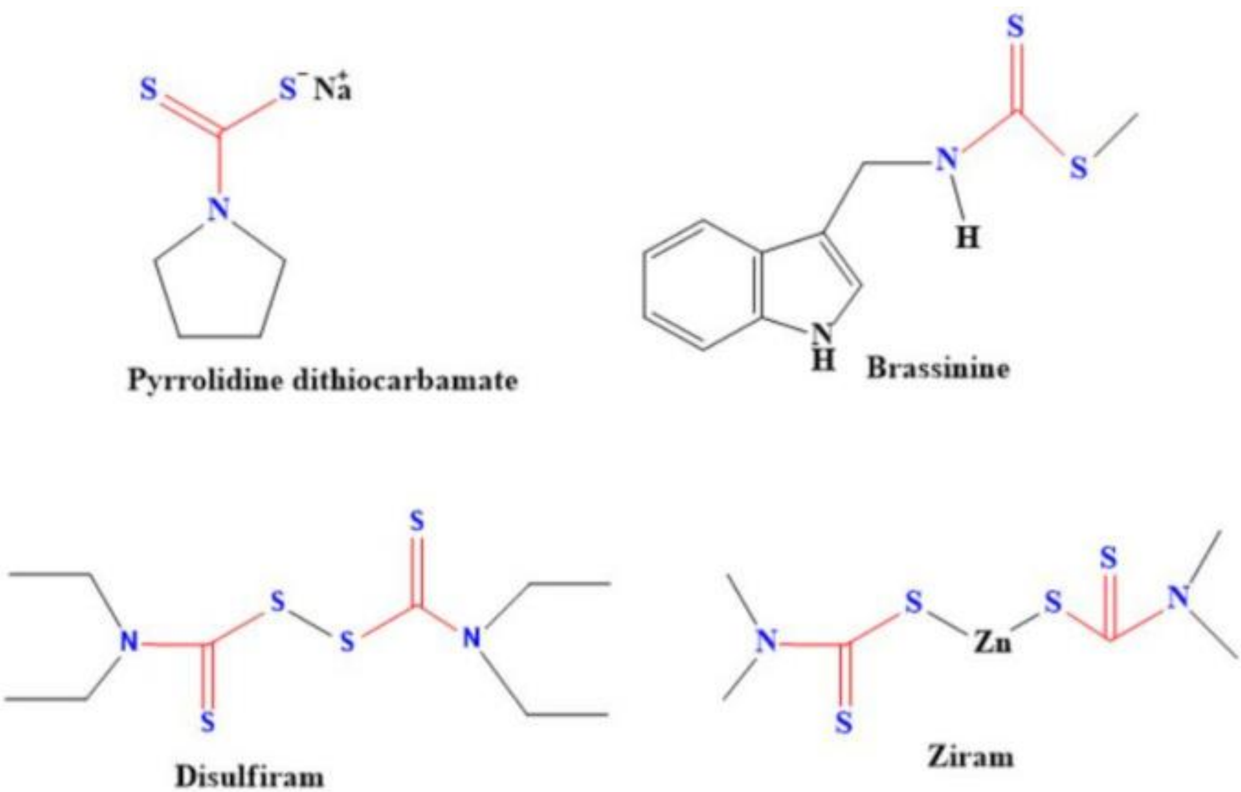
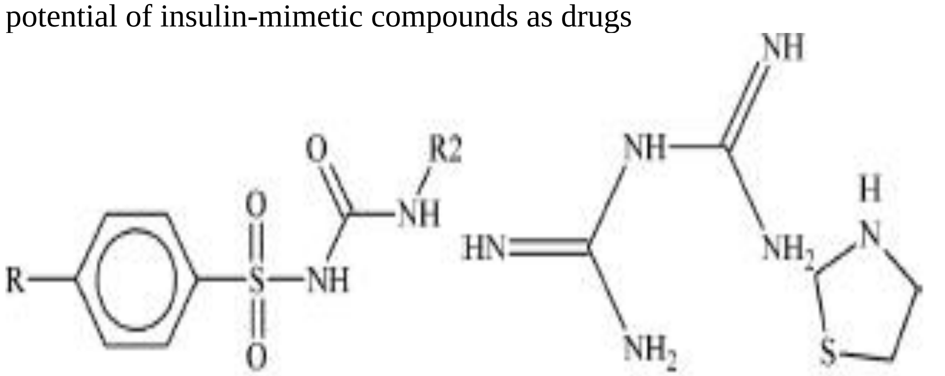


Figure 3: Representative of dithiocarbamates used in medicine

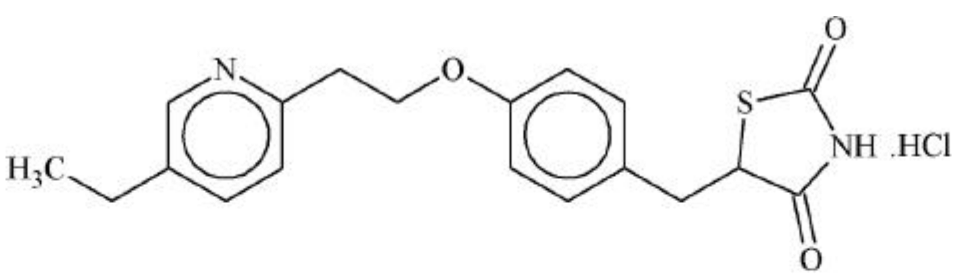
Source: Ajiboye, *et al*., 2022

Antidiabetic properties of dithiocarbamate

According to Elahabaadi *et al*., (2021) and Mollazadeh *et al*., (2021) a hydrolyzing enzyme (α-Glucosidase), which is important in the breaking down of starch and carbohydrate to glucose, is usually a target enzyme in the treatment of diabetes mellitus . Among the compounds that have been used for the inhibition of this enzyme, coumarin-dithiocarbamate scaffold has proven to be very effective and this has made it a useful compound in the treatment of type 2 diabetes. Control of the glucose level in the blood plasma has also been achieved by administration of vanadium and zinc in form of inorganic salts. Vanadium complexes with organic ligands have proved to be less toxic, with improved solubility and lipophilicity. There are a number of vanadium complexes that have been developed, all of which have insulin-mimetic properties (Badmaey *et al*., 1999) in Rafique *et al*., (2010). The discovery of the insulin-like properties of vanadate ions led to research into the clinical use of vanadium compounds as insulin mimics (Thompson *et al*. 1999). The potential of insulin-mimetic compounds as drugs



Sulphonylureas (1) Biguanides (2) Thiazolidenes (3)



Pioglitazone **(4)**

Figure 4: Hyperglycemic drugs for treatment of diabetes

lies in their oral administration. Insulin, as a small protein, is not orally active. The vanadate (V) ion is effective upon oral administration, and an obvious strategy to enhance the pharmacokinetic characteristics and the efficacy of the insulin-mimetic response is complexation of vanadate with suitable biologically compatible ligands (Thompson *et al*. 1999 and Orvig *et al*. 1999). Insulin binding to the extracellular side of cell membranes initiates series of phosphorylation/dephosphorylation steps. A postulated mechanism for vanadium is substitution of vanadate for phosphate in the transition state structure of protein tyrosine phosphatases (PTP) (Huyer *et al*. 1997 and Elberg *et a*l. 1997) In normal physiological conditions, the attainable oxidation states of vanadium are V(III), V(IV) and V(V). Relevant species in solution are vanadate, (a mixture of $HVO_4^{2-}/H_2VO_4^-$) and vanadyl VO^{2+}. Vanadyl is not a strong inhibitor of PTPs, suggesting other potential mechanisms for insulin mimesis for this cation. Both V(IV) and V(V) coordination compounds have been tested as insulin mimics.

Yoshikawa *et al*., (2006) also reported the synthesis and evaluation of orally active Zn(II) complexes that can treat diabetes mellitus (DM) at low doses. Zn(II)-dithiocarbamate complexes with Zn(II)-sulfur coordination bonds were prepared and their *in vitro* insulinomimetic activity and *in vivo* anti-diabetic ability were evaluated. Zn(II)-dithiocarbamate complexes: bis(pyrrolidine-N-dithiocarbamate)zinc(II) (Zn(pdc)(2)) complex was found to be effective in terms of inhibiting free fatty acid-release and enhancing glucose-uptake in adipocytes. After oral administration of the complex to mice with obesity and type 2 DM, it was observed that the high blood glucose levels in the mice were lowered from approximately 500 mg/dL to 350 mg/dL within 6 days. *In vitro* and *in cellulo* antidiabetic activity of Au(I)and Au(III) Isothiourea complexes were reported by Fayyaz *et al*.,(2021). These complexes showed a good to moderate inhibition of dipeptidyl peptidase-IV (DPP-IV) when compared to standard inhibitor sitagliptin. Gold and silver nanoparticles were assessed for their antidiabetic activity in streptozotocin-induced diabetic rats. Results revealed that diabetic rats treated with Au nanoparticles or Ag nanoparticles restored normal glucose level. Specifically, Ag nanoparticle was found to significantly induce a reduction in blood glucose and restore both the high serum insulin level and glucokinase activity (Shaheen *et al*.,2016).

Conclusion

With increasing number of people living with diabetes globally there is need to develop more antidiabetic drugs that are more effective than insulin with less side effects, This article attempted to review the role of dithiocarbamate and dithiocarbamate metal complexes in medicine and specifically in diabetes management. The structure and mode of coordination of dithiocarbamate that have antidiabetic property with metals reported by some researchers have also been discussed. Some DTCs complexes were reported to exhibit insulin mimetic activity out of these a wide class of vanadium, copper, silver, gold and zinc complexes were found to be effective for treating diabetes in experimental animals. Since metallotherapy overcome the problems of painful insulin injection and side effects for type 1 or type 2 DM; the encouraging results of preclinical and clinical studies with dithiocarbamates form the basis for further investigations towards the development of metallodrugs for better healthcare.

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