CHAPTER-3

AIMS AND OBJECTIVES

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Human life is constantly threatened by ailments. Hence, drugs are always in great demand for the prevention and treatment of diseases. To meet the challenges of discovery of a safe drug, techniques/methods of drug discovery and development are in great demand. The process of drug discovery and development is an expensive and time-consuming affair. To introduce a single new chemical entity as a drug in the market requires not less than 10-15 years of hard work and a huge amount of money. Hence, several new technologies have been developed and applied in drug research and development to cut short the research cycle and to reduce the expenses. Computer aided drug design (CADD) is one of such evolutionary technologies. Advent of computers in the drug discovery process has revolutionized medicinal chemistry due to better understanding of the drug-enzyme/receptor binding interactions. It was planned to apply ligand and structure based techniques for the inhibitors of enzymes like TACE, neuraminidase and aromatase which are involved in various diseased states.

After going through the literature it became evident that inhibitors of TACE enzyme do not belong to a particular individual category. They have diverse structures and no particular pharmacophoric group could be identified for binding to the enzyme. It was thought of finding out structural features in molecules that are required essentially for binding to TACE using molecular modeling techniques.

Rheumatoid arthritis (RA) is one of the most common autoimmune inflammatory conditions, affecting approximately 1% of the world's population. It has been proved beyond doubt that TNF-α plays a pivotal role in the origin and progression of the disease. One of the ways of excluding TNF-α from the biological system is to block TACE, the enzyme responsible for maturation of inactive form of TNF. Recently, it has been reported that TACE inhibitors might also be useful for treating certain types of cancers. While a variety of TACE inhibitors have been reported in the literature, a vast majority of these compounds are peptidic and peptide-like compounds that are expected to have bioavailability and pharmacokinetic problems, common to such compounds, limiting their clinical effectiveness. Low molecular mass, long acting and orally bioavailable inhibitors of TACE are, therefore, highly desirable for the treatment of chronic diseases. Hence TACE became one of our choices for carrying out *in silico* experiments.

Due to the current surge of cases of patients suffering from swine flu, neuraminidase became our second choice of targets for the study. Advances in understanding of the molecular and cellular biology of influenza have led to identification of several molecular targets for the design of agents against this disease. The most advanced clinical agents described to date are inhibitors of neuraminidase, a glycoprotein on the surface of the influenza virus. The 2009 swine flu virus (H1N1pdm), which can be transmitted from one human being to another, has become a threat to the global health and economy. The current seasonal flu vaccine, which targets a different H1N1 strain, provides little or no protection against H1N1pdm. In terms of medication, the two FDA approved antiviral drugs, Tamiflu (oseltamivir) and Relenza (zanamivir), are effective against this new type of virus. Unfortunately, such virus types are known for their quick mutations and gene assortments which enable them to escape the host immune systems and resist drugs. A case of swine flu resistant to Tamiflu was observed in Denmark on June 29, 2009 for the first time, and soon after that in Japan and Hong Kong. Developing new vaccinations and antiviral drugs for this new H1N1pdm virus is a matter of extreme urgency. Hence neuraminidase was one of our choices of targets for *in silico* drug design.

Aromatase became the next choice of targets, as a synthetic programme on the development of steroidal aromatase inhibitors was already running in this laboratory. Worldwide, breast cancer is the most common form of cancer in women after skin cancer, reporting 16% of all cancers in females. Expression of aromatase is highest in or near breast tumor sites. A large number of aromatase inhibitors have been developed and utilized in clinical studies over the last 20 years. Treatment with aromatase inhibitors is generally well tolerated with low incidence of serious side effects. However short-term events like hot flushes, vaginal dryness, musculoskeletal pain and headache have been observed. There is a need for the development of new, potent, more selective and less toxic aromatase inhibitors. Hence aromatase was added in the list of our choices of targets for *in silico* drug design.

Keeping the above discussed enzyme targets in mind, it was planned to undertake the following studies:

3.1 Studies on TACE inhibitors

3.1.1 Three-dimensional quantitative structure activity relationship studies on benzothiadiazepine hydroxamates as inhibitors of Tumor Necrosis Factor-Alfa converting Enzyme

3.1.2 Development of predictive 3D-QSAR CoMFA and CoMSIA models for β-aminohydroxamic acid-derived TACE inhibitors

3.1.3 Development of predictive pharmacophore model for *in silico* screening and 3D-QSAR CoMFA and CoMSIA studies for lead optimization for designing of potent TACE inhibitors

3.1.4 Molecular modeling studies of novel 2-imidazolidinones and tetrahydropyrimidin (2*H*)-ones as potential TACE inhibitors

3.1.5 Molecular modeling studies of some new heterocyclic inhibitors of TACE

3.2 Studies on influenza neuraminidase type A inhibitors

3.2.1 Determining of structural requirements of influenza neuraminidase type A inhibitors and binding interaction analysis with the active site of A/H1N1 by 3D-QSAR CoMFA and CoMSIA modeling

3.3 Studies on aromatase inhibitors

3.3.1 Molecular modeling studies of some novel androstanes as potential aromatase inhibitors