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Computer aided drug designing (CADD) for EGFR protein Controlling lung cancer

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ABSTRACT

Lung cancer is one of the commonest malignant neoplasms all over the world. Lung cancer cells grow due to epidermal growth factor receptors (EGFRs) protein. The Protein- Ligand interaction plays a significant role in structural based drug designing. In the research work Human EGFR was taken as a protein and the commercially available drugs as a ligand(such as Gemzar, Gefitinib, Tarceva).The receptor was docked to the above said drugs and the energy value of the docked drugs are GEMZAR(197), Gefitinib(268), Tarceva(248) using the vega zz docking software. Depending on the energy values the best two drugs namely Gefitinib and Tarceva. An attempt was made to improve the binding efficiency and steric compatibility of the two drugs were chosen. Several modifications were also made to the probable functional groups which were interacting with the receptor molecule. Analogs of this drug molecule were prepared using ACD ChemSketch in MOL format converted to 3D structure using Weblab viewer lite program then it was docked using vega zz docking software. Gefitinib Analog 2(281) and Tarceva Analog 7 (260), were detected with significant energy values and probable lead molecules. The Modified drugs were found to be better than the conventional drugs available.

Keywords: Lung cancer, Chemsketch, Docking, vega zz , ADME/T tools. Rasmol, Kegg. Weblab viewer lite program.

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].

Initial studies with small molecules designed to inhibit the tyrosine kinase (TK) domain of the EGFR, such as gefitinib (Iressa) and erlotinib (Tarceva), demonstrated biologic and clinical activity in only a relatively limited subset of lung cancers[4]. Further investigation demonstrated that the highest response rates were seen in patients with somatic mutations within the EGFR-TK domain, 90% of which involve a relatively small number of amino acids within a specific region (exons 19 and 21)[5]. Erlotinib (Tarceva) is a drug, taken orally as a tablet, which interferes with the activity of EGFR. Rash is the most common side effects of erlotinib (Tarceva) in the majority of patients. This resembles acne and primarily involves the face and neck. It is self-limited and resolves in the majority of cases, even with continued use. Interestingly, some clinical studies have indicated a correlation between the severity of the skin reactions and increased survival though this has not been quantitatively assessed[6]. The *Journal of Clinical Oncology* reported in 2004 that "cutaneous [skin] rash seems to be a surrogate marker of clinical benefit, but this finding should be confirmed in ongoing and future studies"[7]. The newsletter *Lung Cancer Frontiers* reported Oct(2003), That "Patients with moderate to severe cutaneous reactions [rashes] have a far better survival, than those with only mild reactions and much better than those with no cutaneous manifestations of drug effects." The side effects of these drugs make the need for the necessity of new improved drugs[8].

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[9]. Docking is the process by which two molecules fit together in 3D space.

MATERIALS AND METHODS

2. Tools and materials used

For the present study we used Bioinformatics tools, biological databases like PDB (Protein Data Bank) ,kegg, PubMed, Drug Bank[13,11], Weblab viewer lite program, mobile portal-admetox, and bioinformatics tools ACD ChemSketch. 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.

VEGA ZZ, is an Interactive Molecular Graphics program for calculating and displaying feasible docking modes of pairs of protein and ligand molecules.The PDB (Protein Data Bank) is the single worldwide archive of Structural data of Biological macromolecules,established in Brookhaven National Laboratories (BNL) in 1971[17]. It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc.

KEGG DRUG

KEGG is a comprehensive drug information resource for approved drugs in Japan, USA, and Europe that are unified based on the chemical structures and/or the chemical components. Specifically, all the marketed drugs in Japan, not only the prescription drugs but also the OTC drugs, are fully represented in KEGG DRUG and linked to the package insert information (labels information). These include crude drugs and TCM (Tradictional Chinese Medicine) drugs[14,15,16].

PUBMED

PubMed is a free digital archive of biomedical and life sciences journal literature at the U.S. National Institutes of Health (NIH), developed and managed by NIH's National Center for Biotechnology Information (NCBI) in the National Library of Medicine (NLM). PubMed is a free search engine for accessing the MEDLINE database of citations and abstracts of biomedical research articles[18].

RASMOL

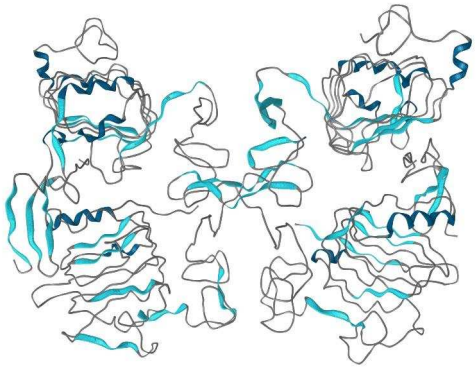
Raster Display of Molecules is a molecular graphics program intended for the structural visualization of proteins, nucleic acids and small biomolecules[20]. The program reads in molecular coordinate files and interactively displays the molecule on the screen in variety of representations and color schemes [19].

3. 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. Computer – Aided Drug Design (CADD) is a specialized discipline that uses computational methods to simulate drug – receptor interactions. CADD methods are heavily dependent on bioinformatics tools, applications and databases [9].

The structure of human epidermal growth factor receptor (EGFR) was retrieved from PDB (1MOX). Using Chemsketch, the structures of the drugs were drawn. They were subjected in Weblab viewer lite program for the generation 3D structure in the PDB file formate. The docking analysis of GEFITINB -2 and TARCEVA-7 and with Human epidermal growth factor receptor (EGFR) by Vega ZZ 2.0.5 Software docking software[10].

Target protein



RECEPTOR:-*PDB ID:- 1MOX*

PROTEIN NAME:-*Crystal Structure of Human Epidermal Growth Factor Receptor*

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 Human epidermal growth factor receptor (EGFR) fit together and dock to each other well, like pieces of a three-dimensional jigsaw puzzle. The molecules binding to a receptor, inhibit its function, and thus act as drug. The collection of TARCEVA and Gefitinb and receptor complexes was identified via docking and their relative stabilities were evaluated using molecular dynamics and their binding affinities, using free energy simulations. The parameters used for the docking process were Rotation step –20, solutions -100, max.collisions – 200, min.charge - -200, Active colour -120, dot density -420, probe rad(A) -1.8. The drug and its analogues were docked with the receptor using the above parameters.

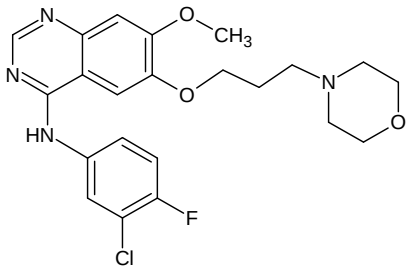
RESULTS AND DISCUSSION

Docking results tabulated between Human epidermal growth factor receptor (EGFR) and the conventional drug GEFITINIB and TARCEVA (Table I) as well as with the modified Analogs are shown below along with the changes or modification within them.

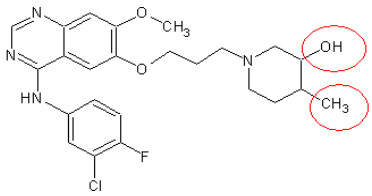
Table I Docking results of epidermal growth factor receptor (EGFR) with gefitinib analogs and tarceva analogs.

COMPOUND	E-VALUE	COMPOUND	E-VALUE
GEFITINIB	**268**	**TARCEVA**	**248**
ANALOG 1	255	ANALOG 1	251
ANALOG 2	**281**	ANALOG 2	251
ANALOG 3	271	ANALOG 3	256
ANALOG 4	271	ANALOG 4	252
ANALOG 5	269	ANALOG 5	248
ANALOG 6	268	ANALOG 6	255
ANALOG 7	269	**ANALOG 7**	**260**
ANALOG 8	270	ANALOG 8	254

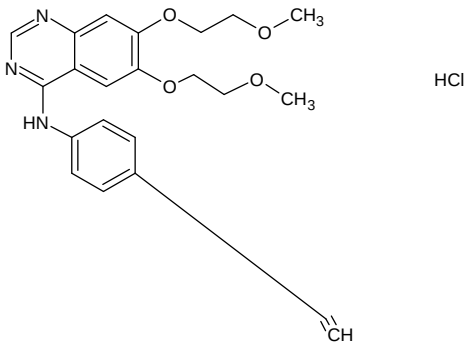
Standard ligand(Gefitinib) for EGFR



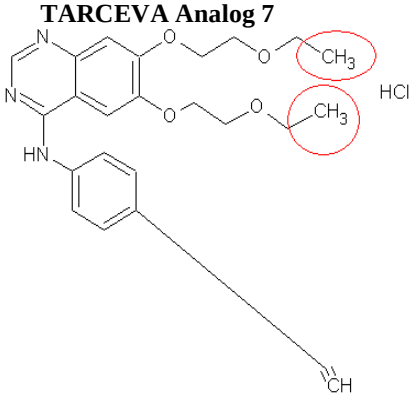
Gefitinb Analog 2



Standard ligand (Tarceva) for EGFR



TARCEVA Analog 7



Based on the literature it has been shown clearly that the drugs Gefitinib and Tarceva[4] have been used to target the Human epidermal growth factor receptor. Gefitinib and Tarceva on docking with Human epidermal growth factor receptor (EGFR) produced an energy value of 248 and 268 respectively.

It was observed using Molegro *Virtual Viwer* that the serine/threonine and tyrosine protein kinases present in the drug was the site of binding to the receptor (1mox) 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 Vega zz. This way the pharmacophoric part of the drug was partially identified. An analog with additional CH3 atom (TARCEVA analog 7) was prepared virtually using ChemSketch. This particular analog showed an increase in the energy values (**260**) and an analog in which methyl groups and hydracyl groups are added (GefitinibAnalog 2) was prepared virtually using ChemSketch. This particular analog showed an increase in the energy values (**281**) which means the analog (Tarceva analog7) and (Gefitinib Analog 2) 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 then predicted to the Admetox Based on the **Lipinski's Rule of Five** The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME"). However, the rule does not predict if a compound is pharmacologically active [21].

Table III ADME result based on the rule of five formulations of gefitinib analogs

COMPOUND	H-BOND DONARS	MOLECULAR WEIGHT	Log P	H-BOND ACCEPTORS
GEFITINIB	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 IV ADME result based on the rule of five formulation of tarceva analogs

COMPOUND	H-BOND DONARS	MOLECULAR WEIGHT	Log P	H-BOND ACCEPTORS
TARCEVA	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

The rule is important for drug development where a pharmacologically active lead structure is optimized step-wise for increased activity and selectivity, as well as drug-like properties as described by Lipinski's rule. The modification of the molecular structure often leads to drugs with higher molecular weight, more rings, more rotatable bonds, and a higher lipophilicity[22].

Lipinski's rule says that, in general, an orally active drug has no more than one violation of the following criteria:

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular weight under 500 daltons
- An octanol-water partition coefficient[23,24] log *P* less than 5

CONCLUSION

The Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work we have taken the Human epidermal growth factor receptor (EGFR) and identified the drugs that were used against Lung Cancer. When the receptor (1mox) was docked with the drugs the energy value obtained was; Tarceva (248), Gefitinib(260). When the modified drugs were docked against the same receptor the energy value obtained was Tarceva Analog 7 (260), Gefitinib Analog 2(281) 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 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.

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5) http://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py?form=admetox