



### Full Length Research Article

## ANTICANCER ACTIVITY OF VARIOUS TRANSITION METAL COMPLEXES: A REVIEW

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#### ABSTRACT

This is a novel approach towards recovering from cancer disease with help of transition metal complexes. Uses of benzimidazole nucleus in plentiful categories of therapeutic agents such as anticancer, immunomodulators, hormone modulators, CNS stimulants as well as depressants, lipid level modulators, antidiabetics, etc. has made it an indispensable anchor for development of new therapeutic agents. Different substituents of the benzimidazole nucleus have provided a wide spectrum of biological activities. The current status of benzimidazole nucleus in medicinal chemistry research is matter interests in present scenario. This discussion will further help in the development of novel benzimidazole compounds. Complexes of benzimidazoles (ligand) with transition metal ions possess antitumor activity.  $\text{Cu}^{2+}$  complex of benzimidazolylmethyl-1, 3-diaminopropane has the ability to intercalate into the double helix of DNA. N-Trimethylsilylpropylbenzimidazole metal complexes exhibit cytotoxic activity on four monolayer tumor cell lines. Assessment of  $\text{Pt}^{2+}$  complexes for antiproliferative properties showed potent activity against human MCF-7 breast cancer cell line and HeLa cervix cancer cell lines. Among the metal (copper, silver, iron, manganese) complexes of 2-methyl benzimidazol-5-carboxylic acid hydrazides, the silver complex is found to display cytotoxicity ( $\text{IC}_{50}$ ) against two human cell lines. A  $\text{Cu}^{2+}$  complex of 2 pyridinyl benzimidazole-5-carboxylic acid has been found to exert potent topoisomerase II inhibitory activity in literature.

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#### INTRODUCTION

Cancer can be termed as the uncontrolled growth of abnormal cells (Mathew *et al.*, 2009). Cancer is the common name for a cluster of more than 100 diseases. Cancer can cause serious illness and death when it remains untreated. The body is made up so-many of living cells. Ordinary body cells grow, divide to make new cells, and pass away in a systematic way. Normal cells divide more rapidly to let the person to grow during the early years of life. Once the person becomes an adult, most cells divide only to replace vanishing cells or to repair injuries. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to nurture and form new, abnormal cells. Cancer cells can also invade other tissues, something like that ordinary cells cannot do. Growing out of control and invading additional cells are what makes a cell a cancer cell (ACS). In the simplest words, cancer can be

described as disease in which typical cells start “behaving badly”, multiplying nonstop, ignoring signals to halt, and accumulating to form a mass that is generally termed a tumour. Unfortunately, research has taught us that cancer is anything but simple (AACR) of all major causes of disease universal, cancer has the greatest economic problem from early death and disability. Among various diseases, cancer has become a big threat to human beings world-wide (Ali *et al.*, 2011). Cancer is a significant community health issue with 8 to 9 lakh cases happening every year. It is estimated that there are approximately 25 lakh cases in the nation at any time. Every year about 4 lakh deaths take place due to this big threat i.e. cancer (NHP). This is due to the poor accessibility/availability of prevention, diagnosis and cure of the disease (Ali *et al.*, 2011). 40% of the cancers in the country are related to tobacco usage. Data from population based registries under the National Cancer Registry Programme indicate that the primary sites of cancer among mankind are cancer of oral cavity, lungs, oesophagus and stomach and among females are cancer of uterine cervix, breast and oral cavity. Cancers namely those of oral and lungs in males and cervix and breast

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in females account for over 50% of all cancer deaths in India. WHO has estimated that 91% of oral cancers in South-East Asia are directly attributable to the use of tobacco and this is the leading cause of oral cavity and lung cancer in India (NHP). All types of cancer start for the reason that abnormal cells grow out of control. Cancer, also termed malignancy, is an abnormal growth of cells. First and primary, there are perhaps as many as 200 different kinds of cancer, each named for the organ or type of cell from which it originates. Besides, complication in cancers are present at every level, from populations, to individuals, to specific cancers, to the molecular and genetic defects that drive these cancers rapidly (AACR), broadly, there are 19 cancers that can be generally related to life style are listed below (ICS) (Tab. 1).

**Table-1. Various type of Cancers**

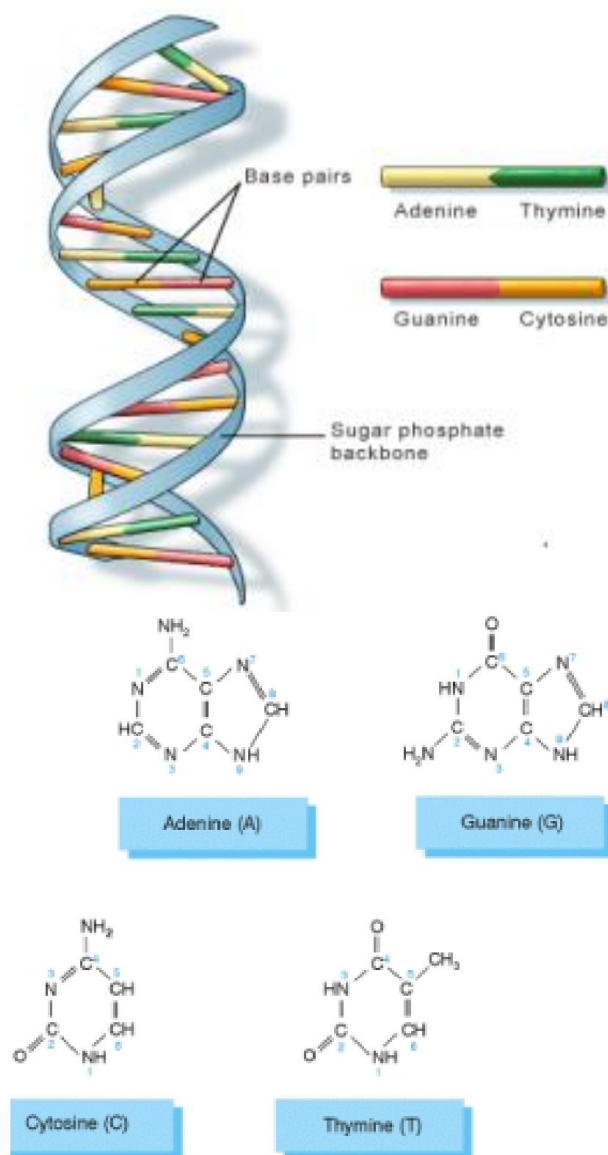
Cancer of the Bladder	Breast Cancer	Cervical Cancer
Colorectal Cancer	Oesophageal Cancer	Cancer In the Eyes
Kidney Cancer	Laryngeal Cancers	Liver Cancers
Lung Cancers	Oral Cancers	Ovarian Cancers
Cancer of the Pancreas	Prostate Cancer	Skin Cancers
Stomach Cancer	Testicular Cancer	Thyroid Cancers
Uterine Cancer		

Breast cancer is the second most common type of cancer after lung cancer (10.4% of all cancer incidence, both sexes counted) and the 5<sup>th</sup> most-common cause of cancer death (Mathew *et al.*, 2009). In 2005, breast cancer caused 502,000 deaths worldwide (7% of cancer deaths; almost 1% of all deaths) (WHO).

**Cause of cancer:** The causes of cancer are varied, complex, and only partly understood. Many factors including environmental (nutrition/diet, tobacco use, certain infections, exposure to radiation, lack of physical activity, obesity, and pollutants) and internal/genetic aspects (Internal aspects (such as inherited mutations/transformations, hormones, and immune conditions), play an important role to increase the threat of cancer. The contribution of genetic factors and environmental factors towards cancer risk is around 5–10% and 90–95% respectively (Anand *et al.*, 2008). In the determination of cancer magnitude person's life style, age composition of the population and aggregate population size play a significant role. These issues gradually changed in the developed ecosphere; as a result cancer has become one of the greater killer illnesses. The precision of the estimates is made more accurate by taking into account the effect of age, period, trend and ecological data (Murthy *et al.*, 2008). During the metabolic process in human body oxygen-centred free radicals and other sensitive oxygen species may yield as by-product by several physiological and biochemical changes. Overproduction of such free radicals can reason of oxidative damage to biomolecules (e.g. proteins, lipids, DNA), ultimately leading to several chronic diseases, such as atherosclerosis, cancer, diabetes, aging, and other degenerative diseases in humans (Halliwell *et al.*, 1994).

**Genomic structure and Genetic basis of Cancer:** The genetic basis of Cancer is distortion of DNA Structure. The genetic material of a cell is made of deoxyribonucleic acid (DNA) strands (Fig. 1-a), which are composed of four units called bases (A-adenine, T-thymine, C-cytosine, and G-guanine)

(Fig.1-b). These bases are structured into genes in a perfect systematic order/sequence. This systematic order of these bases provides the code for synthesis the various proteins for a cell uses to function. The entirety of a person's DNA is called a genome. It is joined together with proteins named histones into thread-like structures called chromosomes (AACR). DNA is in every cell and it directs all its activities. Cells are frequently under risk from the cytotoxic and mutagenic effects of DNA damaging agents which may be exogenous and endogenous. Environmental/exogenous DNA-damaging agents include UV light and ionising radiation, as well as a variety of chemical encountered in foodstuffs, or as air-and water borne agents. Endogenous damaging agents include metabolites that can act as alkylating agents and the ROS (Reactive Oxygen Species) that arise during respiration.



**Fig.1. (a) Structure of DNA and (b) Nitrogen Bases (A, G, C, T)**

DNA repair enzymes continuously monitor chromosomes to correct damaged nucleotide residues generated by these exogenous and endogenous agents and exposure to carcinogens and cytotoxic compounds like inhaled cigarette smoke, or incompletely defined dietary factors. Failure to repair DNA lesions may result in blockages of transcription

and replication, mutagens, and cellular cytotoxicity. In humans, DNA damage is involved in a variety of genetically inherited disorders, in aging, and in carcinogenesis. The major forms of DNA damage include SSB (Single-Strand Breaks), alteration of bases, hydrolytic depurination, hydrolytic deamination of cytosine and 5-methylcytosine bases, formation of covalent adducts with DNA, and oxidative damage to bases and to the phosphodiester backbone of DNA. The vast majorities of these lesions are repaired by BER (Base Excision Repair), NER (Nucleotide Excision Repair), and MMR (Mismatch Repair) (Hull *et al.*, 2001). In an ordinary cell, when DNA is damaged, the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell doesn't die like it should. Instead, the cell goes on making new cells that the body doesn't need. These new cells all have the same structure and activity as the first abnormal cell with damaged DNA (ACS). i.e. Alterations, or mutations, in the genetic material of ordinary cells can disturb the sense of balance of factors governing cell survival and division, and lead to cancer. Since a cell decodes/decrypts the DNA code to produce the proteins it needs to desired function properly, transformations in the code can result in altered protein amounts or functions, finally leading to cancer (AACR).

**Sign and Symptoms of Cancer:** Cancer is a cluster of diseases that can cause almost any sign or symptoms. The signs and symptoms will depend on site where the cancer is started, how enormous it is, and how much it affects the organs or tissues. If a cancer has spread widely, signs or symptoms may appear in various parts of the body. As a cancer grows, it can begin to push on nearby organs, blood vessels, and nerves. If the cancer is in a critical area, such as certain parts of the brain, even the smallest tumour can cause symptoms. But sometimes cancer starts in places where it will not cause any significant signs or symptoms until it has grown quite large. Cancers of the pancreas, for example, generally do not cause symptoms until they grow huge enough to pressurise nearby nerves or organs (this causes back or belly pain). When it grow around the bile duct and block the flow of bile's causes the eyes and skin to look yellow (*jaundice*). By the passes of time a pancreatic cancer causes signs or symptoms like these, it's usually in a progressive stage. This means it has grown sufficiently and spread outside the place it started-the pancreas.

Symptoms like fever, weight loss, extreme tiredness (*fatigue*), may also cause of cancer. This is due to that cancer cells use up much of the body's energy supply, or they may release substances that change the way the body makes energy from food. Cancer may decrease the efficiency of the immune system and cause it to react in ways that produce these signs and symptoms. Sometimes, cancer cells release substances into the bloodstream that cause symptoms which are not usually linked to cancer. For example, some cancers of the pancreas can release substances that cause blood clots in veins of the legs. Some lung cancers make hormone-like substances that raise blood calcium levels. This affects nerves and muscles, making the person feel weak and inconstant (ACS). Protection of cancer incidence is essential for planning cancer control action programme, health care and allocation of resources. A well-conceived, well-managed national cancer control programme let down the cancer frequency and improves the life of cancer patients, no matter what resource

constraints a country faces. A national cancer control programme "National Cancer Registry Programme"—NCRP (governed by National Cancer society of India) is a public health programme planned to decrease the number of cancer cases and deaths and improve quality of life of cancer patients, and this can be achieved by the organized and realistic execution of evidence-based strategies for prevention, early detection, diagnosis, treatment, and palliation, making the best use of available resources (WHO). National Cancer Registry Programme (NCRP) was initiated in 1982 by ICMR, which gives a picture of the magnitude and patterns of cancer. There are two types of registries; Population Based Cancer Registry and Hospital Based Cancer Registries, which was started in January 1982. The mission of the National Cancer society of India is to prevent and cure cancer through research, education, communication, and collaboration (Ministry of Health & Family Welfare, India.). Progress against cancer has been and continues to be the result of the dedicated efforts of many individuals, agencies, and organizations (AACR).

## RESULTS AND DISCUSSION

Cancer is one of the leading health threats which are affecting a wide majority of world population. Various anticancer agents (also referred as antitumor, anti-proliferative and antineoplastic) reported for treatment of different types of cancers act through different mechanisms. However, cytotoxicity towards ordinary cells is the most important side effect related with these agents and it is due to lack of selectivity for the abnormal cells. Therefore exploration on anticancer agent has been in continuum since many years (Bansal *et al.*, 2012). Plants (fruits, vegetables, medicinal herbs, etc.) may contain a wide variety of free radical scavenging molecules, such as phenolic compounds (e.g. phenolic acids, flavonoids, quinone's, coumarins, stilbenes, tannins), nitrogen based compounds (alkaloids, amines, betalains), vitamins, terpenoids (including carotenoids), and some other endogenous metabolites, which show good antioxidant activity (Cai *et al.*, 2003). According to epidemiological studies that many of these antioxidant compounds possess anti-inflammatory, anti-atherosclerotic, antitumor, anti-mutagenic, anti-carcinogenic, antibacterial, or antiviral activities to a greater or lesser extent (Owewn *et al.*, 2000; Sala *et al.*, 2002; Mitscher *et al.*, 1996).

The threats of cancer, cardiovascular disease, diabetes, and other diseases associated with ageing is can be reduced by intake of natural antioxidants, but there is still substantial controversy in this area (Yang *et al.*, 2001). Occurrence of benzimidazole and their derivatives in a wide range of bioactive compounds like antiparasitic, anticonvulsant, analgesics, antihistaminic, antiulcer, antihypertensive, antiviral, anticancer, antifungals, anti-inflammatory agents, proton pump inhibitors and anticoagulants makes it a very important heterocyclic compound and it has also verified by the active research of many years (Mckellar *et al.*, 1990; Spasov *et al.*, 1999; Rossignol *et al.*, 1984; Patil *et al.*, 2008; Dubey *et al.*, 2010; Boiani *et al.*, 2005; Narasimhan *et al.*, 2012). The benzimidazole moiety is a structural element of compounds with a wide range of biological activities (Devinder *et al.*, 2002; Hong *et al.*, 2004; Patel *et al.*, 2008; Lopez *et al.*, 2007). Benzimidazole nucleus can be termed 'Master Key' as it is an important core in many compounds acting at

different targets to elicit varied pharmacological properties (Fig.2). Though all seven positions in the benzimidazole nucleus can be substituted with a variety of chemical entities, but most of the biologically active benzimidazole based compounds bear functional groups at 1, 2 and/or 5(or 6) positions. Accordingly, the compounds may be mono-, di- or tri-substituted derivatives of the nucleus. Many synthetic methods have been developed and modified to get products of high yield, purity and of desired quality (Bansal *et al.*, 2012). A lot of drugs like albendazole, mebendazole, thiabendazole as antihelmintics; omeprazole, lansoprazole, pantoprazole as proton pump inhibitors; astemizole as antihistaminic; envirodine as antiviral; candesartan cilexetil and telmisartan as antihypertensives have been synthesized by optimisation of substituents around benzimidazole nucleus and many chief compounds used in a extensive range of other therapeutic zones. During last 10 years benzimidazole become the principal interested area of research to develop potent bioactive molecules having anticancer and other therapeutic activity. Some reviews on involvement of benzimidazole nucleus in anthelmintic activity (Mckellar *et al.*, 1990; Rossignol *et al.*, 1984; Dubey *et al.*, 2010) and antiulcer activity (Patil *et al.*, 2008) are available in literature. 2-substituted benzimidazole derivatives are an important class of compounds in medicinal and organic chemistry and exhibit inhibitory activity against a range of human tumour cell lines *in vitro* (Starcevic *et al.*, 2007; White *et al.*, 2004; Rangarajan *et al.*, 2000).

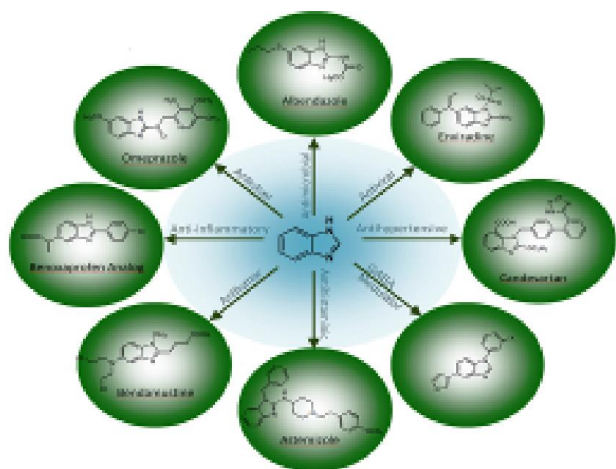


Fig. 2. Benzimidazole in different types of biological activities

copper (II) and cobalt (II), coordination compounds with 2-substituted benzimidazole derived monodentate and bidentate ligands of metal complexes have been synthesized by microanalysis, IR, UV-Vis. Spectroscopy and screened (Azam *et al.*, 2009). Cancer cells are found to have fewer superoxide dismutase activity than ordinary cells (Dionisi *et al.* 1975; Sun *et al.*, 1990) and copper(II) complexes are known to mimic activity of copper, zinc-superoxide dismutase (Cu, Zn-SOD), an antioxidant enzyme that protect cells from the toxic effect of superoxide ion by its dismutation into oxygen molecule and hydrogen peroxide in biological systems (Farmer *et al.*, 1989). Due to their ability to scavenge superoxide, SOD metal complexes considered as antitumor agents (Oberley *et al.*, 1979). The ternary complexes of Cr (III), Mn (II), Fe (II), Fe (III), Co (II), Ni (II) and Zn (II) have been synthesized from lornoxicam and 1, 10-phenanthroline (Phen). The comparative

studies of activity as anti-cancer, antimicrobial of two ligands and ternary metal complexes have been discussed against breast cancer cell line and the results based on different studies showed that parent LOR ligand is less active, but the activity of 1, 10-phenanthroline free ligand is found to be more as compared to metal complexes (Mahmoud *et al.*, 2014). It has evolved by the study and research, the organometallic ruthenium (II) complexes act as a potential antitumor agents (Bruijninx *et al.*, 2008; Bruijninx *et al.*, 2009; Camm *et al.*, 2009; Hartinger *et al.*, 2009; Loughrey *et al.*, 2008; Meggers *et al.*, 2009; Mendoza *et al.*, 2008; Ruiz *et al.*, 2009; Scolaro *et al.*, 2005). Many of their complexes with different ligands have been synthesized and their anticancer activity has been considered. Zobi and etal has been synthesized the complexes of the (arene) ruthenium (II) of type  $(\eta^6\text{-arene})\text{RuCl}(\text{Z})^+$  (Z=chelating ligand) by tagging of a small fluorogenic reporter on to chelating ligand and studied their anticancer characteristics (Zobi *et al.*, 2007).

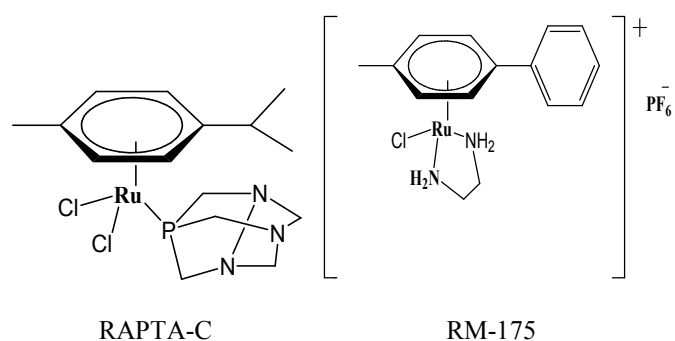


Fig. 3.

Arene ruthenium(II) complexes, especially those coming from the Sadler and Dyson laboratories (Fig. 3) have been reported extensively as potential anticancer drugs (Hartinger *et al.*, 2009; Süss-Fink *et al.*, 2010; Smith *et al.*, 2011; Ang *et al.*, 2006; Dougan *et al.*, 2007). The antitumor activity of the pyrenyl-arene ruthenium complexes ( $M_n$ ) and the corresponding host-guest systems were evaluated *in vitro* in different types of human cancer cell lines (A549, A2780, A2780cisR, Me300 and HeLa) (Furrer *et al.*, 2012). Pyrene and pyrenyl derivatives are known to intercalate between base pairs of DNA, and interfere with transcription, property that can be exploited to design anticancer drugs (Hernandez-Folgado *et al.*, 2010; Guckian *et al.*, 2000) Cisplatin  $\text{cis}(\text{PtCl}_2(\text{NH}_3)_2)$ , and the second generation alternatives carboplatin and oxaliplatin, are still the most extensively used chemotherapeutic agents for cancer (Jamieson *et al.*, 1999; Lippert *et al.*, 2000; Jung *et al.*, 2007).

It is widely used in treatment of testicular cancer, and it is also used in combination regimens for a variety of other tumours, including ovarian, cervical, bladder, lung, and those of the head and neck (Chaney *et al.*, 1996) Besides their clinical success cisplatin has significant side effects due to acquired or intrinsic resistance. Therefore, very much attention has concentrated on designing new platinum compounds with enhanced pharmacological properties and an extensive range of antitumor activity (Zang *et al.*, 2003). Anticancer activity is often correlated to distortions of DNA structure. Hence; it is of great importance to recognize DNA binding properties of transition metal species hence DNA is a significant

prospective biological target for many metal-based anticancer agents drug (Brabec *et al.*, 2006). The platinum atom of cisplatin forms covalent bonds to the N-7 positions of purine bases to afford primarily 1, 2- or 1,3-intrastrand adducts and a lower number of interstrand cross-links (Wang *et al.*, 2005). It is generally believed that biological activity of cisplatin is associated with the recognition of its DNA adducts by cellular proteins such as repair enzymes, transcription factors, histones, and high mobility group (HMG) domain proteins (Brabec *et al.*, 2002). Oxamate complexes of Palladium(II) and platinum(II) are referred as potential anticancer agents and their cytotoxic activity against human carcinogenic cells have been discussed for  $K_2(Pd(opba))_2 \cdot 2H_2O$  (1),  $(Pd(NH_3)_4)(Pd(opba))$  (2), and  $(Pt(H_2opba)) \cdot H_2O$  (3), complexes, where opba = 1,2-phenylenebis(oxamate). Order of activity for these Pd(II) and Pt(II) complexes to inhibit cellular growth is obtained in the following order 1~2 > 3. Compounds (1) and (2) are approximately 20 times more cytotoxic against leukaemia cells than the free ligand (Oliviera *et al.*, 2014). Novel phosphate ester antibiotic drug (CI920) has potent anti-leukemic activity in mice.

It is structurally contains an unsaturated lactone and a conjugated triene system (Leopold *et al.*, 1984). The search for new water-soluble analogues of camptothecin (CPT) with higher activity and less toxicity has led to the development of a novel compound, which showed significant antitumor activity against a broad spectrum of experimental tumour models by i.p., i.v, orral administration (Kunimoto *et al.*, 1987). Toxic side effects of anticancer drugs restrict the utility of cancer chemotherapy to considerable extent and this is due to the fact that the anticancer drugs used in the present chemotherapy has less effective selectivity for malignant cells. Numerous type of polymers, naturally occurring and synthetic polymers have been examined as carriers of anticancer drugs to suppress the toxic side effects of the anticancer drugs to ordinary cells and to enhance their efficiency toward tumour cells. High specificity and wide applicability of immunoglobulin towards many kinds of malignant cells makes it a widely used carrier for anticancer agents.

Utility of immunoglobulin as the polymeric carrier is, however, restricted by its chemical and physical properties (Yokoyama *et al.*, 1990). Transformation of epithelial cells in to malignant cell is frequently associated with the alteration of glycosylation pathways. Tn is a common tumor-associated carbohydrate antigen present in 90% of human carcinomas and its expression correlates with metastatic potential and poor prognosis. Despite its relevance, the functional role of Tn in tumour biology has not been firmly established probably for the lack of suitable experimental tools (Danussi *et al.*, 2009).

## Conclusion

Various type of transition metal complexes have been synthesized and widely used in clinics for treatment of numerous diseases. The present review is expected to provide a wide range of spectrum to a drug designer and medicinal chemist for a broad and target oriented information for development of clinically worthwhile molecules for anticancer activity. Overall, this study concludes that these transition metal complexes functionalized by benzimidazole moiety

could be used as a potent anti-cancer inhibitor or drug in the coming future.

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