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A BRIEF REVIEW ON ROLE OF COMPUTER AIDED DRUG DESIGN IN THE DEVELOPMENT OF VITAL TYROSINE KINASE INHIBITOR COMPOUNDS

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Abstract:

Computer-aided drug design has developed as a prevailing technique playing a vital role in the progress of new drug molecules over the past couple of decades. There are certain drugs which was designed, optimized, synthesized, patented and marketed by the application of computer aided drug designing. This review focussed on the reputation of computer aided drug design in the development of vital tyrosine kinase inhibitor compounds for the treatment of different type of cancers. Drugs with Tyrosine kinase inhibitory activity involves Receptor Tyrosine Kinase Inhibitors (RTK inhibitors), Non-Receptor Tyrosine Kinase Inhibitors (NRTK inhibiotors), and Multi-targeted Tyrosine Kinase Inhibitors. [(1)]

Key Words: *Computer Aided Drug Design, Receptor Tyrosine Kinase Inhibitors, VEGFR*

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INTRODUCTION:

COMPUTER AIDED DRUG DESIGN

Computer Aided Drug Design (CADD) is a multidisciplinary tactic which utilizes computational methods and tools to design, optimize and predict the behaviour of potential drugs. CADD help to combine computer science, biology, chemistry and pharmacology to hasten the drug discovery process. Over the past couple of decades computer aided drug design has emerged as a influential technique playing a major role in the development of new drug molecule.

The main objectives of CADD involves lead discovory, lead optimization, Clinical development, Post marketing surveillance etc..Lead discovery involves identification of hits and Lead generation. Lead optimization involves Struture Activity Relationship (SAR) Analysis, Quantitative Structure Activity Relationship Analysis (QSAR), Pharmacophore modelling, Docking and scoring. Post-Marketing Surveillance mainly involves Pharmacovigilance.[2]

The common CADD techniques includes structure based drug designing (Docking, scoring and virtual screening), Ligand based drug designing (Pharmacophore modelling, QSAR analysis, Molecular similarity analysis), Molecular Modeling (Moecular mechanics, Molecular dynamics, Quantum mechanics), Chemoinformatics (Compound clustering, Compound filtering, Compounds database management), Machine learning (Supervised learning and unsupervised learning, and deep learning), and other technuques such as Fragment based design, Denovo desing and retrosynthetic analysis.

Most popular softwares for molecular docking comprises Commercial softwares, Open-Source software, and web based tools. Commercial software includes Glide (Schrodinger), Surflex-Dock (Tripos), FlexX (BioSolvelT), Dock (UCSF), and Molecular Operating Environment. Open-source software includes AutoDock (Scripps Research Institute), AutoDock Vina (Scripps Research Institute), Dock (UCSF), PLANTS (University of Freiburg), and Rosetta Ligand (University of Washington). Web based tools involves Dock Blaster (UCSF), Autodock Vina Server (Scripps Research Institute), and SwissDock (Swiss Institute of Bioinformatics).

There are several applications of CADD in the arena of drug discovery and development. Certain significant applications are lead discovery, drug design, Pharmacokinetics and Pharmacodynamics, Personalized medicine and other applications. In lead discovery procedure CADD keep role in virtual screening, which is the identification of important lead compound from large databases. High throughput screening is the quick testing of great number of compounds for biological activity. Lead optimization is the method to enhance the potency, selectivity and pharmacokinetic properties of the lead molecule. Structure based drug design, ligand based drug design and De novo design are another important application of CADD. Pharmacokinetc and Pharmacodynamic application consist of ADME prediction, which supports to predict absorption, distribution, metabolism and excretion properties of a drug molecule. Another application, is toxicity prediction. Another imperative applications are in personalized medicine, which consist of Genomic analysis: analysing genomic data to recognize important targets for therapy, Proteomic analysis: analysing proteomic data to find potential targets for therapy, and Precision medicine: Emerging personalized therapies based on an individual's molecular profile and also genetic data. Other applications comprises vaccine design by means of computational process, Cancer research with CADD, to find important targets for neurological disorders and also the determination potential targets for infectious diseases.[3]

TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors (TKIs) are a category of drugs that inhibit the action of tyrosine kinases enzyme. This enzymes involved in the control of cell growth, division, and also signaling. TKIs are a kind of targeted therapy which can be used for the treatment of cancer.

TKIs act by inhibiting the signal transduction pathways of protein kinases. In certain types of cancer cells, tyrosine kinases found at high levels or might be too active. So Blocking of these enzymes result in reduced growth of cancer cells.

TKIs may be used alone or may be in amalgamation with conventional chemotherapeutics. Certain TKIs can inhibit more than one type of tyrosine kinase, and are known as multi Tyrosine Kinase Inhhibitors. Receptor Tyrosine kinase inhibitors mainly involves EGFR inhibitors, VEGFR inhibitors, HER2 inhibitors, PDGFR inhibitors etc..and Non receptor Tyrosine Kinase Inhibitors involves BCR-ABL inhibitors, SRC inhibitors etc..[4]

Examples of TKI drugs and their targets

- **Sunitinib malate:** Targets VEGFR
- **Erlotinib:** Target EGFR
- **Axinitib**: Targets VEGFR
- **Imatinib :** Targets BCR-ABL, KIT, and PDGFR
- **Gefitinib :** Targets EGFR
- **Deucravacitinib:** Targets tyrosine kinase

- **Afatinib:** Targets EGFR

SUNITINIB MALATE

Sumatinib maleate is a compound which possess Tyrosine Kinase inhibitory activiy. Certain cancer types such as intestinal, pancreatic, and renal cancer are treated with the use of this drug. Furthermore, it is also used to treat patients who have a high chance of kidney cancer returning following kidney surgery. Sunitinib obstructs or reduces the growth of cancerous tumors. It also functions by reducing the rate at which new blood vessels form inside the tumor.

Sunitinib malate is an oral receptor TKI that inhibits the tyrosine kinases of VEGF receptor 1 (VEGFR-1), VEGFR-2, VEGFR-3, PDGF receptor-a (PDGFR-a), PDGFR-b, and another receptor. In almost every face of cell biology, protein kinases are essential regulatory enzymes. Imperative functions in angiogenesis and vasculogenesis are played by VEGFR1 and VEGFR2. The pericytes that envelop capillary endothelial cells contain PDGFRb, which is essential for maintaining the stability of the vascular endothelium. Sunitinib reduces signaling via VEGFR1, VEGFR2, and PDGFRb to prevent angiogenesis. In January 2006, the U.S. FDA initially authorized sunitinib for advanced RCC. In addition to patients with advanced pancreatic neuroendocrine tumors and gastrointestinal stromal tumors that are resistant to or intolerant of imatinib, it has since received approval for this indication on a global scale.

When FGFR1's tyrosine kinase domain is complexed with two oxindole inhibitors, crystal structures reveal that the oxindole occupies the site where ATP's adenine binds, while the moieties extending from the oxindole contact residues in the hinge region between the two kinase lobes,Two hydrogen bonds—one between the oxindole's NH and the carbonyl oxygen of Glu-562 and the other between the oxindole's C=O and the amide nitrogen of Ala-564—allow it to interact with the protein backbone of FGFR1K. N-1 and N-6 of the ATP adenine form hydrogen bonds with the same two FGFR1K backbone groups. Initiating the sunitinib discovery effort was oxindole 33, an inhibitor of many RTKs. Later SAR research bring about in the identification of sunitinib.

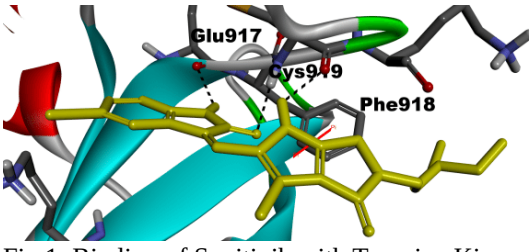
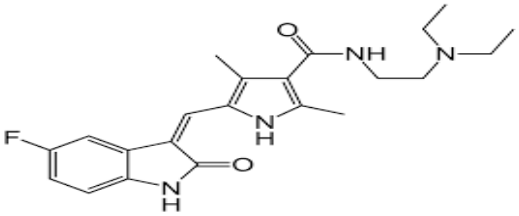


Fig 1: Binding of Sunitinib with Tyrosine Kinase



Structure of Sunitinib

Structure of Sunitinib consist of following parts.

1) Heteroaromatic system (occupy the hinge region)
2) Central aromatic linker (occupy the linker region)
3) HBA-HBD (occupy the DFG domain)
4) Terminal hydrophobic tail (occupy the hydrophobic allosteric pocket).[5]

ERLOTINIB

Erlotinib is an important Tyrosine Kinase inhibitor employed as the treatment option for metastatic cancer, which has already spread non-small cell lung cancer. This medication is mostly used in patients who have certain types of abnormal epidermal growth factor (EGFR) gene mutations.

Saeideh Mohammadzadeh-Asl and co-workers in 2020 has executed Molecular docking analysis to recognize the interaction of erlotinib and the EGFR extracellular domain. Molecular docking study was accomplished by using Autodock4.2 package. For this purpose, the crystal structure of the extracellular domain of the EGFR, PDB code: 1YY9 was downloaded from Protein Data Bank. In the next step, the 3-Dimensional molecular structure of erlotinib was designed. Then the optimization of structure was done by Gaussian 03 package. After that a blind docking simulation has conducted by using the defined grid box of 126 × 126 × 126 Å (spacing parameters: 0.505 Å) to determine the greatest probable binding domain. Following that, the lowermost binding conformation was utilized for subsequent simulation. To explore the interaction of erlotinib along with defined domain more cautiously, an extra molecular docking simulation was precisely run on the binding domain with grid box of 70 × 70 × 70 Å (spacing parameters: 0.375 Å). Polar hydrogen atoms, Gasteiger charges, and Kollman charges were applied to the target molecule in all calculations. Also, the rotatable bonds of erlotinib were documented in all simulations. In entire simulation runs to predict the binding site, Lamarckian genetic algorithm method was applied. In order to picture the interaction in this study UCSF Chimera was used.

Molecular docking simulation is a finest method for estimate of the probable interactions amongst a small ligand and target molecules. The blind docking outcomes displayed that erlotinib has a greater affinity to bind to domain II of EGFR

extracellular province with the binding energy of −4.7 kcal/mol. To determine the interaction among erlotinib EGFR complexes more accurately, another simulation was employed by Autodok4.2 package. Arg 285 residues performs a critical role in the binding of erlotinib to domain II in EGFR. The complete study also designated that functional trails of erlotinib structure could create a hydrogen bonds network amongst free amino group of Arg285 residue and oxygen containing functional groups. The binding energy for this interaction was −10.7 kcal/mol, which is appropriate for binding of erlotinib to domain II in EGFR. Domain II in EGFR is a dimerization arm that has a substantial role in all contact across the dimer interface mediated. Consequently, disruption of this domain activity by erlotinib could effectively encourage functional changes in EGFR.[6]

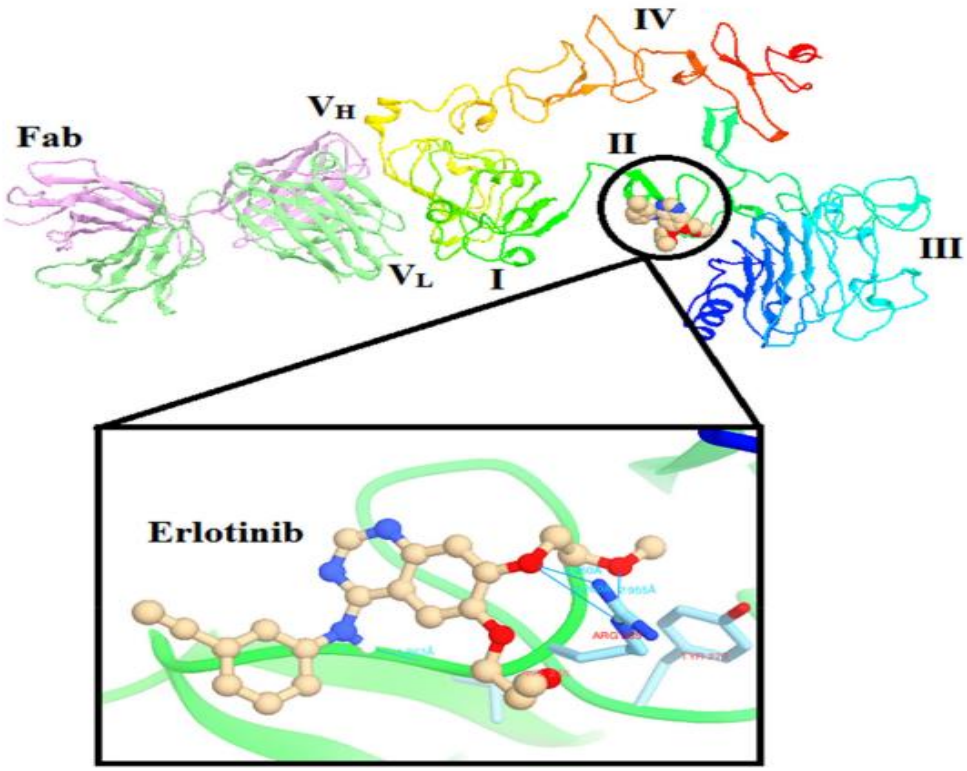
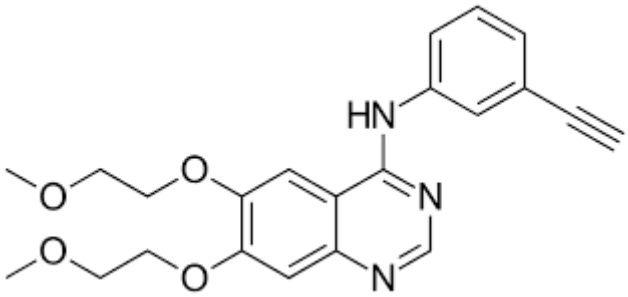


Fig 2: Molecular simulation of interaction between Erlotinib and EGFR



Structure of Erlotinib

AXINITIB

Axitinib come under the class of medication named Kinase inhibitors, which possess interaction with Vascular endothelial growth factor receptor (VEGFR). Its Activity primarily due to inhibition of abnormal protein that signals cancer cells to multiply. It is generally used for treatment of advanced renal cell carcinoma.

Hydrogen bonding and steric interactions were observed in ligand map of Axinitinib. Hydrogen bonding occurred with Gly 65(G), HOH 132(G), HOH 126(F), Tyr 21(F) and HOH 164(G). The strength of the bonds are -2.50, -0.23, -1.48 , -2.50 and -2.50 Kcal/mol respectively. These interactions were favourable due to negative free energy and appropriate bond lengths. Steric interactions occurred with Gln 89(E), Met 81(E), His 90(E), Ile 83(E), Lys 48(E), Tyr 21(F), Leu 66(G) and Asp 63(G). The total contributions from the van der Waals forces and atomic contact energy (ACE) to the best binding energy (minimum energy) and the global binding energy is -22.37 Kcal/mol. The negative value of the binding energy shows that the axitinib can selectively inhibit VEGF.[7]

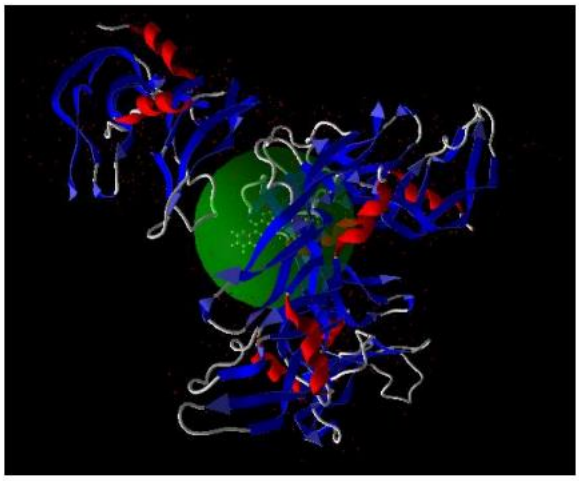


Fig 3: Axitinib docked with vascular endothelial growth factor (VEGF)

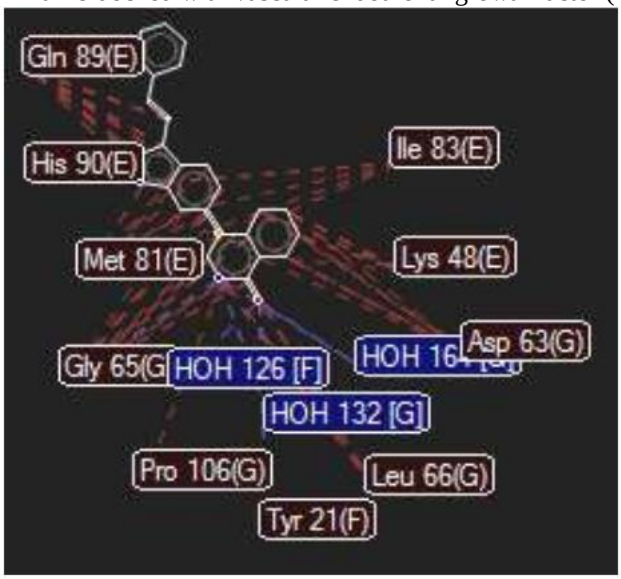


Fig: Interactions of axitinib with vascular endothelial growth factor (VEGF)

IMATINIB

Imatinib is a revolutionary drug in treating Chronic Myeloid Leukemia, whose development was supported by CADD. By targeting the BCR-ABL kinase, imatinib demonstrates how computational techniques and softwares can lead to potent and selective inhibitors[8]

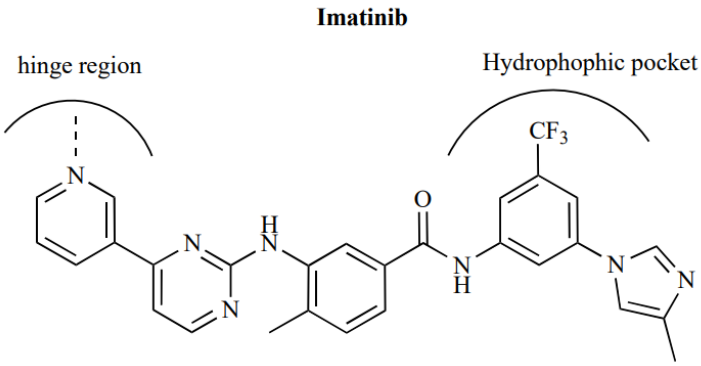


Fig 4: Interaction of Imatinib with Tyrosine Kinase inhibitor

GEFITINIB

Gefitinib is a prescription medication employed to treat a specific type of advanced or metastatic non-small cell lung cancer (NSCLC) by inhibiting certain proteins that cause cancer cell growth. It is provided for patients with specific mutations in their epidermal growth factor receptor (EGFR) genes and is taken orally once a day.

The superposition of the Induced Fit Docking generated gefitinib model illustrates that gefitinib can make a good binding interation with the receptor. The ligand make H-bond interactions with the EGFR through residue Met793. There is a distinct H-bonds in the 1XKK/gefitinib complex involved residues Lys745 and Asp855. The RMSD of all heavy atoms (excluding the hydrogen atoms) between the IFD-generated model and the native gefitinib is 2.99 A˚. The GlideScore for the gefitinib binding is 12.52 kcal/mol. It possess the interactions with Lys745 and Asp855.[9]

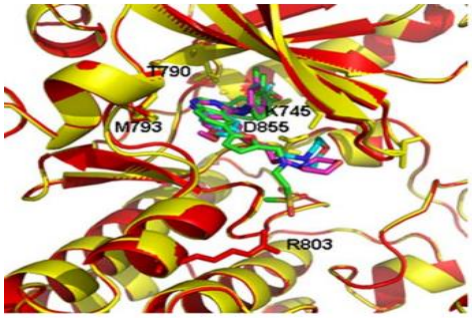


Fig 5: Interaction of Gefitinib with Tyrosine Kinase receptor

DEUCRAVACITINIB

Deucravacitinib (Sotyktu) is a novel and extremely specific oral inhibitor targeting tyrosine kinase 2 (TYK2). Its mechanism of action comprises an allosteric binding, to the catalytically inactive pseudokinase domain of TYK2, which stabilizes an inhibitory contact between the catalytic and regulatory domains. Deucravacitinib successfully interacts with the ATP-binding site of four JAK kinases and also TYK2 pseudo kinase via hydrogen bond formation, electrostatic attraction, and especially, van der Waals interaction. The calculated binding affinity establishes a reduction in the TYK2JH2-deucravacitinib complex owing to an increased favorable intermolecular electrostatic influence. deucravacitinib displays greater selectivity for the TYK2 pseudokinase domain than the other four JAKs. The interaction with DPG motif residues and the hinge region causes the stabilization of deucravacitinib via vigorously formed hydrogen bonds. The interaction of Deucravacitinib with the hydrophobic catalytic region triggered the ATP-binding site to adopt a closed conformation, thus minimizing protein movement at the glycine loop of the JAK pseudokinase protein.[10]

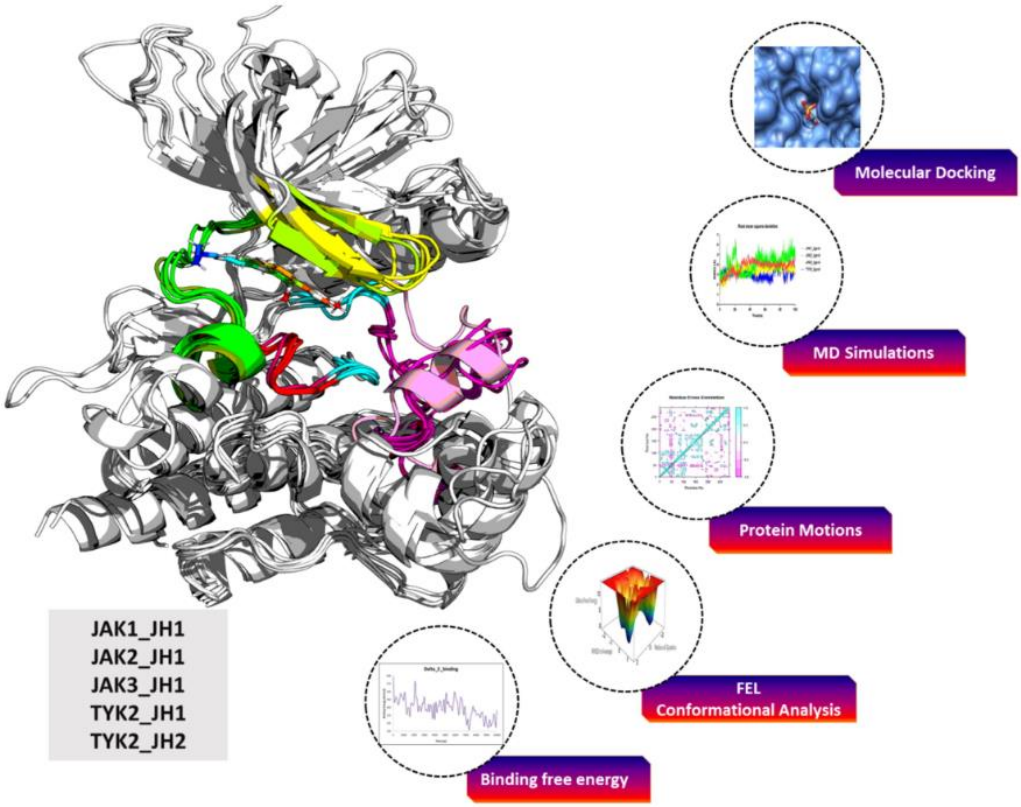


Fig 6: Interaction of Deucravacitinib with Tyrosine Kinase receptor

AFATINIB

Afatinib is a tyrosine kinase inhibitor used for dealing non–small cell lung carcinoma (NSCLC). Afatinib is intended to cause irreversible inhibition of the ErbB family of tyrosine kinases. The FDA has provided approval for afatinib to treat locally advanced or metastatic NSCLC, which is characterized by nonresistant epidermal growth factor receptor (EGFR) mutations. Furthermore, it is a second-line option for advanced squamous NSCLC. It is being explored as a monotherapy for individuals with HER2-positive breast cancer.[11]

Using Schrodinger's molecular docking tools and computational simulations, the study of Afatinib's interaction with potential and pharmacokinetic characteristics is possible. Afatinib displays stronger affinity for EGFR and ALK, which suggest its therapeutic potential could be optimized based on target expression within the tumor microenvironment

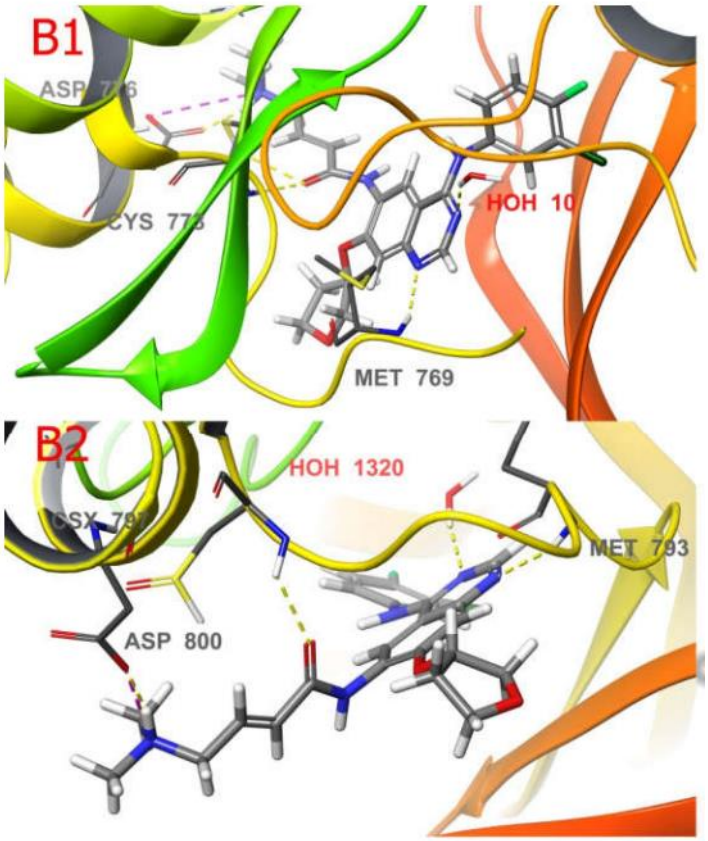


Fig 7: Binding orientation of Afatinib with the crystal structure of EGFR.

It is possible to evaluate the molecular interactions and pharmacokinetic properties of Afatinib with the selected target proteins such as ALK, KRAS, EGFR, PP2A, ROS1 and VEGF by using the Schrodinger Maestro platform. Molecular docking and ADME analyses can be conducted utilizing the GLIDE and QikProp modules respectively. There is a strong binding affinities of Afatinib to the target proteins, facilitated by hydrogen bonding, π–π stacking and , polar interactions. The predicted ADME parameters and also Lipinski's rule scores were found to be within acceptable limits, underscoring the drug's potential drug-likeness. Afatinib exhibited low interaction energies with the lung cancer-related proteins, suggesting effective inhibitory activity. Among these six proteins, EGFR and ALK established the highest binding affinities, followed by VEGF, ROS1, KRAS and PP2A respectively. These results point out that Afatinib's promise as a candidate for targeted anticancer therapy and also the data support the strategic use of Afatinib based on the expression levels of these target proteins within the tumor microenvironment, and potentially aiding in personalized treatment approaches.[12]

CONCLUSION:

This review highlights the substantial role of computer-aided drug design in emerging vital tyrosine kinase inhibitors for the treatment of various cancers. It reveals how these drugs interact with their corresponding receptors and underscores their therapeutic importance. Moving forward, it is crucial to explore strategies that target multiple drug pathways to attain greater treatment efficacy.

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