



ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2019; 5(7): 522-524
www.allresearchjournal.com
Received: 11-05-2019
Accepted: 16-06-2019

Dr. Anju Kumari
Ex. Research Scholar,
Chemistry, B.N. Mandal
Univeristy, Madhepura, Bihar,
India

Metallotherapeutic drugs in current prospects

Dr. Anju Kumari

Abstract

After therapeutic success of anti-cancer drugs metalodrugs have also shown positive results towards the treatment of other diseases also. Many deseases like diabetes, alcer, rheumatoid arthritis, inflammatory and cardiovascular diseases etc. are treated or cured with the help of metal traces. The enzymes of our body and many drugs of organic nature require traces of metal ion for proper functioning. Therapeutic treatment and care of a patient for the purpose of both preventing and combating diseases or alleviating pain or injury. This has lead to treat patient in current and in future by using metal based drugs by making chelates to work with body enzymes, biomolecules and lipophilicity, cell membrane functions cell cycle etc.

Keywords: Pharmacological, ailments chelates, receptors.

Introduction

Metals can play an important role in pharmacological properties of known drugs after co-ordinating to metal with different physical and pharmacological properties. By allowing these drugs to release in controlled fashion or specific location. If it is failed to do so it may lead to complexation of non-steroidal anti-inflammatory drugs to copper overcomes some of the gastric side effects of these drugs. The metal based drugs are also being used for the treatment of a variety of ailments viz. diabetes, rheumatoid arthritis, inflammatory and cardiovascular diseases as well as diagnostic agents (2-4). In medicinal chemistry, metal complexes have received limited attention as compared to organic compounds. Our health, aging physiological disorders and diseases are related to the state of the metal ions and their complexes with biomolecules in the body. Traces of some metals i.e. Fe, Cu, Zn Ni, Mn are essential for the biological processes as about 30-40% of all known proteins require metal confectors (Fe,Cu, Zn Ni, Mn etc.) for their proper folding into an active three dimensional (3D) structure (5-6). The amount of metals present in the human body is approximately 0.03% of the body weight. Chelation causes drastic changes in biological properties of ligands as well as metal moiety and in many cases it causes synergistic effect of metal ion and ligand both (7-8). Various mechanisms have been proposed for the action of metals in chelates including enzymes, interaction with intracellular biomolecules, enhanced lipophilicity, alteration of cell membrane functions and arrest of cell cycle etc.

The importance of metal complexes as imaging agents for various diseases have been recognised. Metal centres being positively charged, favourably bind to negatively charged biomolecules i.e. Protiens, nucleic acids etc for understanding of more specific biological processes including the formation of thrombi and imaging of infection etc.

A wide variety of co-ordination spheres, oxidation states and redox potentials of co-ordination and organometallic complexes give kinetic and thermodynamic properties of complexes towards biological receptors. The recent developments in the field of anticancer metallopharmaceuticals are reviewed recently. (9) Current review includes present and future potential of metal based drugs showed promising results in the treatment of diseases such as diabetes, ulcer, microbial infection, mania, hypertention etc.

Metal Compounds as anti-disease agents

Many metal complexes have been synthesized and evaluated to overcome the problems of painful insulin injection and side effects for type-1/type-2 diabetes mellitus (DM). The insulin like effect of Vanadium salts on cells (10-11) and diabetic animals (12-14) has stimulated research into the clinical use of vanadium compounds as insluin mimetics.

Correspondence
Dr. Anju Kumari
Ex. Research Scholar,
Chemistry, B.N. Mandal
Univeristy, Madhepura, Bihar,
India

Vanadium, an essential trace element is present in almost all mammalian tissues and binding with intracellular phosphate, glutathione and ascorbate(15). Under physiological conditions vanadium exists in three oxidation states of V^{III} , V^{IV} and V^V .

Vanadium complex, bis (pyridine-2-carboxylato) Oxovanadium (IV) $[VO (Pic)_2]$ has shown higher insulin mimetic activity than $VOSO_4$ (16). Despite promising antidiabetic properties, Vanadium compounds have been associated with several toxic effects including diarrhoea, dehydration, hepatotoxicity, nephrotoxicity, teratogenicity and reproductive dysfunctions. Hence it is required to focus on the improvement of therapeutic potential and to reduce the side effects of Vanadium compounds.

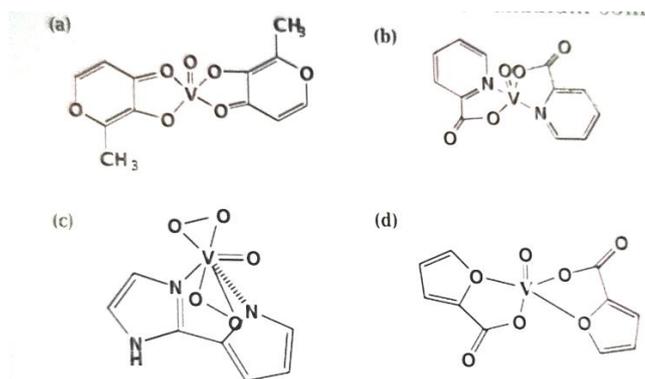


Fig 1: Structures of insulin mimetic vanadium complexes: (A) BMOV (b) VO (pic)₂ (c) $[OV(O)_2 \{2-(2'-Py) -Imi\}]^-$ Vanadium (IV) and (D) Bis(α -Furancarboxylato) Oxovanadium (IV).

As an anti-inflammatory agent copper is used from a long time. The copper bracelets have been used as a folk remedy for the treatment of arthritis. Anti-arthritis properties of cu-complexes such as cupralene and dicuprene had been evaluated in 1940s. Many cu-complexes of anti-inflammatory drugs (Fig-2) have been found more active in animal models than either their parent cu (II) salt or NSAID. Cu (II) complex of salicylate has been found about complex of salicylate has been found about 30 times more effective than aspirin as an anti-inflammatory agent. In addition, Cu (II) complexes of many non-anti-inflammatory agents exhibited anti-inflammatory action. Here the inherent physico-chemical properties of the complex itself is more responsible for pharmacological activity rather than that of its constituents in these complexes. It was suggested that salicylates may deliver copper (Cu) to target cell in the body. SOD activity, redox potential lipophilicity and stability constants may be useful parameters in evaluating the biological activity of these Cu compounds. The possible modes of anti-inflammatory action of the Cu complexes may include inhibition of SOD activity. The role of Cu-complexes in free radicals scavenging and the activation of lysyl oxidases (Collagen cross-linking enzymes) are also proposed modes of action. The structure and stability of the Cu-NSAID complexes have been shown to be a critical determinant of their activity and toxicity for example, the anti-tumor activity of the monomeric Cu(II) complex of aspirin $[Cu(Asp)_2(Py)_2]$ is reportedly more effective than the dimeric $(Cu_2(Asp)_4)$ complex.

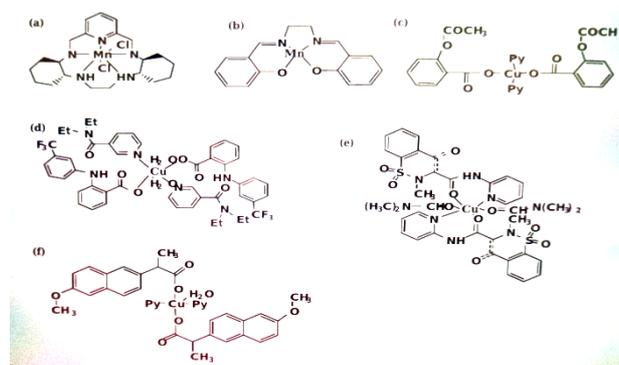


Fig 2: Structures of some anti-inflammatory manganese and copper complexes: (a) & (b) Manganese compounds as SOD mimitits (c) Cu (II) Complex of aspirin $[Cu(Asp)_2 (Py)_2]$ (d) Cu (II) Complex of flufenamate (e) Cu (II) Complex of Piroxicam and (f) Cu (II) Complex of Meproxen $[Cu (Nap)_2 Pyridine]_2$.

Metal compounds are also used as antimicrobial compounds. Silver and mercury salts have a long history of use as antibacterial agents. The antifungal effect of copper ions has been known for many years. Copper (II) and silver (I) complexes of 2-pyridyl-1H-benzimidazoles have shown considerable antimicrobial activity. Bismuth compounds also show antibacterial activity. Zinc glutamate (Fig. 3e) has shown antiviral activity and used to treat common cold.

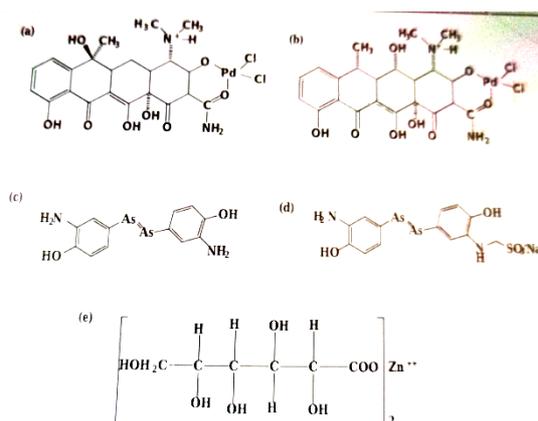


Fig 3: Structures of some promising antibacterial, antiparasitic and antiviral agents: (a) Pd(II) complex of tetracycline (b) Pd(II) complex of doxycycline (c) Salversasne (d) Neosalversane and (e) Zinc gluconate.

Metal complexes of gold (Au), Platinum (Pt), Iridium (Ir), Pd, Rh etc. are also used as an antiparasitic agents. Anti ulcer agents are Bismuth compounds commonly used for treating gastro intestinal disorders because of their antacid and astringent properties. The combination of ranitidine (a histamine H_2 -receptor antagonist) and bismuth citrate is marketed as Ranitidine Bismutrex for the management of peptic ulcer and ulcers associated with *H. pylori* (17).

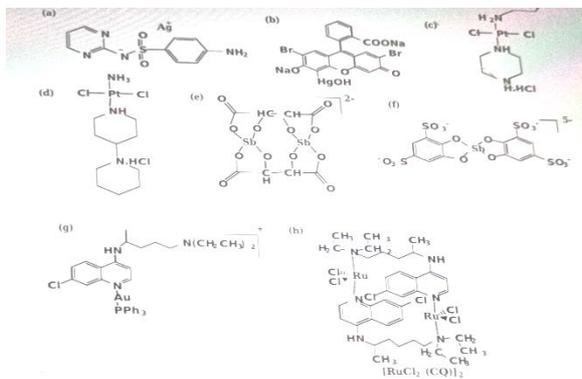


Fig 4: Structures of some antibacterials and antiparasitic agents (a) Silver sulfadiazine (b) Mercurochrome (c) trans-[PtCl₂(NBA)(pz)] (d) trans-[PtCl₂(NH₃)(4-Pippip)] (e) & (f) Antimony-based antiparasitic agents (g) Gold-based antiparasitic agent and (h) Ruthenium-based antiparasitic agent. [RuCl₂(CQ)]₂.

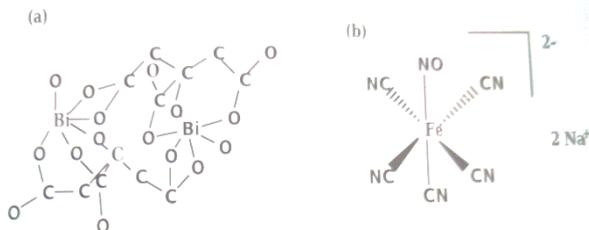


Fig 5: Structures of some bismuth and Iron complexes: (a) Bismuth citrate dimer (b) Sodium nitroprusside.

Bismuth therapy is associated with several side effects including neurological dysfunction and reproductive dysfunction due to lower serum testosterone levels and its toxicity is reversible over several weeks or months when Bismuth intake is stopped (18).

Conclusion and Perspectives

An overview of the metal based drugs with promising results or used in the treatment of diabetes, inflammation, infection, hypertension, ulcer etc. has been presented. For the discovery and development of chemo-therapeutic agents, metal and metal based drugs can be exploited. The encouraging results of pre-clinical and clinical studies with metal compounds form the basis for further investigations towards the development of metallo drugs for better healthcare. Understanding of mechanism of action cellular target and the properly designed metal compounds will increase the selectivity and the specificity of new metal compounds. It is clear that metal compounds after new properties that cannot be found amongst purely organic agents. The area of research and continued work for the therapeutic application of metal complexes is still an unexplored area. A wide variety of co-ordination spheres, ligands design, oxidation states and redox potential, co-ordination and organometallic complexes can systematically alter the kinetic and thermodynamic properties of the complexes towards biological receptors. Thus there is a wide range of opportunities for the design of novel agents for the treatment of a variety of diseases and conditions.

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