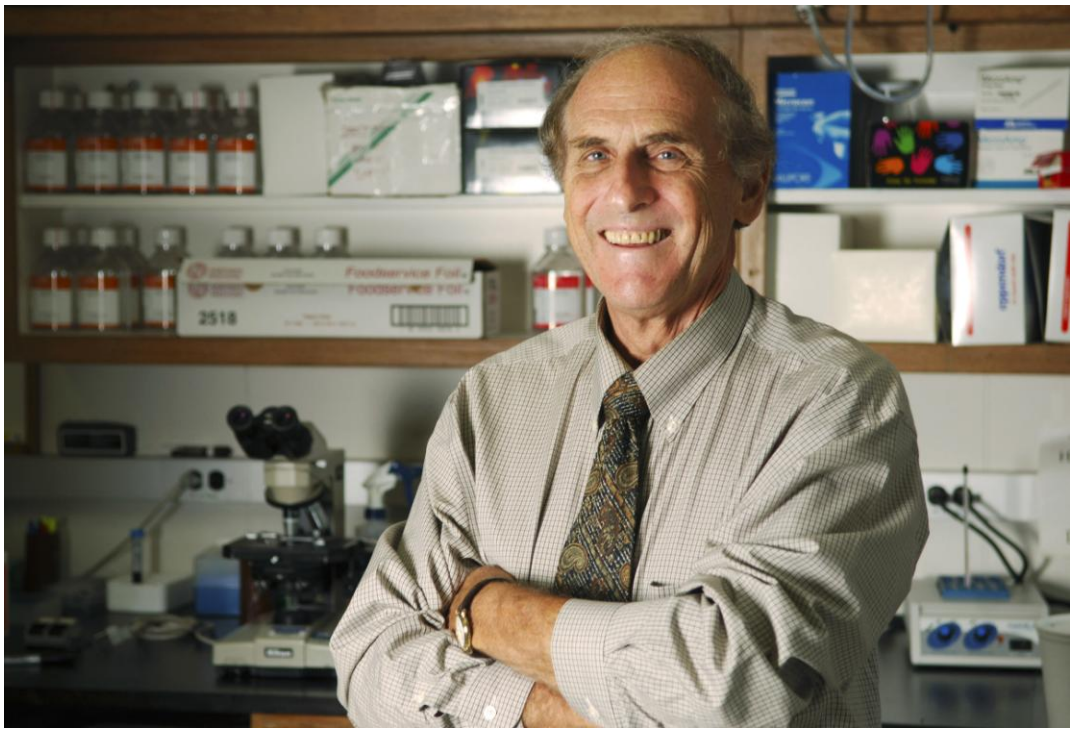
CHAPTER 7

General Conclusion and Future Challenges



Canadian Ralph M. Steinman shares Nobel Prize in Physiology or Medicine (2011)

Picture Source: https://www.theguardian.com/science/2011/oct/03/nobel-prize-officials-dead-scientist

"I WANTED AS MUCH TO INITIATE A CANCER IMMUNE RESPONSE AS I WANTED TO INITIATE ONE AGAINST INFECTION."

-DR. RALPH M. STEINMAN

7.1 Conclusion

This thesis deals with density functional theory (DFT) and its application, both from conceptual as well as computational viewpoint to correlate the activity and properties of several newly developed bioactive molecules. Here, we presented different computational strategies to identify potential drug candidates from a list of possible ones.

In the present thesis, we have employed DFT based descriptors in order to correlate the structure-reactivity of some selected Gold (III) complexes and camptothecin anticancer agents. The binding affinity of the molecules against their cellular targets are investigated using molecular docking. The pharmacokinetic properties of the molecules are carried out using ADME toxicity study which provides absorption, distribution, metabolism, excretion and toxicity properties. We have also studied the hydrolysis process of a novel transplatin complex, *trans*-[$PtCl_2$(dimethylamine)(isopropylamine)] using density functional method. The interaction of *trans*-[$PtCl_2$(dimethylamine)(isopropylamine)] with DNA was investigated with hybrid QM/MM technique. The important findings of the present investigation are summarized chapter wise below:

7.1.1 General Introduction and methodology

This chapter prides a brief introduction and background of cancer, its classes and causes. We have included some newly developed bioactive molecules *viz.* gold (III) complexes, camptothecins (CPTs) and a novel trans-platinum complex which are potent against cancer. 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, details of basis sets and energy functionals.

7.1.2 Application of physicochemical and DFT based descriptors for QSAR Study of camptothecin derivatives

In this chapter we have investigated two different set of camptothecin molecules using DFT-based descriptors. We have built some effective regression models using a combination of DFT and physiochemical parameters. A very good correlation between

the biological activity and DFT based descriptors are obtained in multiple regression analysis. The developed models further clarify that density functional based reactivity descriptors such as electrophilicity (ω), Fukui functions (f_k^+, f_k^-), energy of the frontier orbitals along with the physicochemical parameters (logP, hydration energy, molar refractivity and surface area) are very powerful in describing the cytotoxicity of this class of compounds.

7.1.3 A comparative QSAR analysis and molecular docking studies of camptothecin derivatives as DNA-topoisomerase I inhibitor: A impartial approach to anticancer drug design

This chapter emphasizes uses of DFT based reactivity descriptors in combinations with physicochemical descriptors to study the activity of substituted camptothecins (CPTs) against different cancer cells. The binding affinities of the molecules are also ascertained with the help of molecular docking software. 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. The derived models signify the importance of the DFT based descriptors in predicting the activity as well as cytotoxicty of the CPTs. Docking studies reveals that 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.

7.1.4 Kinetics and thermochemistry of hydrolysis mechanism of a novel anticancer agent trans-[$PtCl_2$(dimethylamine)(isopropylamine)]: A DFT study

In this chapter, we have study the two step hydrolysis mechanism of *trans*-[$PtCl_2$(dimethylamine)(isopropylamine)] in both gas as well as aqueous phases using DFT. The existence of transition states on the corresponding PES is ascertained by performing intrinsic reaction coordinate calculations (IRC). The activation barrier for the first hydrolysis process is found to be lower compared to that of the second hydrolysis 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. Thus, monoaquo species of the complex is the most preferable species that react with the cellular DNA *in vivo*.

7.1.5 Theoretical investigation on the interaction of transplatin with DNA: A QM/MM

In this chapter, we have studied different interacting species that has been involved during the course of the incoming transplatin complex towards its cellular target DNA with the help of hybrid QM/MM method. During this work, we have calculated the binding energies of the complex with DNA and also evaluated the interaction energy of the incoming molecule towards the DNA. The results show that the interaction energy gradually decrees with decrease of distance and the final Pt-DNA 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 signifies the feasibility of the reaction under normal body temperature.

7.1.6 Gold anticancer metallodrugs: computational strategies to identify potential candidates

This chapter deals with the different computational strategies to identify some potential gold (III) anticancer drug candidates which help in accelerating the drug discovery process. We have employed regression, molecular docking along with the ADME toxicity study to predict the most relevant chemical entity in terms of stability, safety and efficacy. From the overall combined study we conclude that ethylenediamine, cyclam and meso-tetraarylporphyrins ligand containing compounds are the best molecules compared to that of the others. This initial work will eventually lead to the development of drug with higher success rates.

7.2 Future prospects of the present investigation

In this thesis, we have explored the behavior, activity and stability of some newly developed bioactive anticancer agents. Still there are many scopes in this field to investigate.For instance,

- Based on the developed regression models a new class of the bioactive systems can be developed with higher activity.
- Study of different superparamagnetic clusters as carriers in the magnetic drug delivery process for platinum based drugs.
- Extension of these computational strategies to similar types of biologically active molecules.