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Computational molecular docking studies on anticancer drugs

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ABSTRACT

Objective: Cancer can be described as the uncontrolled growth of abnormal cells. Lung cancer is one of the commonest malignant neoplasms all over the world. Oncogenic fusion genes consisting of EML4 and anaplastic lymphoma kinase (ALK) are present in non–small–cell lung cancers, representing 2 to 7% of such tumors. ALK proteins play a vital role in deactivating the apoptosis process in cancer disease. Some of the most commonly used non–small–cell lung cancer drugs are Crizotinib, Sunitinibmalate, Tandutinib etc..., Non–small–cell lung cancer Cells need anaplastic lymphoma kinase (ALK) to cell growth and proliferation the role of ALK in malignant proliferation and as a valid drug target. These drugs mainly work against the effects of ALK on these cells. **Methods:** The Protein– Ligand interaction plays a significant role in structural based drug designing. In our research work we have taken the Human anaplastic lymphoma kinase (ALK) and the commercially available drugs against non–small–cell lung cancer. The ALK was docked to the above said drugs and the energy value obtained as follows Crizotinib(–9.86), Sunitinib malate(–8.26), Tandutinib(–8.05) using the Argus Lab docking software. **Results:** Depending on the energy values we have chosen the best two drugs they are Crizotinib(–9.86) and Sunitinib malate(–8.26). We tried to improve the binding efficiency and steric compatibility of the two drugs namely Crizotinib(–9.86) and Sunitinib malate(–8.26). Several modifications were made to the probable functional groups which were interacting with the receptor molecule. Analogs of this drug molecule were prepared using ACD ChemSketch and docked using Argus Lab docking software. **Conclusions:** Crizotinib Analog 2 and Sunitinib malate analog 1 were detected with significant energy values and probable lead molecules. The Modified drugs was sketched using Chemsketch were found to be better than the conventional drugs available. Further from this work we can improve the steric compatibility and then ADME/T properties of the Analogs can be analyzed using Inslico ADME/T tools available.

1. Introduction

The vast majority of primary lung cancers are carcinomas of the lung, derived from epithelial cells. Lung cancer, the most common cause of cancer–related death in men and women, is responsible for 1.3 million deaths worldwide annually, as of 2004^[1]. The most common symptoms are shortness of breath, coughing (including coughing up blood), and weight loss^[2]. Epidermal growth factor receptor (EGFR), a receptor tyrosine kinase, is frequently overexpressed in non–small cell lung cancer (NSCLC). These receptors play an important role in tumour cell survival and activated phosphorylated EGFR results in the phosphorylation of downstream proteins that cause cell proliferation, invasion,

metastasis, and inhibition of apoptosis. Expression appears to be dependent on histological subtypes, most frequently expressed in squamous cell carcinoma but also frequently expressed in adenocarcinomas and large cell carcinomas.^[3]

Activating mutations or translocations of the anaplastic lymphoma kinase gene (ALK) have been identified in several types of cancer, including anaplastic large–cell lymphoma^[4], neuroblastoma^[5,6], inflammatory myofibroblastic tumor^[7], and non–small–cell lung cancer^[8]. In non–small–cell lung cancer, EML4–ALK is an aberrant fusion gene that encodes a cytoplasmic chimeric protein with constitutive kinase activity. Multiple distinct EML4–ALK chimeric variants have been identified, representing breakpoints within various EML4 exons, all of which are transforming in vitro^[9,10]. In preclinical analyses of more than 600 cell lines derived from human cancers, an investigational selective ALK inhibitor specifically reduced the proliferation of cells carrying genetic alterations in ALK, supporting the role of ALK in malignant proliferation

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and as a valid drug target^[11]. Crizotinib (PF-02341066, Pfizer) and Sunitinib malate is an oral ATP-competitive selective inhibitor of the ALK and MET tyrosine kinases that inhibits tyrosine phosphorylation of activated ALK at nanomolar concentrations^[11,12].

Computational Biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational Drug Design (RDD) helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds^[12,13]. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor. Docking is the process by which two molecules fit together in 3D space.

2. Materials and methods

2.1. Tools and materials used

For our present study we used biological databases like PubChem, Drug Bank, PDB (Protein Data Bank) and software's like Arguslab, Weblab viewer lite program, molinspiration, FROG^[13]ADME Tox. Drug Bank is a unique Bioinformatics/Cheminformatics resource that combines detailed drug (i.e. chemical) data with comprehensive drug target (i.e. protein). Each Drug Card entry contains greater than 80 data fields with half of the information being devoted to drug/ chemical data and the other half devoted to drug target or protein data^[14]. The PDB (Protein Data Bank) is the single worldwide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL) in 1971^[15]. It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc. Molinspiration is an independent research organization focused on development and application of modern cheminformatics techniques, especially in connection with the internet. Arguslab offers quite good on-screen molecule-building facilities, with a moderate library of useful molecules. It is a free molecular modeling package that runs under Windows^[16]. The program reads in molecular coordinate files and interactively displays the molecule on the screen in variety of representations and color schemes. RASMOL [Raster Display of Molecules] is a molecular graphics program intended for the structural visualization of proteins, nucleic acids and small biomolecules. The program reads in molecular coordinate files and interactively displays the molecule on the screen in variety of representations and color schemes^[17]. ADME/TOX is an acronym in pharmacokinetics and pharmacology for absorption, distribution, metabolism, and excretion, and describes the deposition of a pharmaceutical compound within an organism. The four criteria all influence the drug levels and kinetics of drug exposure to the tissues and hence influence the performance and pharmacological activity of the compound as a drug (<http://www.pharma-algorithms.com/webboxes/>). ACD/ChemSketch is the powerful all-

purpose chemical drawing and graphics package from ACD/Labs developed to help chemists quickly and easily draw molecules, reactions, and schematic diagrams, calculate chemical properties, and design professional reports and presentations. ACD/ChemSketch can convert SMILES notations to Structure and vice versa.

2.2. Methodology

Bioinformatics is seen as an emerging field with the potential to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace.

2.2.1. Protein preparation and optimization

The crystal structure of Anaplastic lymphoma kinase (ALK) Taken in this study was retrieved from RCSB protein data bank (<http://www.rcsb.org/pdb>). The missing residues were corrected and the complexes bound to receptor molecule removed using Accelrys Discovery Studio Visualizer 2.5.5. The PDB files were energy minimized using ArgusLab. The non-essential water molecules were removed and polar hydrogens were merged.

2.2.2. Ligand preparation and optimization

Using Chemsketch Software the structures of the drugs and analogs were sketched draw and generated their MOL File followed subsequent generation of their 3-D structures by using tool Weblab viewer lite program a molecule format converter in to PDB. Appropriate force field applied to them and then optimization was carried out using Argus Lab 4.0 (<http://www.arguslab.com>). The docking analysis of Crizotinib, Sunitinibmalate and their analogs with Anaplastic lymphoma kinase receptor was carried by Argus lab docking software.

2.2.3. Docking simulations

The docking analysis of Crizotinib, Anaplastic lymphoma kinase receptor and their analogs with Anaplastic lymphoma kinase receptor was carried by Argus lab docking software. Docking allows the scientist to virtually screen a database of compounds and predict the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an Anaplastic lymphoma kinase receptor fit together and docks to each other well. The molecules binding to a receptor, inhibit its function, and thus act as drug^[18]. The collection of Crizotinib, Sunitinibmalate, its derivatives and receptor complexes were identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations. All the parameters used for Arguslab docking are selected by default.

3. Results

Docking results tabulated between Anaplastic lymphoma kinase receptor and the conventional drug Crizotinib (Table I) as well as with the modified drugs are shown below along with the changes or modification within them.

Docking results tabulated between Anaplastic lymphoma kinase receptor and the conventional drug Sunitinibmalate (Table II) as well as the modified drugs are shown below along with the changes or modifications within them

Based on the literature it has been shown clearly that the drugs Crizotinib and Sunitinibmalate have been used to target the Anaplastic lymphoma kinase receptor. Crizotinib and Sunitinibmalate on docking with Anaplastic lymphoma kinase receptor produced an energy value of -9.85 and -8.25 respectively.

Table 1. Docking results of anaplastic lymphoma kinase receptor with crizotinib analogs

COMPOUND	E-VALUE
CRIZOTINIB	-9.85
ANALOG 1	-10.38
ANALOG 2	-11.21
ANALOG 3	-10.65
ANALOG 4	-10.13
ANALOG 5	-9.18
ANALOG 6	-8.90
ANALOG 7	-10.14

Table 3. adme result based on the rule of five formulations of crizotinib analogs

COMPOUND	H-BOND DONARS	MOLECULAR WEIGHT	Log P	H-BOND ACCEPTORS
CRIZOTINIB	1	446.7	3.180000	7
ANALOG 1	1	486.8	5.790000	6
ANALOG 2	2	474.7	3.710000	7
ANALOG 3	2	462.7	2.610000	8
ANALOG 4	1	442.7	3.240000	7
ANALOG 5	1	463.2	3.640000	7
ANALOG 6	1	446.7	3.180000	7
ANALOG 7	1	446.7	3.180000	7
ANALOG 8	2	444.7	2.610000	8
ANALOG 9	1	446.7	3.180000	7

Table 4. adme result based on the rule of five formulations of sunitinibmalate analogs.

COMPOUND	H-BOND DONARS	MOLECULAR WEIGHT	Log P	H-BOND ACCEPTORS
SUNITINIBMALATE	1	429.7	3.640000	7
ANALOG 1	1	464.2	2.610000	7
ANALOG 2	1	443.7	3.640000	7
ANALOG 3	1	522.6	5.790000	7
ANALOG 4	1	555.6	5.290000	7
ANALOG 5	2	445.7	3.340000	8
ANALOG 6	2	459.7	3.280000	8
ANALOG 7	1	457.7	3.180000	7
ANALOG 8	1	457.7	2.610000	7
ANALOG 9	1	447.7	3.240000	7
ANALOG 10	1	447.7	3.240000	7
ANALOG 11	2	480.2	2.610000	8

Table 2. Docking results of anaplastic lymphoma kinase receptor with sunitinibmalate analogs

COMPOUND	E-VALUE
SUNITINIBMALATE	-8.25
ANALOG 1	-10.85
ANALOG 2	-8.89
ANALOG 3	-9.34
ANALOG 4	-8.87
ANALOG 5	-9.98
ANALOG 6	-8.89
ANALOG 7	-8.82

It was observed using RasMol that the carbonyl groups present in the drug was the site of binding to the receptor and methyl group present in the probable functional groups, which resulted in a decrease in the energy values. These modifications were made using ChemsKetch and the energy values were calculated using Argus lab. This way the pharmacophoric part of the drug was partially identified.

Docking results of the drug and its derivatives via Arguslab docking software reveals that the e-value of crizotinib analog 2 (-11.21) is better as compared to that of original (-9.86) and e-value of sunitinibmalate analog 1 (-10.85) is better as compared to that of original (-8.26). An analog with additional CH₃ atom (crizotinib analog 2) was prepared virtually using ChemSketch. This particular analog showed an increase in the energy values (-11.21) and an analog in which methyl groups are added (sunitinibmalate

analog 1) was prepared virtually using ChemSketch. This particular analog showed an increase in the energy values (-10.85) which means the analog (crizotinib analog 2) and (sunitinibmalate analog 1) was more compatible with the receptor than its predecessor. However, the binding site of the analog was similar to that of its predecessor, which means that functional groups involved were the same and by preparing the analog only the steric compatibility was increased.

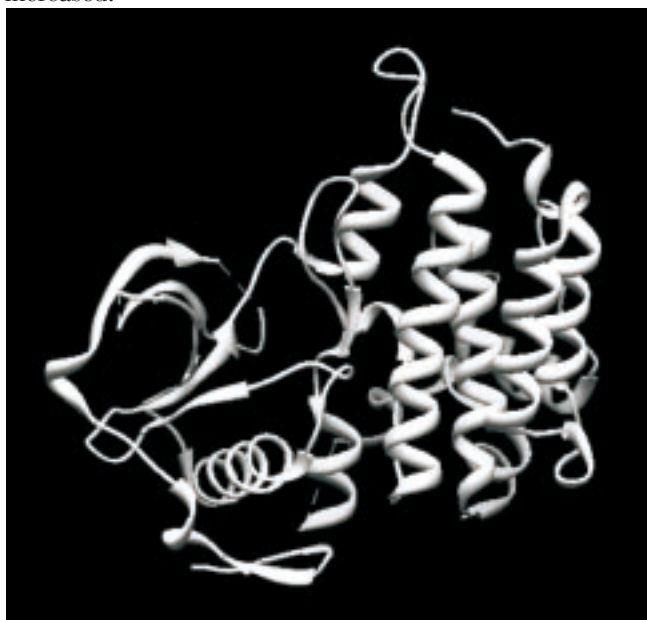


Figure 1. Crystal Structure of Anaplastic lymphoma kinase receptor

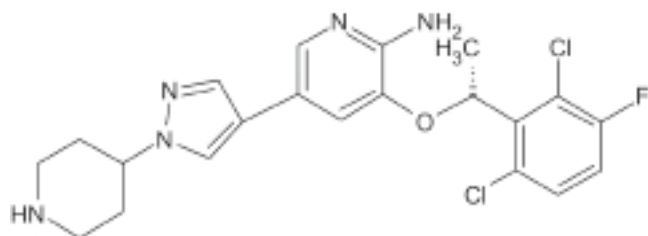


Figure 2. Standard ligand (crizotinib) for alk receptor.

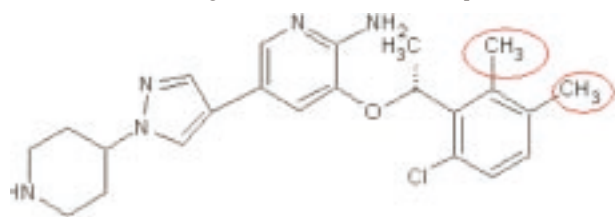


Figure 3. Crizotinib analog 2

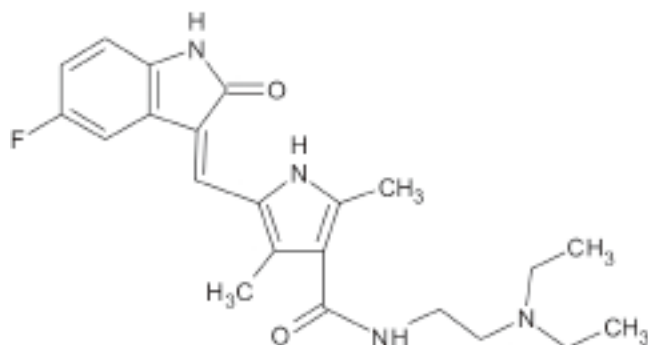


Figure 4. Standard ligand (sunitinibmalate) for alk receptor.

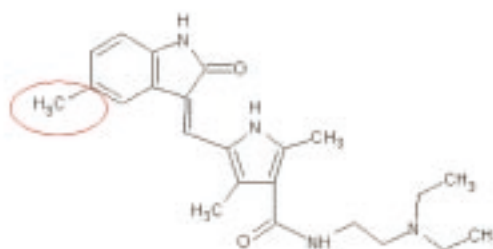


Figure 5. Sunitinibmalate analog 1

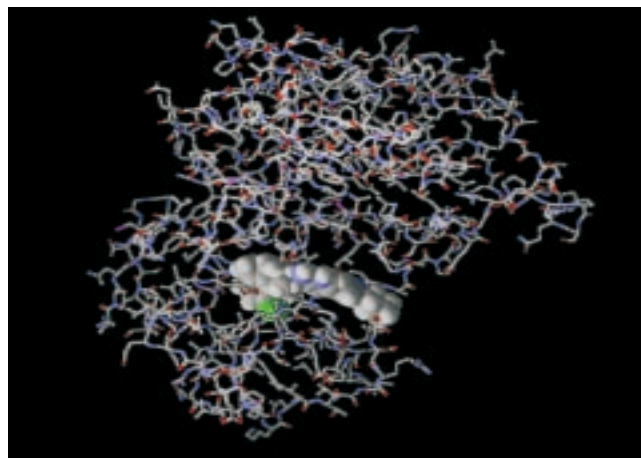


Figure 6. Docking of crizotinib analog 2 with Anaplastic lymphoma kinase receptor using ArgusLab.

4.1. ADME and Lipinski's Rule of five

The analogs were drawn in 2D format in the online available portal (<http://preadmet.bmdrc.org/>) and were then subjected to ADME (Absorption, Distribution, Metabolism and Excretion) analysis. Hit/lead compounds can be identified either through high-(medium) throughput screening approaches and/or using virtual screening computations. In all situations, a compound collection is screened with the goal of finding molecules that could enter the drug discovery process or that could help to explore molecular mechanisms; yet, it is well documented that to avoid costly failures in screening projects, ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties should be considered at an early stage^[19]. The analogs were drawn in 2D format in the online portal (<http://www.organic-chemistry.org/prog/peo/>) and then subjected to Lipinski's Rule of Five. The Drug-likeness of the analogs were checked against 'The Lipinski Rule of Five', using the Lipinski Filter facility available online at Supercomputing Facility for Bioinformatics & Computational Biology, Indian Institute of Technology, New Delhi, India. The Lipinski's rule, formulated by Christopher A. Lipinski in 1997, is a rule to evaluate whether a given chemical compound with a certain pharmacological, biological and ADME (absorption, distribution, metabolism and excretion) activity, has the potential that would likely make it orally active drug in humans^[20]. The ADME profile and toxicity analysis of Crizotinib and Sunitinibmalate analogs.

The Protein-Ligand interaction plays a significant role

in structural based drug designing. In the present work we have taken the Anaplastic lymphoma kinase receptor (ALK) and identified the drugs that were used against Lung Cancer. When the receptor was docked with the drugs the energy value obtained was; Crizotinib(−9.86) and Sunitinib malate(−8.26). When the modified drugs were docked against the same receptor the energy value obtained was crizotinib analog 2 (−11.21), sunitinibmalate analog 1(−10.85) from this we can conclude that some of the modified drugs are better than the commercial drugs available in the market. In future research work the ADME/T (Absorption, Distribution, Metabolism, Excretion/Toxicity) properties of these compounds can be tested in wet lab and research can be proceed for clinical trials. In future research work can be used further in clinical trials to test it effectiveness and for social benefit thus reducing the time and cost in drug discovery process.

Conflict of interest statement

We declare that we have no conflict of interest.

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