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In Silico molecular docking analysis to identify PI3K inhibitors as possible NSCLC agents

Awantika Shrivastava[1]*, K Durga Prasad[1] and Archana Giri [2]

[1]*Natco Research Centre, B-13, Industrial estate, Sanath Nagar, Hyderabad, India*
[2]*Department of Biotechnology, JNTU, Kukatpally, Hyderabad, India*

* Corresponding author. email: awantika31@rediffmail.com

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ABSTRACT

Phosphatidylinositol 3-kinase is a very promising anti cancer drug target which is being actively investigated for treatment of various cancers such as RCC, prostrate, NSCLC and solid tumors. In this article, we have made an attempt to study the role of PI3K pathway inhibitors in the treatment of lung cancer through Insilco Molecular Docking studies. It was indicated from our study that the docking protocol could reliably predict how PI3K inhibitors act in NSCLC. The docking study carried out with 1M17 revealed that all six PI3K inhibitors have potential to work for NSCLC, but GDC-0941 (-7.03 kcal/mol) and GSK 2126458 (-8.30 kcal/mol) fits better than the rest.

Keywords: Molecular Docking, NSCLC, PI3K, *In Silico*, AutoDock

INTRODUCTION

PI3Ksare activated by receptor tyrosine kinase (RTK) signaling through EGFR, IGF1-R, HER2 etc [1-4]. It consists of three classes in which Class IA PI3K is the most widely implicated type in cancer. Class IA PI3K is a heterodimer consisting of a p85 regulatory and a p110 catalytic subunit. As per literature survey in NSCLC, PI3K/AKT/mTOR signaling is frequently deregulated due to mutations affecting one of its upstream regulators, the EGFR receptor, and other components within the pathway [5]. The most direct way to shut down the PI3K signaling pathway is to inhibit PI3K or Akt directly (Fig 1); such drugs are referred to as PI3K inhibitors. Because of the relationship between EGFR and PI3K, researchers believe that PI3K inhibitors will be most effective in combination with EGFR inhibitors as well as inhibitors of other related pathways.

Recently a number of PI3K inhibitors (GDC-0941, BKM-120 etc) have entered into clinical trials for diseases requiring new approach, such as NSCLC. The purpose of our study is to identify how PI3K inhibitors are working for NSCLC using Insilco Molecular Docking method. To obtain more precise results we have used docking process AutoDock for our studies.

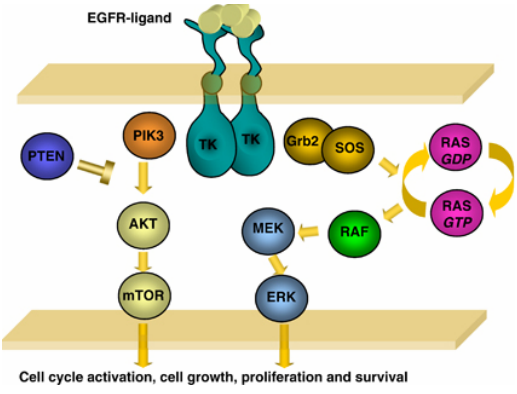
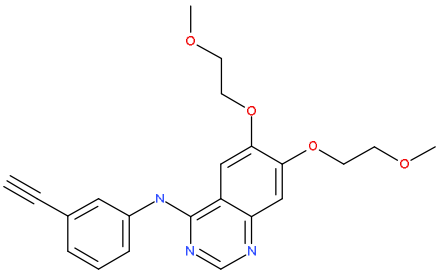


Figure 1. EGFR signaling pathway [from *The Pharmacogenomics Journal (2012) 12, 277–286*]

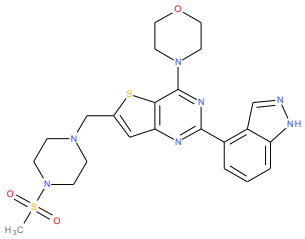
MATERIALS AND METHODS

To investigate the impact of PI3K inhibitors in EGFR we have docked a set of known PI3K inhibitors, which are in various stages of clinical trials, in PDB ID 1M17 using AutoDock software. The list of selected inhibitors is given below in Table-1.

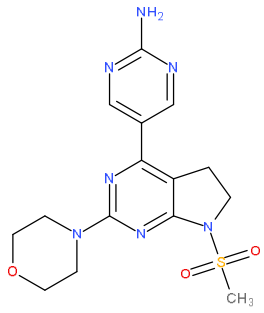
Table 1. List of PI3K inhibitors docked in EGFR target (PDB ID -1M17)



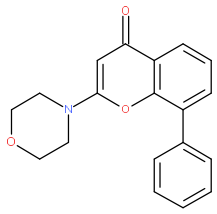
ERLOTINIB



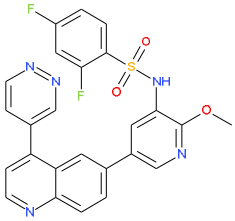
GDC -0941



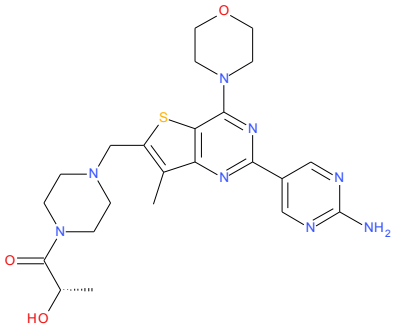
CH5132799



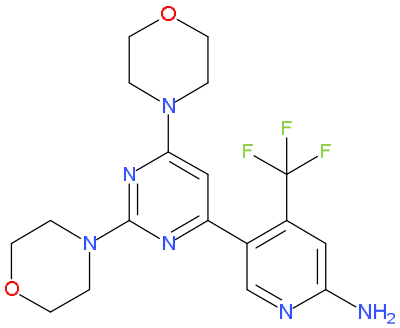
LY294002



GSK 2126458



GDC0980



BKM-120

AutoDock

The crystal structure of EGFR kinase domain with its bound inhibitor Erlotinib {[6, 7-bis (2-methoxy-ethoxy) quinazoline-4-yl]-(3-ethynylphenyl) amine} was taken from the Protein Data Bank (PDB entry 1M17) and was docked with AutoDock software and the docking score values are predicted. The protein-ligand interactions were also studied. All the inhibitors were drawn using Accelrys Draw 4.0. To perform the task, genetic algorithm method implemented in the program autodock was employed. The grid dimension were with points separated by 0.375 A. For all ligands, random starting position and random torsions were used. All five water molecules in the active site were included. The acidic and basic residues in the active site are in the ionic form [8].

Validation of the Molecular Docking method

To ensure the ligand orientation and the position obtained from the docking studies were likely to represent valid and reasonable binding modes of the inhibitors; the docking parameters are first validated for the crystal structure 1M17. The conformational state of the ligand erlotinib as found in the crystal structure was extracted and docked in to the corresponding binding pocket, and the ability of ligand to reproduce the orientation and position of the inhibitor observed in the bound form was determined.

AutoDock Scoring

The AutoDock scoring function is based on an empirically-derived linear free energy model that is designed to reproduce observed binding constants for small organic molecules bound to proteins. AutoDock had terms for van der Waals energy, hydrogen bond energy and Coulombic energy. Scoring function calculates (1) the change in desolvation free energy and (2) the loss of torsional degrees of freedom upon binding.

Hydrogen bond Interaction

It has been proposed that H-bond interaction of MET-769 and HOH 10 have important role in binding site of EGFR. The interaction mode of EGFR-TK with erlotinib

wasanalyzed by Ligand Interaction module in Discovery Studio 2.5 (Accelrys Inc., San Diego, CA, USA) as shown in Figure 2. The docking results revealed that the main interaction force of the candidate compounds with the EGFR-TK active site is hydrophobic (see below). The important residues in the hydrophobic regions that interact with the hit compounds are Phe699, Leu764, Ile765, Val702, Leu694, Ile720, Lys721 and Met742. All these residues are located near the gatekeeper residue Thr766 (Thr790 in alternative numbering in EGFR), which are the most common kinase-inhibitor interactions. Our docking results with PI3K showed that almost all PI3K inhibitors selected for docking studies are involved in this H-bond interaction.

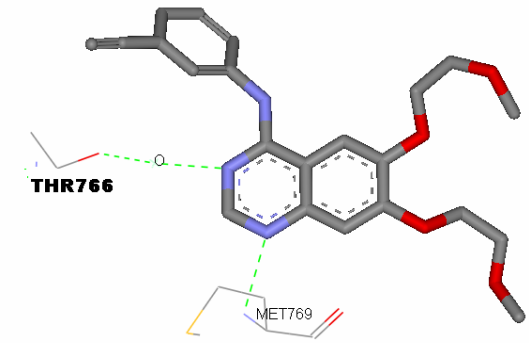


Figure 2. Important H-bond interactions of Erlotinib.

RESULTS AND DISCUSSION

Selected PI3K inhibitors were docked using AutoDock software and docked scores of these molecules were presented in Table-2, with their number of hydrogen bonds and interacting residues. The docking results have indicated that all PI3K inhibitors displayed important H-bond interaction with MET 769 which is an important interaction in EGFR. GDC-0941, BKM-120, GSK-2126458, LY29002, CH5132799 and GDC-0980 (Fig 3) are docked within the active site region of EGFR and the study indicated the importance of MET769 interaction for PI3K inhibitors.

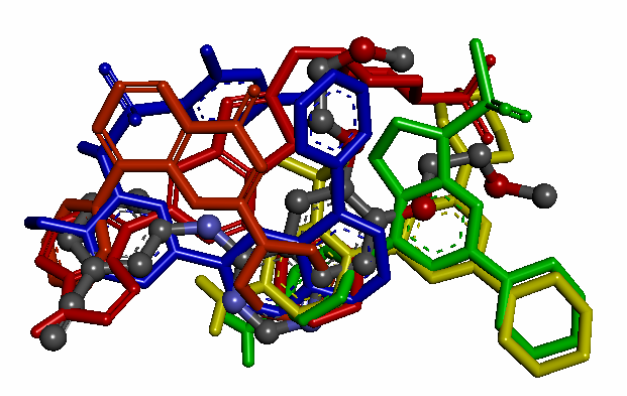


Figure 3. Superimposed Structure of Erlotinib (Grey) with PI3K inhibitors- BKM-120 (yellow), GSK-2126458 (blue) CH5132799 (green), GDC-0941 (red), GDC-0980 (pink), LY294002 (orange).

For easy comparison we have listed Scoring values in Table 2. As we can see from scoring table that GSK-2126458, GDC-0941and LY29042 is highly comparable with Erlotinib scoring values which indicate the binding affinity. In docking terms also these are better fits than other docked PI3K inhibitors as shown below in Fig 4.

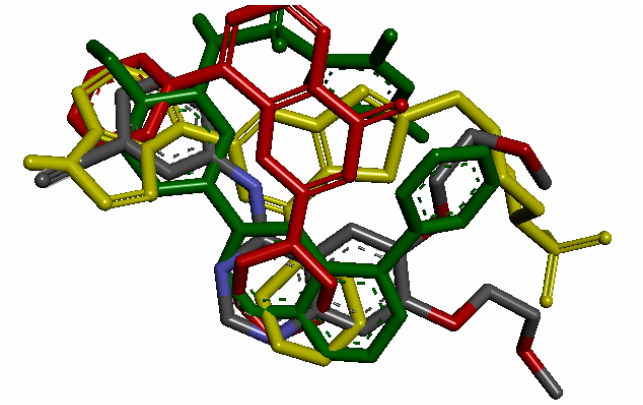


Figure 4. Superimposed Structure of Erlotinib (Grey) with PI3K inhibitors - GDC-0941 (yellow), GSK-2126458 (green) and LY294002 (red)

Table-2. Dock scores and H-bond interacting residues of molecules studied.

S No	Molecule	H bond residues and distances	Binding affinity (kcal/mol)
1	Erlotinib	MET 769- 1.78 HOH 10-1.77	-7.68
2	GDC-0941	MET 769- 2.15 HOH 10-3.04 THR 766- 2.40 CYS 773- 2.69	-7.03
4	LY294002	MET 769- 1.69	-7.29
5	GSK 2126458	MET 769- 2.40 ASP 831- 2.09 LYS 721- 2.07 CYS 773- 2.73	-8.30
6	GDC0980	MET 769- 2.40 HOH 10-1.92	-5.0
7	BKM-120	MET 769- 2.09 HOH 10-2.25 CYS 773- 2.65	-6.32
8	CH5132799	MET 769- 2.02 HOH 10-2.25 GLN 767- 2.01	-6.19

CONCLUSION

The insight gained from the study herein is that PI3K inhibitors especially GDC-0941 and GSK 2126458 have great potential to work against NSCLC. GDC-0941 and GSK 2126458 which are at various stages of clinical studies can be considered as potent NSCLC agents.

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