# ABSTRACT

Conventional drug design processes use trial and error methods for screening natural and synthetic compounds. It costs millions of dollars and very long time approximately 10-15 years. To meet these severe challenges nowadays pharmaceutical companies rely very much on computer-aided design techniques to discover potential drugs. Throughout the research work, various natural inhibitors that regulate a variety of physiochemical processes in bacteria and human beings have been studied. Derivatives of them have been designed and developed in such a way that they may be used as potent drugs producing no or minimal side effects and overcome the antibiotic resistance property. We hope, *in silico* drug design processes followed in different studies would save precious time and millions of dollars, leading to novel alternate therapeutics.

**CHAPTER I**

Microorganism including bacterium communicates among themselves through a unique mechanism called quorum sensing. The different QS pathways of Gram-negative and Gram-positive bacteria have been discussed elaborately in this chapter. Bacteria develop antibiotic resistance through various mechanisms among them biofilm formation is regulated by quorum sensing. Quorum sensing inhibitors (QSIs) interrupt the expression of virulence factors production and inhibit biofilm formation without killing bacteria or inhibiting bacterial growth. The QSIs are of two types natural and synthetic. It includes a details study of different types of QSIs and inhibition mechanisms. Hamamelitannin (HAM) a phytochemical has the capability to inhibit *Staphylococcus aureus agr* QS system. Our approach is to modify HAM by incorporating an active functional group for better efficacy. We have followed the same *in silico* process in another study where the target protein was chosen as heat shock protein 90 rather known as HSP90 and found in all species ranging from bacteria to humans. Over expression of this client protein may lead to several refractory diseases including cancer, inflammation, neurodegeneration, and viral infection. It discussed the various roles and functions of HSP90 in the human body. Besides, we have performed quantitative structure activity relationship (QSAR) analysis in two different cases. Phophodiesterase-4 (PDE4) and lysine-specific demethylase 1 (LSD1) are two key proteins that regulate various physiochemical processes in humans. Over expression of PDE4 may lead to severe diseases including chronic obstructive pulmonary disorder (COPD), and cardiovascular disease whereas unregulated LSD1 may result in tumorigenesis, neurodegenerative disorders, viral infection, diabetes, fibrosis, and various types of cancers including prostate, gastric, breast, lung, and leukemia. Separate studies of QSAR on these two proteins help us to identify best-fitted designed molecules as potent inhibitors of the target proteins. Detailed information on both PDE4 and LSD1 is described here.

**CHAPTER II**

The major *in silico* techniques that are widely popular among researchers are molecular docking, density functional theory (DFT) calculation, molecular docking, molecular dynamics (MD)

simulations, and absorption, distribution, metabolism, excretion, toxicity (ADMET) prediction. Collective use of all of the mentioned computer aided techniques is necessary to predict potential QS inhibitors. It includes methodologies of all of the above mentioned techniques in detail.

**CHAPTER III**

A set of 26 derivative compounds have been designed by incorporation of different active functional groups at various positions of hamamelitannin (HAM) shown here. All structures were optimized using Gaussian software. Gaussian outputs were used to perform molecular docking with the help of Autodock Vina software. Docking results of HAM with three target proteins of PDB ID 4AE5, 4G4K, and 2FNP exhibited the binding energy value of -6.7, -6.5 and -6.6 kcal/mol respectively. Out of 26 derivatives of HAM, 14 compounds have shown higher binding affinity than that of HAM. The above *in silico* studies concluded that 14 ligands could be developed as effective inhibitors of S. aureus biofilm formation and considered for *in vitro* and *in vivo* analysis.

**CHAPTER IV**

It includes the natural product oroidin (ODN) considered a potent inhibitor of heat shock protein 90 (Hsp90) and its derivatives had been designed by substituting various functional groups in the various position of five membered rings. A library of thirty nine derivatives was designed by introducing various functional groups such that amide, amine, phosphate, hydroxyl, fluorine, methoxy, and carboxylic acid in the active pharmacophore of oroidin. All the analyses expressed that seven analogues possessed better chemical activity and docking capabilities than that of the source molecule ODN. These seven computationally designed derivatives may be used as novel beneficial agents in various cancer therapies including breast, ovarian, colon, pancreas, liver carcinoma, and leukemia treatments, and could be considered to develop as effective anticancer drug candidates in the future.

**CHAPTER V**

Keeping in mind the importance of PDE4 inhibitors it includes a study where a quantitative structure-activity relationship (QSAR) modeling method was performed to develop a standard model on a dataset of sixty-six significant PDE4A inhibitors encompassing common scaffolds in pyrazolo-oxazine, and imidazo-pyridazine compounds. According to QSARINS software, the model comprises three descriptors namely MoRSEM11, MoRSEP26and MoRSEC11 were found to be the best ones. The three descriptor model which was employed to predict pIC50 values as the studied response exhibited good $R^2$ (0.8185), and F (73.658) values. Internal validation parameters $Q^2_{loo}$= 0.7845, $Q^2_{LMO}$= 0.7771and external validation parameters $Q^2_{F1}$= 0.8277, $Q^2_{F2}$= 0.8246, $Q^2_{F3}$= 0.8626, confirmed the stability and robustness of the developed model. On the basis of this model equation, pIC50 values of thirty-nine designed compounds were calculated. The potent lead molecules, predicted from the QSAR model, were further investigated by performing *in silico* approaches such as molecular docking, molecular dynamics simulation, bioavailability assessments, and toxicity prediction. The study revealed that the eight compounds possessed

potent PDE4A inhibitory activity and might be considered as future drugs subject to the viability of *in situ* and *in vivo* proceedings.

**CHAPTER VI**

In this chapter quantitative structure activity relationship (QSAR) model was built from a dataset of 44 compounds as LSD1 inhibitors. The best 10 compounds have fully satisfied all the criteria of drug-like properties and these designed lead molecules would have more potency to treat LSD1 target after going through in vivo and in vitro analysis.

**CHAPTER VII**

3D-QSAR analysis and application of ANN validation in CADD to design potential inhibitors of many critical diseases in future.