Anticancer activity of some newly developed bioactive molecules: A density functional approach

ABSTRACT

Research Background and Challenges

Cancer is one of the most mortal diseases characterized by the development of abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. It occurs due to the mutations in cellular level, the consequence of which is the DNA damage and eventually leads to the mutation of DNA. There are various approaches including surgery, chemotherapy, radiation therapy and/or combination therapies available to treat cancer. The nature of the treatment depends upon the location, type and stage of cancer, possible side effects, and the patient's preferences and overall health. Due to the immense research efforts in this field, the curing rate using the chemotherapy and combination therapies have been improved in the last few decades. Organic drugs and natural products are most commonly used chemotherapeutic agents. However, after the discovery of cisplatin, the interest towards the use of metal based chemotherapeutic drugs are gradually increasing.

Designing and development of the new drugs in laboratory bench to clinical trial is an intense, lengthy and an inter-disciplinary venture. In this context, rational computational chemistry and molecular modeling for computer-aided drug design have proved to be an emerged promising alternative tool to visualize the scenario of the potential drugs, taking into account the laws of quantum mechanics. It is helpful in understanding the anticancer activity of lead compounds by means of their structures, reactivity and stability. Moreover, it also gives us a platform to understand the interactions of the drugs with their cellular targets.

During the process of selection of novel drug candidates, many essential steps are taken to eliminate such compounds that have side effects. In the present thesis, we have employed density functional theory (DFT) to perform the structure-reactivity of some selected Gold (III) complexes and camptothecin anticancer agents using $DMol^3$ program. The binding affinity of the camptothecin and Au (III) complexes has been investigated using Molegro Virtual Docker (MVD) 5.0 molecular docking software. The pharmacokinetic properties of the molecules are carried out using ADME toxicity study where absorption, distribution, metabolism, excretion and toxicity are investigated. We have also study the hydrolysis process of a novel transplatin

complex, *trans*-[$PtCl_2$(dimethylamine)(isopropylamine)], using GAUSSIAN 09 program package. Hybrid QM/MM calculations have been performed with the help of QMERA associated with of Materials Studio package to investigate the interaction as well as feasibility of the various adduct formed during the course of the incoming *trans*-complex towards its cellular target DNA.

The thesis comprises of seven chapters:

Chapter 1 provides motivation and background information on cancer, its classes and causes. In this chapter, we have included the general introduction of DNA, its structure and the factors that may lead to the mutation on the DNA molecule. An overview of platinum based anticancer drugs and their chemistry are presented which start with the history of cisplatin and its systematic evaluation to newer platinum based drugs. Mechanism of action of platinum based drugs on molecular and cellular level are described in details. We have also included some gold (III) complexes and camptothecin systems along with their mode of action. Here, we have also discussed the different computational methods used in the field of drug design emphasizing the growing role of quantum-mechanical methods. It includes the fundamental of DFT and details of basis sets and energy functionals. We have presented the global and local reactivity descriptors which have been extensively used in the present study to investigate the stability as well as reactivity of the studied systems. The usefulness of the descriptors in the structure and activity analysis have been studied elaborately during the whole study. We have also used various molecular docking tools in order to find the inhibitory activity as well as the binding affinity for the gold and camptothecin molecules to their cellular targets. Further, we have discussed the applications of the hybrid quantum mechanics/molecular mechanics (QM/MM) method in the study of the drug-DNA interaction.

Chapter 2 is the study of DFT based reactivity descriptors such as electrophilicity (ω), Fukui functions (f_k^+, f_k^-), energies of LUMO and next LUMO along with the physicochemical parameters (logP, hydration energy, molar refractivity and surface area) for QSAR studies of two different sets of camptothecin molecules. A good correlation between the biological activity and the DFT based descriptors is obtained using multiple linear regression analysis. In literature, the importance of the various classical 2D descriptors such as logP, molar refractivity (MR), surface area have been greatly emphasized but in this report we have focused mainly on the importance

of the DFT based reactivity descriptors in understanding the behaviors of campothecins. The modeled QSAR equations derived by regression analysis predicted that the camptothecin inhibitory activity is highly correlated with the DFT-based descriptors, lowest unoccupied molecular orbital (E_{LUMO}), hydration energy and solvent accessible surface area of the molecules.

Chapter 3 emphasizes on the study of DFT based reactivity descriptors in combinations with physicochemical descriptors to study the activity of substituted camptothecins (CPTs) against different cancer cells. A quantitative structure-activity relationship (QSAR) model was build up with cytotoxicity (pIC_{50}) as dependent variable and the reactivity parameters as independent variable using both simple and multiple linear regression analyses. We have demonstrated that DFT based descriptors like Fukui function and electrophilicity can be used as potential parameters for modeling QSAR equations. Based on the QSAR study it is found that hydration energy, energy of HOMO, LUMO and next LUMO have positive effect on the activity of the camptothecin derivatives. On the other hand, logP, refractivity, polarizability and surface area are found to have negative effects on their activities. Docking studies are performed in order to ensure the binding affinity of the selected molecules against 1T8I, a known target protein of the selected complexes. Docking studies reveals some of the molecules under study fit well into the binding cavity of the targeted protein, indicating that the selected CPTs are effective inhibitors of the protein target 1T8I.

Chapter 4 deals with the detailed theoretical investigation performed on the two step hydrolysis mechanism of a novel transplatin anticancer agent *trans*-[$PtCl_2$(dimethylamine)(isopropylamine)] in both gas as well as aqueous phase using DFT. The penta-coordinated transition state (TS) geometries along with other stationary points on potential energy surface (PES) are optimized and characterized. The existence of transition states on the corresponding PES is ascertained by performing intrinsic reaction coordinate calculations (IRC). The calculated values of the activation barrier for the two successive steps are in good agreement with the experimental data reported in the literature and shows that the first hydrolysis process is faster compared to that of the second hydrolysis step. The predicted relative free energies of the complexes are also in accordance with experimental observations. The rate constants are calculated at 298K and 1atm using Eyring equation for each step. The calculated rate constant

results show that the second step of the hydrolysis is the rate-limiting process having higher activation energy compared to that of the first step.

Chapter 5 deals with the calculations on trans-DNA adduct using combined Quantum Mechanics/Molecular Mechanics (QM/MM) method. The binding energy of trans-DNA adduct is calculated using Generalized Gradient Approximation (GGA) including PBE, HCTH and PW91 level of theories with DNP basis set. During this work, we have evaluated the binding energy of the complex with DNA and also calculated the interaction energies when the drug molecule is approaching towards the DNA strand. The results show that the interaction energy gradually decreases with decrease of distance and the final adduct attains its most stable configuration. The feasibility of the species is also ascertained with the help of the change in Gibb's free energy at different temperature ranges. The change in Gibb's free energy at a particular temperature also shows similar trend and signifies the feasibility of the reaction under normal body temperature.

Chapter 6 describes how *in silico* approaches will further increase our ability to predict and model the most relevant pharmacokinetic, metabolic and toxicity endpoints, of some selected anticancer Au (III) candidates; thereby accelerating the drug discovery process. We have tried to implicate DFT in order to find the stability as well as reactivity order of the studied complexes. We have also performed the molecular docking calculations along with ADME toxicity study for all the studied complexes to find the inhibitory activity as well as to study the effect in the body after administration of the drug.

DFT study reveals that compound 1 and 3 are found to be the most stable based on the MEP and MHP and compound 5 is found to be the least stable one. We have also build some DFT based effective regression models in order to correlate with the cytotoxictiy of the selected compounds. These regression models reveal that DFT based descriptors certainly play a role on the cytotoxicity of such biologically active systems. From the developed models it has been found that DFT based descriptors such as lowest unoccupied molecular orbital (E_{LUMO}), highest occupied molecular orbital (E_{HOMO}), electrophilicity (ω), chemical potential (μ) and $E_{(HOMO-1)}$ are very much sufficient in describing the activity of the studied compounds.

Molecular docking study confirms that the selected gold complexes are effective inhibitor of the target protein *h*TrxR. Compound 18 is found to be the best inhibitor amongst all the studied molecules and thus, can induce mitochondrial inhibition by targeting the protein *h*TrxR.

We have also performed the ADME toxicity study of the selected gold complexes and selectively evaluated the different pharmacokinetic properties in terms of absorption, distribution, metabolism, excretion and toxicity.

Based on regression, molecular docking calculations along with ADME toxicity study, it has been found that ethylenediamine, cyclam and meso-tetraarylporphyrins ligand containing compounds are the best molecules in terms of stability, safety and efficacy.

Chapter 7 summarizes the concluding remarks and highlights the findings and future scopes of the present investigation. This work paves the way to explore different computational techniques to screen out potential drug candidates from the list of possible ones. Combine study of DFT along with molecular docking, hybrid QM/MM and ADME toxicity provide a better insight towards the discovery of novel chemical entity with relatively lesser side effects and efficacy. Thus, with the work presented here, we not only demonstrate the relevance of computational grids in drug discovery, but also identify several promising compounds which will eventually lead to the development of drug with higher success rates.