DEVELOPMENT OF SOME NOVEL COMPUTATIONAL TECHNIQUES FOR SCREENING AND OPTIMIZING HIT MOLECULES FOR PROTEIN TARGETED LEAD MOLECULE DISCOVERY

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by

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Submitted

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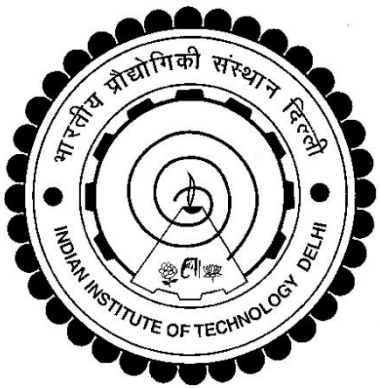

INDIAN INSTITUTE OF TECHNOLOGY DELHI

October 2018

Dedicated to

my parents

and

brothers

Certificate

This is to certify that the thesis entitled, "**Development of some novel computational techniques for screening and optimizing hit molecules for protein targeted lead molecule discovery**", being submitted by **Mr. Abhilash Jayaraj** to the Indian Institute of Technology Delhi for the award of the degree of **Doctor of Philosophy** in Biological Sciences, is a record of bonafide research work carried out by him. Mr. Abhilash Jayaraj has worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard. The results contained in this dissertation have not been submitted in part or full to any other University or Institute for the award of any degree or diploma.

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Abstract

Drugs play a vital role in human health care. Drug design is the process by which we develop suggestions for new drugs to treat diseases and disorders. Constant effort is required to develop new methodologies to make this process time and cost efficient. This thesis focusses on providing some new solutions towards this end.

The thesis is divided into seven chapters. Chapter I provides a brief overview of the current state of computer aided drug discovery (CADD). It assesses the merits and limitations of some of the methodologies currently used in CADD. Emphasis is laid on emerging fields of study which hold the potential to open avenues for new and better methodologies for drug design.

Chapter II elaborates a new methodology for predicting biomolecular targets for organic molecules called BAITOC. This methodology has the potential to predict targets for known bioactive compounds as well as their off target binding. This methodology can be helpful to predict Adverse Drug Reactions (ADR) and toxicity early in drug development cycle. BAITOC methodology also holds the potential to be used for drug repurposing. The accuracy of the methodology has been tested on 100 FDA approved drugs. The methodology has been web enabled and provided free of cost for the scientific community.

Chapter III describes a new methodology and web server for multi target drug design. Multi targeting is an upcoming field of work which utilizes a single drug compound to modulate activity of more than one biomolecule. The methodology described is capable of selecting compounds binding to multiple drugs in a time efficient manner. The methodology has been tested using FDA approved drugs. The server is web enabled and provided free of cost to the scientific community.

Chapter IV studies the case of allosteric control of Human Serum Albumin by Testosterone. This study based on a series of molecular dynamics simulations provides a

plausible mechanism of allosteric control. The results of the study have been verified in collaboration with experimental group using 2D NMR. The study is expected to be helpful in designing novel drugs capable of harnessing the benefits of allostery.

Chapter V describes a new, first of its kind, free and user friendly Android application (App.) capable of performing all major steps involved in computational structure based drug design. The App. has been made freely available on Google play store and the results can be downloaded to desktops if required using a user friendly web portal.

Chapter VI is an extension of the work done in chapter II. It aims to develop a new methodology for elucidating a scaffold for better binding to a defined protein target. The methodology is under development but shows promising results.

Finally, Chapter VII presents summary and perspectives that have evolved from this thesis work. It also discusses the merits and limitations of the work presented. Future work which can be done is also considered.

सारांश

मानव स्वास्थ्य की देखभाल में दवाएं महत्वपूर्ण भूमिका निभाती हैं। ड्रग डिज़ाइन वह प्रक्रिया है जिसके द्वारा हम बीमारियों और विकारों के इलाज के लिए नई दवाओं के लिए सुझाव विकसित करते हैं। इस प्रक्रिया को समय और लागत प्रभावी बनाने के लिए नई पद्धतियां विकसित करने के लिए लगातार प्रयास की आवश्यकता है। यह थीसिस इस लक्ष्य की ओर कुछ नए समाधान प्रदान करने पर केंद्रित है।

थीसिस सात अध्यायों में बांटा गया है। अध्याय १ में कंप्यूटर सहायता प्राप्त दवा खोज (CADD) की वर्तमान स्थिति का एक संक्षिप्त अवलोकन प्रदान किया गया है । यह वर्तमान में CADD में उपयोग की जाने वाली कुछ पद्धतियों की योग्यता और सीमाओं का आकलन करता है। अध्ययन के उन उभरते क्षेत्रों पर जोर दिया गया है जिसमें दवा डिजाइन के लिए नई और बेहतर पद्धतियों के लिए मार्ग खोलने की क्षमता है।

अध्याय २ BAITOC नामक पद्धति का विवरण करता है । यह प्रौद्योगिकी कार्बनिक अणुओं के लिए बायोमोलेक्यूलर लक्ष्यों का पूर्वानुमान करने के लिए एक नई पद्धति का विस्तार करता है। इस पद्धति में ज्ञात बायोएक्टिव यौगिकों के साथ-साथ उनसे अलग लक्ष्य बाध्यकारी के लिए लक्ष्य की पूर्वानुमान करने की क्षमता है। यह पद्धति दवा विकास चक्र में प्रतिकूल दवा प्रतिक्रियाओं (ADR) और विषाक्तता की पूर्वानुमान करने में मददगार हो सकती है। BAITOC पद्धति में दवा पुनर्वितरण के लिए उपयोग की जाने वाली क्षमता भी है। 100 एफडीए अनुमोदित दवाओं पर पद्धति की यथार्थता का परीक्षण किया गया है। पद्धति को वेब सक्षम किया गया है और वैज्ञानिक समुदाय के लिए निःशुल्क प्रदान किया गया है।

अध्याय ३ बहु लक्ष्य दवा डिजाइन के लिए एक नई पद्धति और वेब सर्वर का वर्णन करता है। बहु-लक्ष्यीकरण एक आगामी कार्य क्षेत्र है जो एक से अधिक जैव-अणुओं की गतिविधि को संशोधित करने के लिए एक एकल दवा परिसर का उपयोग करता है। वर्णित पद्धति एक समय कुशल तरीके से कई दवाओं के लिए बाध्यकारी

यौगिकों का चयन करने में सक्षम है। एफडीए अनुमोदित दवाओं का उपयोग करके पद्धति का परीक्षण किया गया है। सर्वर वेब सक्षम है और वैज्ञानिक समुदाय को निःशुल्क प्रदान किया जाता है।

अध्याय ४ टेस्टोस्टेरोन द्वारा मानव सीरम अल्बुमिन के एलोस्टेरिक नियंत्रण के मामले का अध्ययन करता है। आणविक गतिशीलता सिमुलेशन की एक श्रृंखला के आधार पर यह अध्ययन एलोस्टेरिक नियंत्रण का एक व्यवहारिक तंत्र प्रदान करता है। अध्ययन के परिणाम 2D NMR का उपयोग कर प्रयोगात्मक समूह के सहयोग से सत्यापित किए गए हैं। इस अध्ययन से अपेक्षा है की यह एलोस्तेरी के लाभ को प्राप्त करने के लिए अदभुद दवाएं डिज़ाइन करने में सहायक रहेगा ।

अध्याय ५ कम्प्यूटेशनल स्ट्रक्चर आधारित दवा डिजाइन में शामिल सभी प्रमुख कदमों को करने में सक्षम नए, पहले और उपयोगकर्ता के अनुकूल एंड्रॉइड एप्लिकेशन (ऐप।) का एक नया वर्णन करता है। एप्प गूगल प्ले स्टोर पर निर्बाध रूप से उपलब्ध कराया गया है और उपयोगकर्ता एक अनुकूल वेब पोर्टल का उपयोग करते हुए परिणामों को डेस्कटॉप पर डाउनलोड कर सकता है।

अध्याय ६, अध्याय २ में किए गए कार्यों का विस्तार है। इसका उद्देश्य परिभाषित प्रोटीन लक्ष्य के लिए बेहतर बाध्यकारी के लिए एक मचान (saffold) को स्पष्ट करने के लिए एक नई पद्धति विकसित करना है। यह पद्धति अभी विकासशील क्रम में है, लेकिन आशाजनक परिणाम दिखाती है।

अंत में, अध्याय ७ इस अध्यन का सार और दृष्टिकोण प्रस्तुत करता है जो इस थीसिस कार्य से विकसित हुए हैं। यह प्रस्तुत किए गए कार्य की योग्यताओं और सीमाओं पर भी चर्चा करता है। साथ ही, भविष्य में किए जा सकने वाले अनुसन्धान कार्य पर भी विचार किया गया है।

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