ABSTRACT

The work in this thesis utilizing various *in silico* techniques to explore potential leads against aurora kinase, hepatitis C virus, COVID-19, monkeypox virus, adenovirus, HKMT, and GOAT. CADD accelerates lead discovery and optimization, leveraging both high speed and low cost, thus enhancing drug development success rates. In this study, both structure-based (molecular docking) and ligand-based (QSAR) techniques were employed, providing a robust tool for ligand investigation. Drug repurposing emerges as a transformative strategy, offering innovative therapeutic avenues for approved drugs. Additionally, QSAR aids in lead optimization, minimizing time, cost, and animal use. Key steps in QSAR model development include dataset collection, descriptor calculation, model construction, and validation. This thesis proficiently employs QSAR to understand structural activity relationships, improve selectivity, and design molecules with enhanced efficacy, predicting the activity of newly designed compounds.

CHAPTER I

This chapter contains the in details about CADD which has been extensively explored for facilitating lead discovery and optimization with advantages in terms of both high speed and low cost, increases the probability of success in the drug development process. A variety of *in silico* methods have evolved in CADD that have two major application areas, i.e., LBDD and SBDD. The first part of the chapter deals with the object of CADD with aurora kinase and hepatitis C. The second part of the chapter deals about drug repurposing with COVID-19, monkeypox, and adenovirus. The last part deals about QSAR study with HKMT, and GOAT.

CHAPTER II

The major *in silico* techniques that are usually popular among researchers are molecular docking, molecular dynamics (MD) simulation, density functional theory (DFT), molecular mechanics Poisson Boltzmann surface area (MM-PBSA), quantitative structure activity relationship (QSAR), artificial neural network (ANN) and absorption, distribution, metabolism, excretion, toxicity (ADMET) prediction. Collective use of all of the mentioned computer aided techniques is necessary to predict potential inhibitors. It includes methodologies of all of the above mentioned techniques in detail.

CHAPTER IIIA

Aurora kinase (AURK) belongs to the serine/threonine kinase family and play a crucial role in regulating the cell cycle. Therefore, AURKs are the hopeful target for anticancer therapies and these findings have encouraged researchers to rigorously hunt small molecule aurora kinase inhibitors, not only for research articles but also for use as therapeutic agents. This study helped us to identify and screen the best phytochemicals as potent inhibitors against AURK. These potent inhibitors came from the various substitution of rosmarinic acid (RA). Here, we selected different tested derivatives for designing anticancer drugs by substituting various functional groups of standard drug RA. *In silico* studies were carried out to

appreciate better drug candidature of some of these derivatives. This study was performed on 56 derived compounds of the standard RA. Out of the 56 derivatives, 11 have passed all the rules of drug candidature, to serve as best AURK inhibitor, in a theoretical manner. This study should be supported by a new proposal to explore future studies with these 11 compounds against cancer.

CHAPTER IIIB

The NS3/4A protease is a common target for HCV infection. Telaprevir and danoprevir have promising activity in combating these virus-associated infections and are used as HCV protease inhibitors. In this study, we have found different tested derivative compounds for developing various HCV NS3/4A protease inhibitors by designing the chemical structures of telaprevir and danoprevir. *In silico* studies were carried out to find better drug candidature from these derivative compounds. The docking studies were performed on HCV NS3/4A protease receptors (PDB: 3SV6 & 5EQR). DFT, global reactivity, ADME (Absorption, distribution, metabolism & excretion), and toxicity analysis were also performed for these designed compounds. The stability of the protein-ligand complexes was quantified by MD simulation and MM-PBSA studies. 16 derivatives (four as telaprevir and twelve as danoprevir) have satisfied higher binding affinity of interaction with NS3/4A protease, compared to telaprevir and danoprevir. These compounds have also passed all rules of drug candidature to serve as the best HCV inhibitors. These 16 ligands can be used as effective inhibitors against HCV NS3/4A protease. These ligands could be considered to follow the drug candidate behaviour by *in vitro* and *in vivo* analysis to inhibit HCV infection.

CHAPTER IVA

Novel coronavirus disease, COVID-19 caused the outbreak situation of global public health. In that pandemic situation, all the people lives of 212 Countries and Territories were affected due to partial or complete lockdown and also as a result of mandatory isolations or quarantines. This was due to the non-availability of any secure vaccine. This study helped us to identify and screen the best phytochemicals as potent inhibitors against COVID-19. In this study, we have selected two standard drugs namely hamamelitannin and rosmarinic acid as a probable inhibitor of pandemic COVID-19 receptor, compared to antimalarial drugs hydroxychloroquine, anti-viral drug remdesivir, and also baricitinib. This study was done by taking into consideration of molecular docking study. This work has provided an insightful understanding of protein-ligand interaction of hamamelitannin and rosmarinic acid showing comparable binding energies than that of clinically applying probable COVID-19 inhibitors hydroxychloroquine (an anti-malarial drug) and remdesivir (an anti-viral drug). We would expect that if its anti-SARS-CoV-2 activity is validated in human clinical trials, these two drugs may be developed as effective antiviral therapeutics for infected patients with COVID-19.

CHAPTER IVB

In view of the non-availability of any secure vaccine for COVID-19 caused by SARS-CoV-2, scientists around the world have been running to develop potential inhibitors against SARS-CoV-2. This study helped us to identify and screen best phytochemicals (chemical

drugs or plant based compounds) as potent inhibitors against COVID-19. Here, we have measured the virtual interactions of COVID-19 main protease (PDB: 6LU7) with lung cancer, bronchitis and blood thinner drugs as well as some natural plant based compounds. Best docking results have been considered on the basis of disulfiram, tideglusib and shikonin. ADME and toxicity were also predicted for these compounds. From this study, we would expect these drugs to undergo validation in human clinical trials to be used as promising candidates for antiviral treatment with high potential to fight against COVID-19.

CHAPTER IVC

Monkeypox virus (MPXV) is considered as zoonotic disease with characteristics comparable to smallpox virus. The disease was also a global epidemic concern. Tecovirimat was approved by US Food and Drug Administration (FDA) for MPXV treatment. The aim of this *in silico* study was to repurpose approved pharmaceutical drugs as potential inhibitors of MPXV target. In this study, molecular docking was performed on 406 pharmaceutical drugs, and results were compared with reference tecovirimat. Results showed that 7 compounds, bictegravir, glimepiride, glyburide, lasmiditan, olaparib, rimegepant, and ubrogepant, have shown higher binding energies compared to the reference. After that, these best hits were further assessed by 100 ns molecular dynamics simulation and the best results were observed for bictegravir, glimepiride, glyburide, olaparib, and ubrogepant. The docking analysis was further validated by MM-PBSA binding free energy calculations. In addition, pharmacokinetics and density functional theory (DFT) studies were also discussed for these best hits. In conclusion, three compounds, bictegravir, glimepiride, and glyburide, have satisfied all the criteria for better leads against MPXV.

CHAPTER IVD

Human adenovirus (HADV) infection can pose a serious threat to children, leading to a variety of respiratory illnesses and other complications. Particularly, children with weak immune systems are vulnerable to severe adenovirus infections with high mortality. The main focus of this study was to propose new antiviral agents as lead HADV inhibitors for children. So, several antiviral agents used in children were subjected to finding new HADV inhibitors using important computational methods of molecular docking, molecular dynamics (MD) simulation, MM-PBSA binding free energy calculations, DFT, and pharmacokinetic analysis. Molecular docking of standard cidofovir along with other ligands, suggested that sofosbuvir has the highest binding energy (-10.8 kcal/mol), followed by baloxavir marboxil (-10.36 kcal/mol). Further, the analysis of molecular interactions using MD simulation (100 ns) and MM-PBSA indicated that baloxavir marboxil has formed the most stable protein-ligand complex with HADV, followed by sofosbuvir. The binding free energies of baloxavir marboxil and sofosbuvir were found to be -61.724 kJ/mol and -48.123 kJ/mol, respectively. The DFT and drug-likeness properties of these compounds were also investigated. Overall, two antiviral agents, such as baloxavir marboxil, and sofosbuvir, were suggested as lead repurposed candidates against HADV.

CHAPTER VA

Initiation and progression of several diseases by post-translational histone modifications are considered a worldwide problem. Enhancer of Zeste Homologue 2 (EZH2), which belongs to HKMT family, has been emphasised as a promising target for cancer therapy. It is a major challenge for the scientific community to find novel approaches to treating this disease. In this study, a series of 51 derivatives of the benzofuran and indole families, previously experimentally evaluated against HKMT, was used to develop the best QSAR model with promising anticancer activity. The multiple linear regression (MLR) method was used with a genetic algorithm (GA) for variable selection. The model with two descriptors (minHBint4 and Wlambdal.unity) was found to be the best and its parameters fit well, and its validation was well established. The applicability domain was also validated for this model. Furthermore, its robustness (R^2 = 0.9328), stability (Q^2_{LOO} = 0.9212, Q^2_{LMO} = 0.9187), and good predictive power (R^2_{ext} = 0.929) were also verified. Hence, this model was assumed to have predictive HKMT anticancer activity for designing active compounds. Molecular docking was also performed to identify binding interactions, and new molecules with better predicted biological activity (pIC50) were designed. The binding energy of the three designed compounds demonstrated higher binding activity at the target receptor, followed by complex stability, determined by a 100 ns molecular dynamics simulation and binding free energy calculation. DFT and pharmacokinetic analyses also confirmed their drug-like properties. Finally, it could be declared that the proposed tools allow rapid and economical identification of potential anti-HKMT drugs (anticancer drugs) for further development.

CHAPTER VB

Diabesity is a major global health concern, and GOAT acts as an important target for the development of new inhibitors of this disease. This work highlighted a detailed QSAR study, which provides an excellent model equation using descriptors. Here, the best model equation developed has two variables, namely MLFER_E and XlogP, with statistical parameters R^2 = 0.8433, LOF = 0.0793, CCC_{tr} = 0.915, Q^2_{LOO} = 0.8303, Q^2_{LMO} = 0.8275, CCC_{cv} = 0.9081, R^2_{ext} = 0.7712, and CCC_{ext} = 0.8668. A higher correlation of the key structural fragments with activity was validated by the developed QSAR model. Furthermore, molecular docking helped us to identify the binding interactions. Thirty four new molecules with better predicted biological activity (pIC50) were designed. The binding energy of four compounds have shown higher binding activity into the membrane protein. Molecular dynamics simulation has established the stability of the protein-ligand complex over 100 ns. DFT and ADME-toxicity analyses also confirmed their drug-like properties. Based on our findings, we would expect these new oxadiazolo pyridine derivatives to undergo further development.