Preface

In drug discovery process, there is need for a common tool for chemists and biologists that would benefit in the day-to-day efforts of enhancing the design of new therapeutic agents. The centre of gravity of approach of medicinal chemistry has shifted from how to make a drug to what drug to make i.e. QSAR based drug design. In the thesis, I have applied this concept by using various computational chemistry based software, enormous data have been generated and several important findings achieved. For compiling the work made, I have used recent publication and reviews up to 2010 collected from extensive survey of literature by visiting CDRI-Lucknow, ITRC-Lucknow, National Medical Library-New Delhi, IIT-Kanpur, IIT-Guwahati and IIT-Kharagpur, and from internet. The work has been reported in eleven chapters, including the introduction and methodology, also. The first chapter introduces the overview of acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), replicative cycle of HIV, targets for anti-HIV chemotherapy, HIV-1 protease, HIV-1 protease inhibitors, paradigms for drug discovery, quantitative structure-activity relationship and lights on the aim of the present work and planning of the work. The second chapter deals with the description of principles, concepts, theories, software and methods used throughout this work to achieve the goal. In third chapter, I have discussed “Lipinski’s ROS in extended form” on peptidic HIV-1 protease inhibitors to construct graphical abbreviated profile of drug for pharmacokinetic study. Pharmacokinetic properties such as absorption, distribution, metabolism, excretion and toxicity (ADMET) are important in order to determine the success of the compound for human therapeutic use because it is estimated that around half of all drugs in development fail to make it to the market because of poor pharmacokinetics. All physicochemical parameters examined in this study well describe the pharmacokinetics of the drugs. The computer friendly numerical string representation of GA-POD makes the comparison of any properties possible. The graphical representation also gives a snapshot of properties and their relative changes. Biological activity is the result of chosen molecular species interacting with a biological entity. The binding of the drug to the receptor will initially depend upon the types of chemical bonds (covalent bond, ionic bond, hydrogen bond and hydrophobic interaction) that can be established between the drug and its receptor. The overall strengths of these bonds will vary and will determine the degree of affinity between the drug and the receptor. Chapter fourth to seventh discussed the drug-receptor interaction. The fourth chapter presents the hydrophobic interaction governing the drug-receptor interaction of peptidic HIV-1 protease inhibitors with their receptor on HIV-1 protease enzyme. The fifth chapter deals with the study of electrostatic attractions that strength the formation of enzyme-inhibitor complexes. The principles applied are difference in energies of frontier orbitals, charge transfer, energy lowering and interaction energy. In sixth chapter effective atomic softness has been used for site selectivity, polar interaction and QSAR modeling. In seventh chapter I have discussed hydrogen bonding based drug-receptor interaction of peptidic HIV-1 protease inhibitors. The last four chapters eighth, ninth, tenth and eleventh well describes the QSAR study of inhibitors. QSAR methodologies save resources and expedite in the development of new molecules and drugs. QSAR techniques increase the probability of success, reduce the time and cost involved in drug discovery and in exploring the medicinal characteristics of molecules. The eighth chapter describes the use of pharmacokinetic descriptors in the QSAR parlance and the usefulness of such application is evident from this chapter. The ninth chapter describes the suitability of quantum chemical reactivity parameters, ΔE_{sH}, ΔN; ΔE; ΔE_{s}; ΔE_{z} and ΔE_{ext}, as possible bioactivity descriptors in the development of QSAR. The tenth chapter of the thesis well shows the relationships between biological activity of inhibitor and quantum-chemical energy descriptors, heat of formation; total energy; HOMO energy; LUMO energy; electron affinity and ionization potential, and also well describe the role of these descriptors in the QSAR modeling. Finally the last chapter i.e., chapter eleven, discussed the comparative QSAR study of peptidic HIV-1 protease inhibitors. The work of the thesis may be helpful for further research in the study of compounds of same series, on the basis of the derived models one can build up a theoretical basis to access the biological activity of the compounds of the same series and one can used the parameters discovered in this work for the study of inhibitors of diverse nature.