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RESEARCH ARTICLE

MACROCYCLIC COMPLEXES: A NEW WAY FORWARD INTO THE MEDICINAL WORLD.

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Abstract

The unique fundamental physicochemical properties of macrocyclic complexes have attracted researchers to conduct extensive research to discover novel molecules that could be useful for developing alternative medicines for the treatment of several diseases including cancer. The current advances in the field of macrocyclic chemistry, especially, having the ability to prepare metallomacrocycles have enabled human beings to invent new techniques for the preparation of antimicrobial and anti-tumor agents. This article throws light on application of macrocyclic complexes in the field of medicinal chemistry.

Introduction:-

Over the past several years, the prevalence of biologically active macrocyclesin medicinal chemistry literature has been increasing. Many scientists have discussed the role that macrocycles can play in medicinal chemistry, in particular looking beyond the established importance of natural product macrocycles in drug discovery (Oyelere, 2010). The use of drug–like macrocycles is emerging as an exciting area of medicinal chemistry, with several recent examples highlighting the favorable changes in biological and physicochemical properties that macrocyclization can afford. Although the structural complexity and synthetic intractability limit their pharmaceutical application, macrocycles have broad applications in drug discovery and development; and numerous natural macrocyclic compounds present exceptional therapeutic potential and unrivalled biological activities (Driggers*et al.*, 2008). Natural product macrocycles and their synthetic derivatives have long been clinically useful and attention is now being focused on the wider use of macrocyclic scaffolds in medicinal chemistry (Fig 1) in the search for new drugs for increasingly challenging targets (Mallinson*et al.*, 2012). Historically, macrocyclic molecules represent a successfully documented drug class in the clinic. It has been argued that macrocyclic structures are underexploited in drug discovery, and presented different classes of natural product macrocycles and their applications to highlight the suitability of the structural class for further development (Driggers*et al.*, 2008). Medicinal inorganic chemistry offers additional opportunities for the design of therapeutic agents not accessible to organic compounds. The wide range of coordination numbers and geometries, available redox states, thermodynamic and kinetic characteristics, and intrinsic properties of the cationic metal ion and ligand itself offer the medicinal chemist a large variety of reactivity's to be exploited (Santini*et al.*, 2014).

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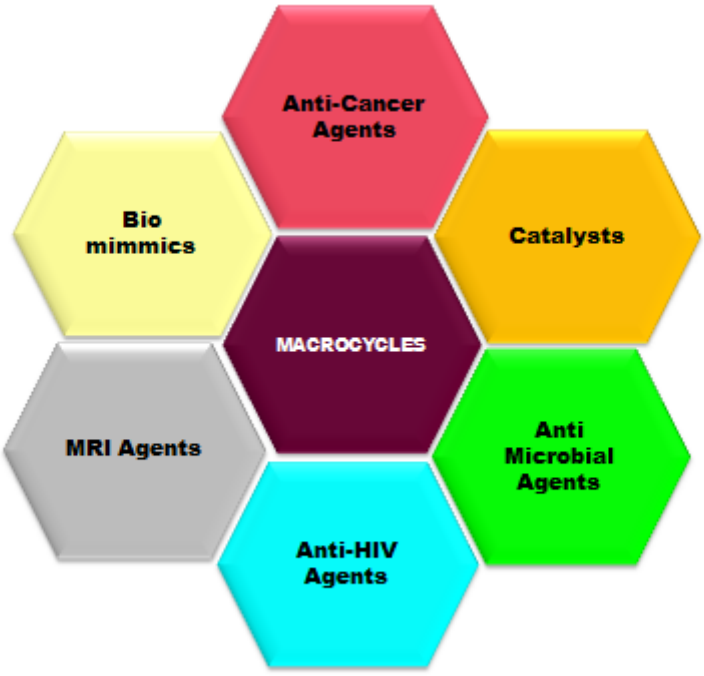


Fig. 1:- Applications of macrocyclic complexes.

Chemistry of macrocycles and their metal complexes has attracted much attention and has become a growing class of research (Mandal*et al*., 2014), largely as a result of their remarkable applications in biology, supramolecular chemistry and new materials (Raman *et al*., 2014), etc. To some extent the interest in macrocyclic complexes especially those with polydentate ligands stems from the chemical properties that the macrocyclic ligands bring to the complexes as well as the variety of geometrical forms available and the possible encapsulation of the metal ion (Ferraudi*et al*., 2005), Rings of sufficient size may envelop guests within their internal cavities, and thereby enhance interaction selectivity. This strategy is exemplified by some of the simplest biomolecules showing the capacity for molecular recognition; and its application towards the development of synthetic receptors represents a rich field of research (Liu *et al*., 2013). The design and study of synchronized metal containing macrocycles is an interesting field of chemistry (Chandra *et al*., 2007). The macrocyclic ligands are highly significant in bioinorganic chemistry, catalysis, extraction of metal ions from solution and many more (Salih*et al*., 2007). Macrocyclic when complexes with transition metal ions show some interesting properties and biological functions, such as being models for metalloproteins and oxygen carrier systems (Kumar *et al*., 2006). Structural factors such as ligand rigidity, the type of donor atoms and their disposition have been shown to play significant roles in determining the binding features of macrocyclic ligands toward metal ions (Chandra *et al*., 2010). Macrocyclic ligands containing a heteroatom are important complexing agents for cations, anions and molecules (Ganbari*et al*., 2016). Cyclic and macrocyclic complexes of transition metals are of interest because of their use as diagnostic agents in magnetic resonance imaging and their resemblance to natural systems (Ilhan*et al*., 2014). The macrocyclic Schiff bases have been widely studied due to their selective chelation to certain metal ions depending on the number, type and position of their donor atoms, the ionic radius of metal ion and coordinating properties of counterions (Hernandez-Moling*et al*., 2004). Macrocyclic complexes are of great importance due to their resemblance to many naturally occurring macrocycles, such as porphyrins and cobalamines. A number of nitrogen donor macrocyclic derivatives have long been used in analytical, industrial and medical applications (Hariprasath*et al*., 2010). Macrocyclic metal chelating agents are useful for detecting tumor lesions (Kosmos*et al*., 1992).

Transition metal macrocyclic complexes have received much attention as an active part of metalloenzymes as biomimic model compounds (Chandra *et al*., 2004) due to its resemblance with natural proteins like hemerythrin and enzymes. The chemistry of macrocyclic complexes is also important due to their use as dyes and pigments (Seto*et al*., 1996). This remarkable growth is due to the synthesis of a large number and variety of synthetic macrocycles, which behave as coordinating agents for metal ions (Thompson *et al*., 1962). Template reactions have been widely

used as the synthetic routes for macrocyclic complexes (Veber*et al*., 1981). Nitrogen containing macrocycles have a strong tendency to form stable complexes with transition metals and received a great attention because of their biological activities, including antiviral, anticarcinogenic as well as antifertile (Chandra *et al*., 2008).

Macrocycles are ideal in efforts to tackle "difficult" targets, but our understanding of what makes them cell permeable and orally bioavailable is limited. Analysis of approximately hundred macrocyclic drugs and clinical candidates revealed that macrocycles are predominantly used for infectious disease and in oncology and that most belong to the macrolide or cyclic peptide class. A significant number of these macrocycles are administered orally, revealing that oral bioavailability can be obtained at molecular weights up to and above 1 kDa and polar surface areas ranging toward 250 $Å^2$.However, the number of oral macrocycles is still low and it remains to be seen if they are outliers or if macrocycles will open up novel oral druggable space (Giordanetto*et al*., 2014).A significant number of macrocyclic drugs are currently on the market, predominantly of natural product origin with complex structures. Concerns that synthetic tractability will limit opportunities for lead optimization and increase costs for scale up are reasons why the pharmaceutical industry has been cautious about development of macrocyclic drugs.However, significant progress has recently been made that has increased the synthetic tractability of macrocycles (Terrett, 2010).

Applications of Macrocyclic Complexes:-

Applications of the transition metal macrocyclic complexes (TMMC) can be divided in to several sections such as antibacterial drugs, catalysts, MRI scanning agents, antioxidants, ion transporters, radiopharmaceuticals etc, according to the way they use.

Catalytic Activity:-

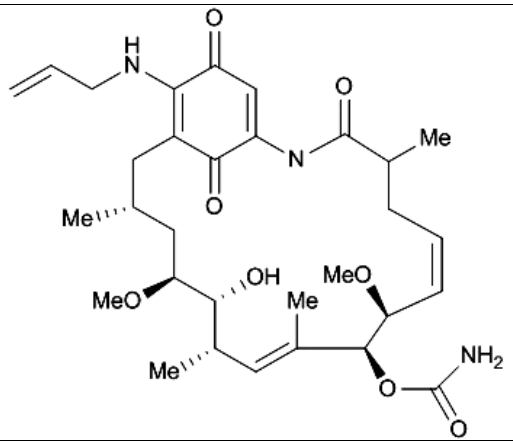
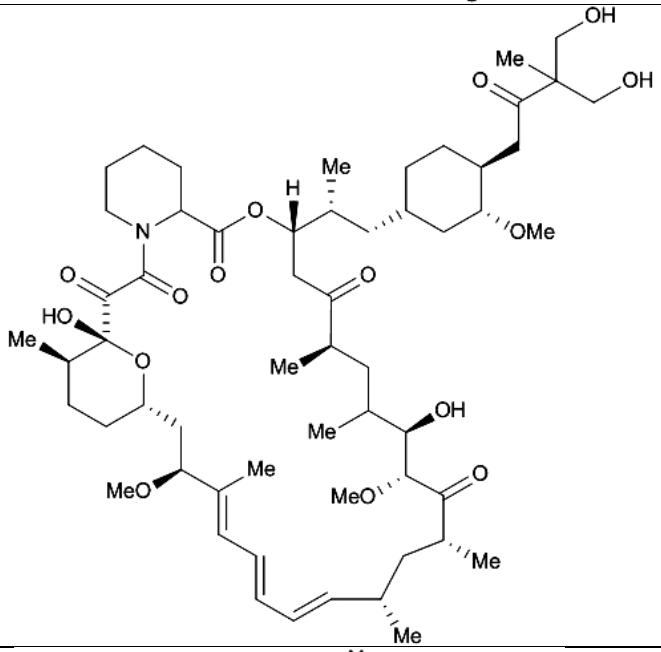
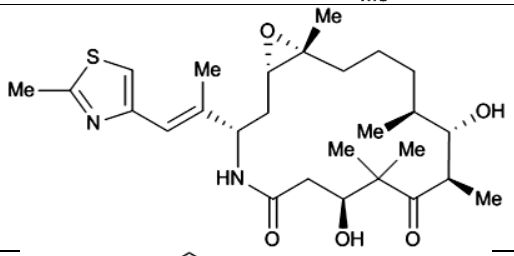
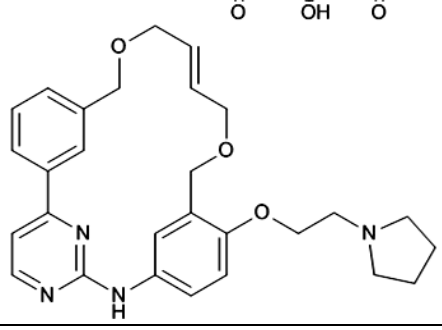
Among these applications catalytic activity of these macrocyclic complexes has a major contribution to the green chemistry. Most of the TMMC are synthesized to act as the catalyst for various reasons, due to their high thermal stability, unusual structural, electronic and electrochemical properties. Some natural macrocyclic complexes have shown the capability of using as catalysts for many transformations such as vitamin B12. Catalysis can be divided into a number of areas, depending on the substrate and the catalytic reaction. One of the prime areas of the initial effort in catalysis (Delgado *et al*., 2005) has been the small molecule activation, such as O_2, NO_2, NO, H_2S and CO_2.

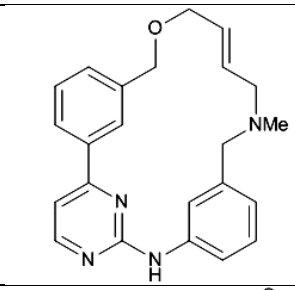
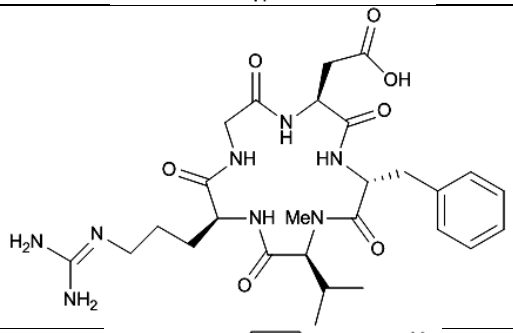
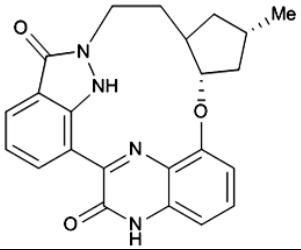
Transition metals such as Cu, Ni, V, and Fe also act as catalysts itself, but these metal catalysts have several drawbacks. These metals show the catalytic activity only when it is in 100% pure form, but the pure metals such as Pt are highly expensive. Another thing is, in higher potentials these metals can undergo oxidations that changes their surface properties. Dust, moisture, higher and lower temperatures will directly influence the catalytic activity of the metal. Many of these drawbacks can be eliminated by using these metals in the macrocyclic form. The common transition metals used in macrocyclic catalysts are Fe, Co, Ni, and Cu, and the macrocyclic ligands include chelating atoms N_4, N_2O_2, N_2S_2, O_4, and S_4. This can be further explained by considering the interaction between small molecules and a transition metal. Electron transition occurs first from small molecules such as oxygen and carbon dioxide into the empty dz^2 orbital, forming a π bond, lowering the anti-bonding π orbital's and raising the energy of the dxz and dyz orbitals of the transition metals. This allows the electron transition from these filled orbital's to the anti-bonding π orbital, and resulting in catalytic activity. These TMMC are also very popular in the medicinal field (Sharma *et al*., 2010) due to their resistivity towards the gram (-) and gram (+) bacteria, fungal growth and as the virus inhibitors.

Anticancer properties:-

Despite many efforts, cancer is among the top three causes of death in modern society, demanding improved treatments, that currently includes surgery, chemotherapy, and various types of radiation therapy (Blasiak*et al*., 2013). Cancer causes over 8.2 million deaths world–wide, set to rise to 12 million by 2030 (WHO, 2014). Inorganic medicinal chemistry has been dominated by the study of the anti–cancer properties of macrocyclic metal complexes. There are a compelling number of drug targets where macrocycles have the potential to bind with good affinity. The potential for macrocycles as drugs is already evident. Exploitation of natural product macrocycles has yielded several oncology drugs (Table 1) that are either approved for clinical use or have reached late–stage clinical development.

Table 1 Several macrocyclic oncology drugs.

Name and Class	Structure	Target
17–allylamino–geldanamycin Natural product analogue		Hsp90 inhibitor
Torisol (temsirolimus) Natural product analogue		mTOR inhibitor
Ixempra (ixabepilone) Natural product analogue		Microtubulin stabilizer
Pacritnib Synthetic macrocycle		JAK2/FLT3 kinase inhibitor

TG02		CDK2/JAK2/FLT3 kinase inhibitor
Cliengitide Synthetic macrocycle		Anti–angiogenic
Synthetic macrocycle		Pan–CDK kinase inhibitor

Reactive oxygen and nitrogen species, which are normal products of cell metabolism, may play a dual beneficial/deleterious role, depending on local concentration and mode of generation (Fig 2).

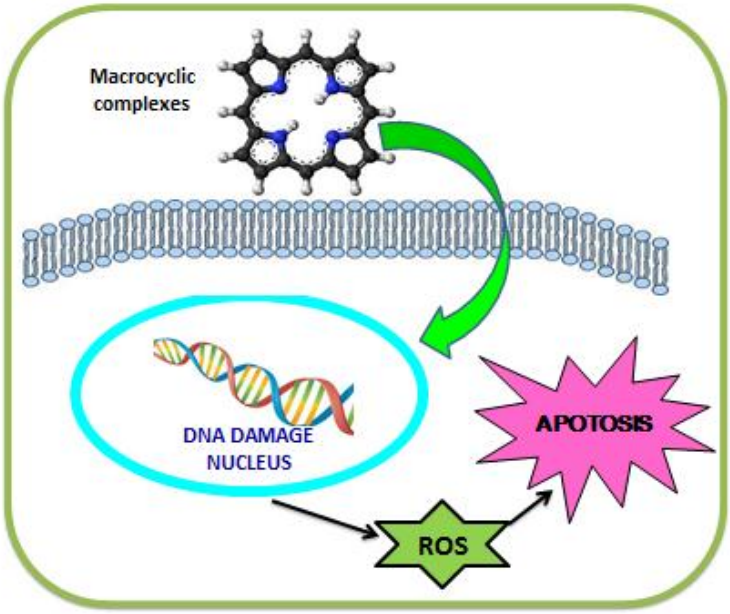


Fig. 2 Mechanism of intracellular ROS in cancer cells.

Metallomacrocycles is an outstanding tool for making structurally matching complexes with drastically different anticancer potentials. The widespread success of *cis*–platin in the clinical treatment of various types of neoplasias

has placed coordination chemistry of metal–based drugs in the frontline in the fight against cancer. Although highly effective in treating a variety of cancers, the cure with *cis*–platin is still limited by dose–limiting side effects (Jung *et al*., 2007) and inherited or acquired resistance phenomena, only partially amended by employment of new platinum drugs (Gust *et al*., 2009). These problems have stimulated an extensive search and prompted chemists to develop alternative strategies, based on different metals, with improved pharmacological properties and aimed at different targets. Synthetic superoxide dismutase mimetics have emerged as a potential novel class of drugs for the treatment of oxidative stress related diseases. Among these agents, metal complexes with macrocyclic ligands constitute an important group. Fernandes and coworkers synthesized macrocyclic metal complexes and evaluated their ability to scavenge the superoxide anions generated by the xanthine–xanthine oxidase system (Fernandes*et al*., 2015) shown in Fig 3.

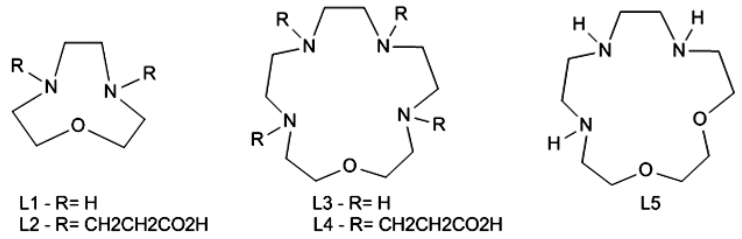
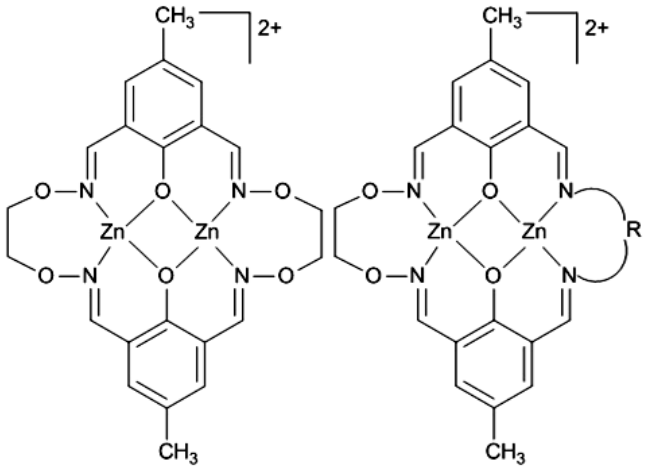


Fig. 3:-Macrocyclic superoxide anions generated by oxidase system.

To further the field of organotin carboxylate macrocycle with aesthetic architecture and to explore the rules of molecular ring formation, we suppose to synthesize novel organotin carboxylate macrocycle with fascinating supramolecular structure. Two unique macrocyclicorganotin(IV)carboxylates were generated by the reactions of dibutyltin oxide with amide dicarboxylic acids and the cell cytotoxicity against mouse sarcoma cells S180 was studied by MTT assays (Xiao *et al*., 2014). A wide repertoire of Zn(II) complexes have been utilized as radioprotective agents, tumor photosensitizers, antidiabetic insulin–mimetic, and antibacterial or antimicrobial agents (Fig 4).



R $-(CH_2)_2-$, $-(CH_2)_3-$ $-(CH_2)_4-$, ,

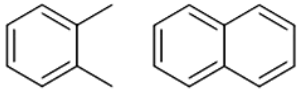
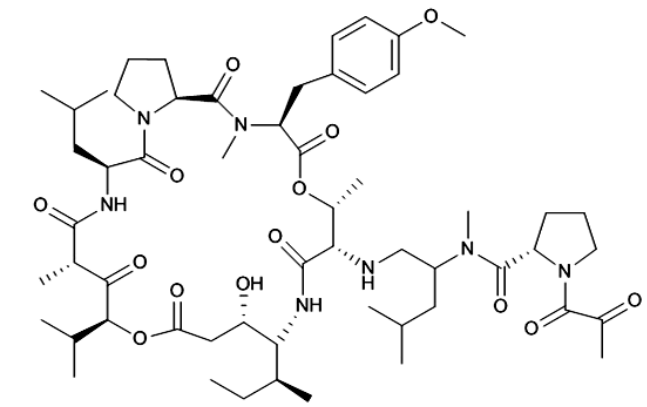


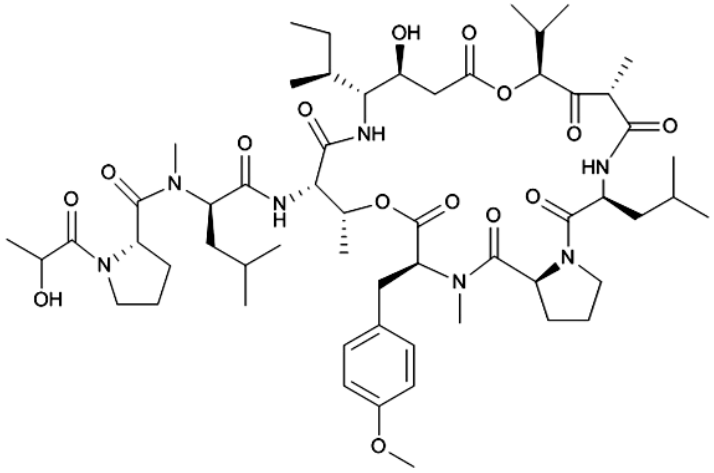
Fig. 4:-Dizinc(II) complex with potent antiproliferative activity.

Also, certain Zn(II) complexes, which strongly bind and cleave DNA, exhibit prominent anticancer activities and regulate apoptosis. A symmetrical macrocyclicdizinc(II) complex has been synthesized by using the ligand. A series of unsymmetrical macrocyclicdizinc(II) complexes has been synthesized. The ligand and dizinc(II) complexes showed cytotoxicity in human hepatoma HepG2 cancer cells (Anbu*et al*., 2012). The biggest change in drug development, particularly in the anticancer field, has been the move away from cytotoxic to molecularly targeted

agents, though related changes have occurred in most areas of drug development (Hambley, 2007). Although highly effective in treating a variety of cancers, the cure with*cis*–platin is still limited by dose–limiting side effects and inherited or acquired resistance phenomena, only partially amended by employment of new platinum drugs. Therefore, attempts are being made to replace these platinum–based drugs with suitable alternatives, and numerous metal complexes are synthesized and screened for their anticancer activities (Ramakrishnan*et al*., 2009). The three globally approved complexes i.e. *cis*–platin, oxaliplatin and carboplatin–play a major role in cancer chemotherapy (Anton *et al*., 2014). However their effectiveness is still hindered by clinical problems, including acquired or intrinsic resistance, a limited spectrum of activity, and high toxicity leading to side effects (Sara *et al*., 2011). The search for anticancer agents with improved properties has focused on the synthesis of a new generation of compounds (Carreira*et al*., 2012). Apoptosis as a form of programmed cell death is one of the major mechanisms of cell death in response to cancer therapies. Its deregulation, i.e. either loss of pro–apoptotic signals or gain of anti–apoptotic signals, can lead to a variety of pathological conditions such as cancer initiation, promotion and progression or results in treatment failures (Zheng*et al*., 2013). Fig 5 summarizes several marine peptides, based on their effects on apoptotic signalling pathways.

(a)





(b)

Fig. 5:- Structure of marine peptides, based on their effects on apoptotic signaling pathways.

Antimicrobial Resistance:-

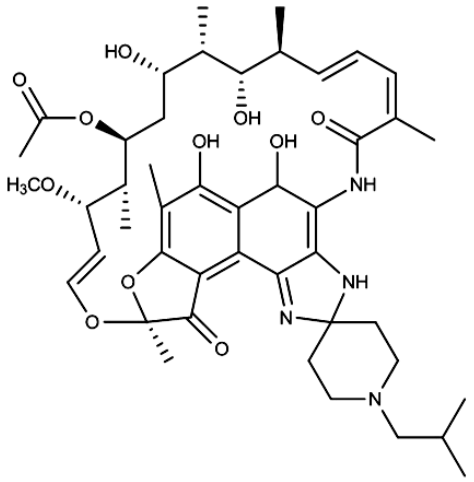
The inexorable rise in antibiotic–resistant bacteria has led to a steady decline in the efficacy of existing therapies for the treatment of bacterial infections. Moreover, the pace at which new antibacterial agents are being generated has decreased dramatically in recent decades, a legacy of insufficient investment in fundamental antibacterial research by pharmaceutical companies since the 1960s (O'Connell *et al*., 2013). Consequently, humanity is facing the very real and disturbing possibility of a future without an effective method for the treatment of some common bacterial

infections. Thus, there is a clear and critical medical need for the discovery of novel antibiotics (Galloway *et al*., 2009). In recent years, there has been a growing interest in researching and developing new antimicrobial agents from various sources to combat microbial resistance. Antimicrobial susceptibility testing can be used for drug discovery, epidemiology and prediction of therapeutic outcome. Antibiotics have revolutionized medicine in many aspects, and their discovery was a turning point in human history (Palidini*et al*., 2015).

The intensive use of antibiotics during the last 70 years has resulted in the emergence of bacterial resistance to many antimicrobial agents (Sandergren*et al*., 2014) and has posed a serious concern to global healthcare (Rai*et al*., 2014). Throughout their evolution, bacteria have gradually adapted to resist environmental stress and have become very efficient in tolerating external insults (De la Fuente-Nunez *et al*., 2013). Moreover, bacteria are frequently exposed to nonlethal concentrations of drugs, and this has an important role in the evolution of antibiotic resistance (Anderson *et al*., 2014). Bacteria can evolve by mutation and can develop several protective mechanisms to reduce their susceptibility to antibiotics (Hogberg*et al*., 2010). After the revolution in the "golden era", when almost all groups of important antibiotics (tetracyclines, cephalosporins, aminoglycosides and macrolides) were discovered and the main problems of chemotherapy were solved in the1960s, the history repeats itself nowadays and these exciting compounds are in danger of losing their efficacy because of the increase in microbial resistance (Mayers*et al*., 2009). Currently, its impact is considerable with treatment failures associated with multidrug–resistant bacteria and it has become a global concern to public health (Martin *et al*., 2015).

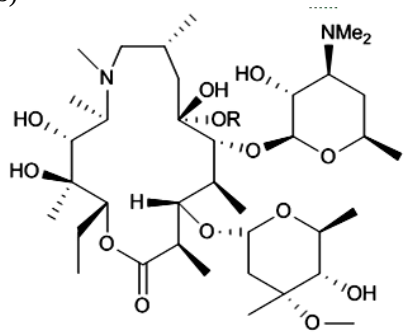
A multidisciplinary approach to drug discovery and the exploration of nature as a source of novel active agents are strongly encouraged today (Newman *et al*., 2012). In this context, the macrocyclic lactones which include the avermectins (e.g., ivermectin [IVM]) and milbemycins (e.g., moxidectin [MOX]) are natural fermentation products of soil–dwelling microorganisms which have been commercialized and are used to control nematode infections (Demain*et al*., 2009). The avermectins are produced by Streptomyces avermilitis and IVM is arguably the most widely used drug in this group. MOX is the most commonly used milbemycin due to its versatility, stability, high potency and safety (Bygarski*et al*., 2014). Notably, the macrocyclic antibiotics (Fig 6) constitute one of the most successful classes of macrocyclic drugs in clinical practice. Among them, vancomycin is a macrocyclicglycopeptideantibiotic for the treatment of Gram–positive bacterial infections, such as methicillin–resistant *Staphylococcus aureus*(MRSA) and penicillin–resistant *Streptococcus pneumonia* (Yu *et al*., 2013).

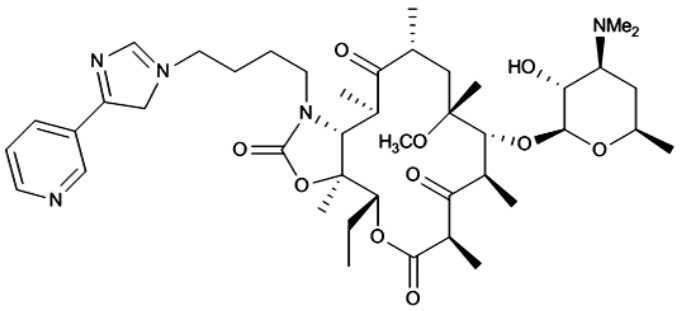
(a)



Rifabutin

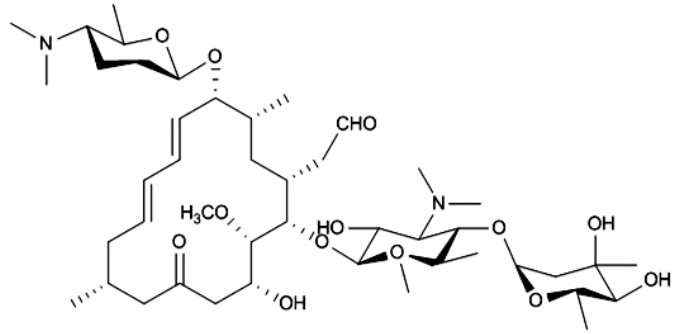
(b) (c)

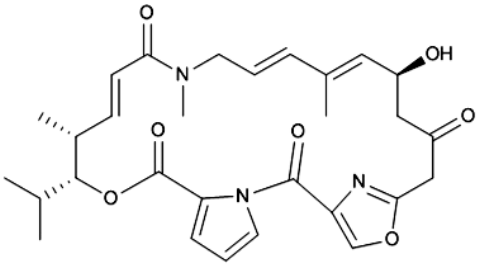




Azithromycin Telithromycin

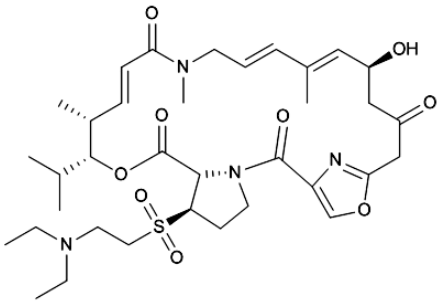
(d) (e)

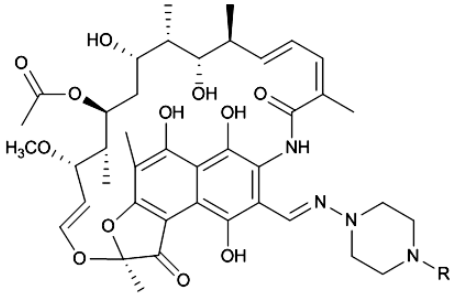




SpiramycinStreptogramin

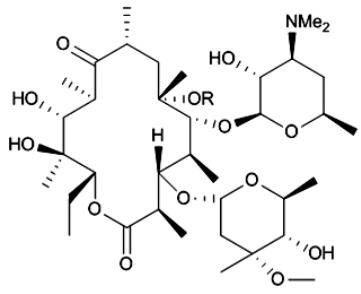
(f) (g)

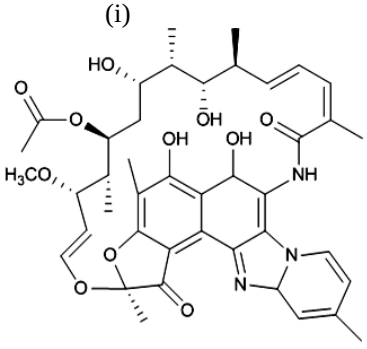




DalfopristinRifampin: R=CH_3, Rifapentine: R= -C_5H_9

(h) (i)





Erythromycin, R= H, Rifaximin

Fig. 6:- Some clinically used macrocyclic antibiotics.

Macrocyclic lactones (MLs) are broad spectrum anthelmintic used to control nematode parasites of animals and humans. They increase the permeability of muscle cell membranes to chloride ions by opening glutamate–gated chloride channels, resulting in inhibition of pharyngeal pumping, motility and egg laying. Kotze*et al.* aimed to observe the effects of the ML abamectin on movement of individual worms in vitro by careful observation of subtle changes in both the degree of movement and its distribution along the body of the worm in response to the drug. Such observations were then compared to the effect of the drug on worm feeding levels (Kotze*et al*., 2012).

TMMC are also very popular in the medicinal field (Sharma *et al*., 2010) due to their resistivity towards the gram (-) and gram (+) bacteria [2], fungal growth and as the virus inhibitors. Few of the drugs such as VL-1, NIL-3 (Fig 7) show the inhibitor activity towards the microbial growth.

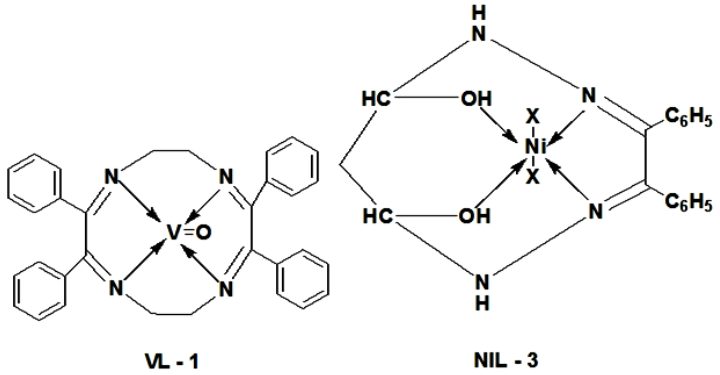


Fig. 7:- Transition metal macrocyclic antibiotics.

Conclusion:-

As macrocyclic chemistry has developed, the variety and scope of the applications of these molecules have continued to multiply. These applications paint out a veracious picture that macrocycles belong to "privileged" class of molecules for therapeutic intervention, the kind that holds clear answers to the challenges facing modern drug discovery. This review frames out the applications of macrocyclic complexes in world of medicinal chemistry.

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