Synthesis and Biological Activity Evaluation of Transition Metal Complexes of Thiosemicarbazones

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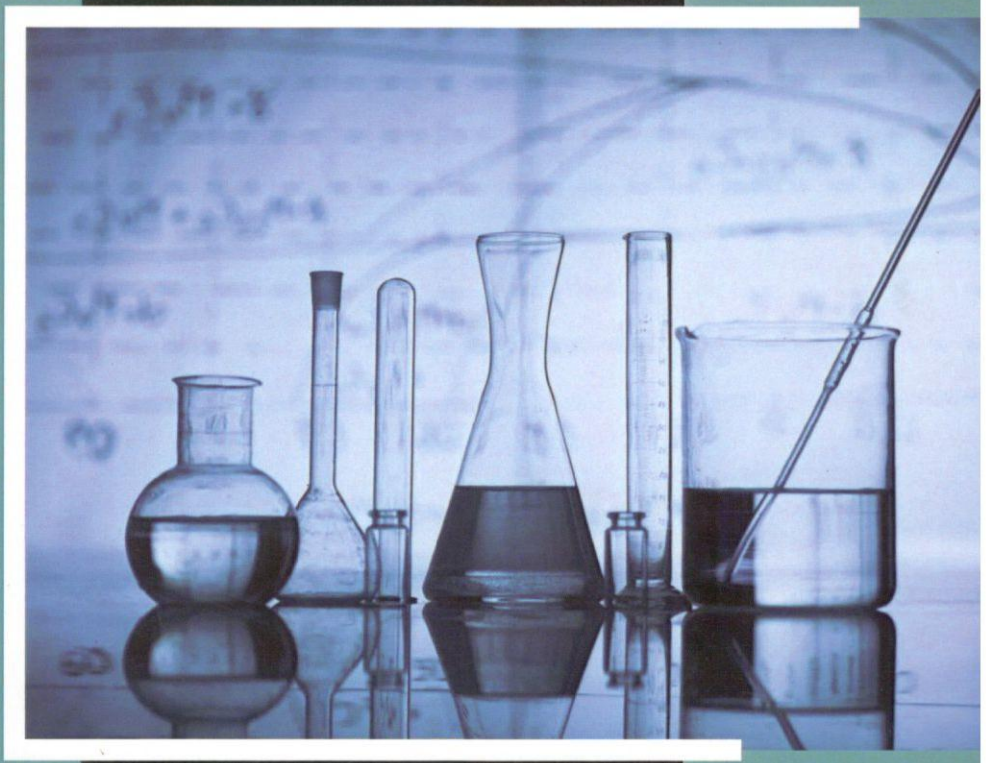

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CHAPTER 1

Review of Literature

1.1 Introduction

Transition metals and their therapeutic importance

Transition metals, also known as d block elements are placed in groups 3-12 in the long form of periodic table. They have vacant d orbitals in their penultimate (n-1) shells and positioned between the s and p blocks, hence, they are commonly referred to as transition elements. They usually exhibit variation in their oxidation states making them suitable for coordination complexes. Coordination complexes result from the bonding between a metal atom with electron donating agents known as ligands. Therapeutic uses of transition metal complexes date back to sixteenth century. Cisplatin or cis-diammine-dichloridoplatinum (II) (DDP)was discovered in 1960 for its anti-tumor activity and was found to be very efficient in the treatment of solid carcinomas (Rafique et al., 2010, Jamieson & Lippard, 1999). The mechanistic action of cisplatin involved movement in the cell through diffusion and active transport. The compound caused platination of deoxyribonucleic acid (DNA) involving cross-linkage of inter and intra strands.The process involved formation of addition products, usually with guanine residue because of its electron richness. Formation of adducts with cisplatin caused distortion and inhibition of DNA synthesis (Lee et al., 2002). These DNA adducts also bound to cellular proteins like repair enzymes, histones (Louie & Meade, 1999) and also to HMG-domain proteins etc., thereby enhancing anticancer potential. Cisplatin also bound with negatively charged species like metallothioneins and glutathiones which areneeded to sequester heavy metals like Pt and

CHAPTER 2

Computational Drug Designing and Rediction of Important Parameters

2.1 Introduction

Drug discovery and development is a tedious and time consuming process involving a lot of money. Computational predictions about the structure and properties of a probable lead compound can come handy and reduce the phase time and also help in prediction of side effects, if any and in identification of disease-specific target. It is a multistep procedure involving *in vivo* validations. Through computational evaluation, it can be predicted whether the molecule is suitable to enter the drug discovery process. It is of utmost importance that the ADMET properties are known in early stage of drug development (Selick et al., 2002, Kubinyi, 2003, Lyne, 2002). ADMET predication can also help in the investigation of several mechanisms including crossing of physiological barriers, group activity to metabolism. Computational predictions have strengthened the knowledge bank and, presently widely used in almost every discipline of science for better understanding and integrated studies. Computationally molecular sequence analysis, complex interactions of genes and non-coding regions have been identified (Meyer et al., 2000, Shinde et al., 2015). Protein estimation and identification of their important features has been possible using computational tools. Computational approaches have been used to study interaction of proteins with other molecules. With the advent of genomics, proteomics and bioinformatics tools, drug discovery process has been revolutionized. Before the wet lab or synthesis stage it is a prerequisite to know whether the molecule is-

CHAPTER 3

Computationla Studies, Synthesis, Characterization and Biological Activity Evaluation of 2-Butanone Thiosemicarbazone and its' Complexes

3.1 Introduction

Thiosemicarbazone complexes are comparatively easy to prepare through simple condensation reactions (Bjelogrlic et al., 2010). Since they are polydentate ligands, transition metals can bind to them through a variety of coordination modes (Beraldo & Gambino, 2004). The coordination capacity can be additionally enhanced if some electron donating groups are attached to the parent ligand moiety which further enhances the coordination power (Kowal et al., 2008). Activity enrichment can be significantly attained by structure optimization (Khan et al., 2015). The π-delocalization of charge and the flexibility in configuration can improve the coordination ability. In this chapter, preparation and biological activity assessment of 2-(butan-2-ylidene) hydrazinecarbothioamide (2-butanone thiosemicarbazone) and its metal complexes with Cu, Fe, Co and Zn has been described. Drug like properties of the complexes were predicted through molecular docking, toxicity assessment and bioactivity score prediction using different automated softwares. To check oral bioavailability Lipinski's rule was applied. *In vitro* Anticancer activity was tested against MDA-MB-231 (human breast cancer and abbreviated as MDA) and A549 (human lung cancer) cell lines using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and trypan blue (TBE) assays. The antibacterial activity was tested against *S.aureus* and *E.coli* using the disc diffusion method. The antioxidant potential of the ligand and complexes was also assessed using the 2,2'-diphenyl-2-picryl-hydrazyl-hydrate (DPPH) free radical scavenging assay.

CHAPTER 4

Computer-aided Drug Design and Virtual Screening of Targeted Combinatorial Libraries of Mixed Ligand-Metal Complexes of 2-Butanone Thiosemic Arbazone

4.1 Introduction

Drug development and discovery processes are expensive and time taking (Prashansa, 2014). Computational predictions have proved to be useful tools to predict druglikeness of proposed new compounds before the wet lab stage. An ideal drug compound should be efficacious, selective in its action, and shave good oral absorbance (Egan et al., 2000). The main aim of computational analysis is to search for suitable drug like molecules which possess potential pharmacodynamics and pharmacokinetic properties (Egan et al., 2000). Evaluation of druglikenesscan be doneby applying certain simple rules like Lipinski, Veber, Ghose and leadlikeness which evaluate the pharmacokinetic ADME parameters and drug like or lead like properties and are useful for lead optimization. This chapter deals with computational designing of mixed ligand-metal complexes of 2-butanone thiosemicarbazone with hetero bases viz. pyridine, 2,2'-bipyridine, furan, thiophene, 1,10-phenanthroline, piperazine, 2-picoline and ammonia. The complexes were virtually screened for drug like properties. Hetero ligand complexes of thiosemicarbazones have been used as probes for DNA in bioinorganic chemistry and some of these compounds also possess interesting anticancer properties and may be prospective drug candidates (Erkkila et al., 1999, Schatzschneider et al., 2008). There has been a growing interest in the formation of hetero ligand-metal chelates involving ligands with sulfur, nitrogen and/or oxygen atoms in different oxidation states

CHAPTER 5

Mixed Ligan-Metal Complexes of 2-Butanone Thiosemicarbazone and their Biological Activity Evaluation

5.1 Introduction

Mixed ligand complexes are comprised of two different ligands. They also activate numerous enzymes and play an imperative role in transportation of substances (Hughes 1987). Mixed ligand complexes containing hetero atoms sulphur, nitrogen and oxygen have been probed for their biological significance (Gupta &Narayana 1999).They are efficient chelating agents because of flexible donor ability. Due to a variety of benefits, there has been a growing interest in the synthesis of mixed ligands chelates involving metals in different oxidation states (Tsukahara et al., 2003, Yao et al., 2004). Pyridine is one of the important examples of hetero ligands. Pyridine containing compounds have shown various pharmacological properties and its'derivatives act as components of several vitamins, nucleic acids, enzymes and proteins (Altaf et al., 2015). They have also exhibited antitumor properties. 2-Amino-3-cyanopyridines have been identified to have antimicrobial (Mungra et al., 2011), antifungal(Gholap et al., 2007) and cardiotonic activities (Bekhit et al., 2005). Phenanthroline is another heterocyclic nitrogen containing ligand. Derivatives of phenanthroline have been widely used in coordination chemistry (Chelucci et al., 2007). Many of the derivatives have numerous biological activities (Shabaan et al., 2012). Phenanthroline has a rigid framework and possess good chelating properties and can bind to many metal ions. The presence of two nitrogens enhances the coordination and charge transfer ability (Felder et al., 2001, Liu et al., 2005). The π-electron deficiency makes it a good π-acceptor (Liu et al., 2005). 2,2'-