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DOCKING STUDIES OF ERLOTINIB AND AEE788 ON EGFR RECEPTOR

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ABSTRACT

Cancer is major health problem worldwide. The epidermal growth factor receptor (EGFR) play a considerable role in carcinogenesis through their involvement in proliferation, apoptosis, enhanced cell motility etc. Two anilinoquinazoline EGFR tyrosine kinase inhibitors: Gefitinib and Erlotinib have gained approval for patients with Non Small Cell Lung Cancer. Use of these drugs associated with resistance due to secondary point mutation T790M, which substitutes methionine for threonine at amino acid position 790 of EGFR gene domainis major drawback. These findings will certainly affect the development of the next generation of EGFR inhibitors with the ability to overcome T790M. This article include molecular docking simulation of Erlotinib with EGFR receptor so that we can use the same dimension for docking of various molecules with corrected Lipinski's parameters. Docking of other EGFR inhibitor AEE788 with wild type EGFR and T790M mutant EGFR support the preparation of new EGFR inhibitors which will act also in resistant conditions of first generation EGFR inhibitors. In this docking study binding energy for Erlotinib docking was found to be -6.44Kcal/mol, for AEE788 in wild type EGFR found to be -10.79Kcal/mol and for AEE788 in T790M mutant EGFR found to be -11.05Kcal/mol.

KEYWORDS

Cancer, Epidermal growth factor receptor (EGFR), EGFR TK inhibitors (EGFR TKIs), Non small-cell lung cancer (NSCLC), T790M, Erlotinib, AEE788 and Molecular docking simulation.

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INTRODUCTON

The epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases (TKs), referred to as the HER or ErbB family, consists of four members EGFR (HER1/ErbB1), HER2 (ErbB2), HER (ErbB3) and HER4 (ErbB4)-that regulate several developmental, metabolic and physiological

processes. The epidermal growth factor receptor and members of its family play a significant role in carcinogenesis through their involvement in proliferation, apoptosis, enhanced cell motility, and neoangiogenesis. In cancer cells, the TK activity of EGFR may be deregulated by various oncogenic mechanisms, including EGFR gene mutation, increased gene copy number and EGFR protein overexpression[1]. EGFR over expressions observed in tumors from more than 60% of patients with metastatic non-small-cell lung cancer (NSCLC) and is correlated with poor prediction[2]. These findings have provided a basis for the development of novel anticancer agents that target EGFR. Therefore, the predictive and prognostic significance of EGFR over expression in NSCLC has over the years become important, resulting in the development of numerous targeted therapies[3-7]. The discovery of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) has led to a new paradigm of lung cancer treatment. The use of EGFR TKIs for NSCLC began in 2003[8]. Two anilinoquinazoline epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors: Gefitinib and Erlotinib have gained approval for use in unselected patients with NSCLC[9,10]. Treatment with the reversible EGFR TK inhibitors (TKIs), Gefitinib and Erlotinib, results in striking antitumor activity in a subset of patients with NSCLC. Sequencing of the EGFR gene exposed that a majority of tumors responding to EGFR TKIs harbored mutations in the TK domain of EGFR[11,12].

Problem associated with marketed EGFR TKIs

As Gefitinib is a selective chemotherapeutic agent, its tolerability profile is far superior to previous cytotoxic agents. Adverse drug reactions do still occur however, but may be preferable to the fatal consequences of not taking the therapy. Other common adverse, effects (≥1% of patients) include: diarrhoea, nausea, vomiting, anorexia, stomatitis, dehydration, skin reactions, paronychia (skin infection that occurs around the nails), asymptomatic elevations of liver enzymes, asthenia, conjunctivitis, blepharitis (inflammation of eyelash follicles). Acne is reported very commonly. Infrequent adverse effects (0.1-1% of patients) include: interstitial lung disease, corneal erosion, aberrant eyelash and hair growth[13]. Gefitinib and Erlotinib treatment cause mutation which is responsible for resistance to these drugs.

Gefitinib and Erlotinib treated patients with NSCLC were identified to have somatic mutations in TK domain of ErbB1 mostly in exons 19 and 21, these comprise small in-frame deletions around the ATP binding site of TK domain. However, the cells containing an activating mutation are interestingly more sensitive to ErbB1 inhibition. In contrast, a secondary mutation has been observed in Gefitinib and Erlotinib-responsive advanced NSCLC patients. This mutation resulted threonine to methionine change at position 790 in the kinase domain of ErbB1 (T790M) and this unlikely mutation is reported to have resistance to gefitinib and erlotinib treatment[14].

Mechanisms of Acquired Resistance to Gefitinib and Erlotinib

Several mechanisms of resistance to Erlotinib and Gefitinib have been described in laboratory-based models:

a) A mutant form of EGFR termed EGFR vIII has an in-frame deletion mutation that produces a truncated 150 kDa protein, which is constitutively phosphorylated in a ligand-independent manner[15].
b) EGFR-dependent tumors that are initially sensitive to EGFR TKIs gain a mutation at threonine 790. Substitution of this residue in EGFR with a bulky methionine may cause resistance by steric interference with binding of TKIs, with gefitinib and erlotinib[14].
c) Tumors can become resistant when individual tumor cells undergo an oncogenic shift, which has been noted with several other RTKs, including HGF receptor, AXL and IGF1R[16].
d) In count to IGF1R as a mechanism of escape, down regulation of the IGF- binding proteins IGFBP3 and IGFBP4, have been drawn in resistance to TKIs. These proteins are crucial for regulating the levels of IGF1R ligands, and loss leads to over activation of the receptor[17].

e) Mutations in both PTEN have been implicated in impaired response to TKI therapy.
f) Mutations in both Ras have been implicated in impaired response to TKI therapy[18].
g) Cells that developed acquired resistance to gefitinib *in vivo* were shown to have increased VEGF production leading to altered angiogenesis and enhanced escape from cetuximab therapy[19].
h) VEGFR1 has also been implicated in the contribution to resistance to EGFR TKIs[20].

Among the resistance causing factors, the secondary point mutation T790M, which substitutes methionine for threonine at amino acid position 790 of EGFR gene domain, might play the most important role. Furthermore, the majority clinical reports indicated that T790M accounted for half of the acquired resistant TKI cases[21].

Secondary mutation: EGFR T790M

The first identified mechanism of acquired resistance to EGFR TKIs was the EGFR T790M mutation in 2005. Patients with NSCLC harboring either exon 19 deletions or the L858R mutation that progressed after a period of response to Gefitinib or Erlotinib. In post-progression biopsies, the original EGFR mutation and the novel T790M in exon 20 were identified. When T790M was introduced in vitro to sequences containing wild-type EGFR, exon 19 deletion-EGFR, or L858R-EGFR, the resulting proteins were significantly more resistant to Gefitinib in the constructs containing T790M[14,22]. The inhibitory concentrations to Erlotinib and Gefitinib in T790M-containing constructs exceeded 5μM, which is a concentration more than 100-fold higher than that required to inhibit exon 19 deletions or L858R-EGFR[23]. A NSCLC cell line with the L858R-T790M mutation was significantly more resistant to Gefitinib or Erlotinib than lines with L858R and an exon 19 deletion[14,22,24]. The T790M mutation is most often seen in cis; however, it can occur in trans, to L858R or exon 19 deletions[22,24]. EGFR-mutated cell lines that have L858R-T790M or exon 19 deletions-T790M continue to be dependent on EGFR, because alternative EGFR inhibitors halt cell proliferation and lead to apoptosis[22,24,25]. Some EGFR-mutated NSCLC cell lines (H3255 and PC-9) that are exposed to incremental concentrations of Gefitinib in culture end up acquiring T790M[24,26] and mouse lung cancer models of L858R-T790M confirmed that these tumors are resistant to Gefitinib and Erlotinib[27]. These preclinical and clinical data support T790M as a main mechanism of resistance to EGFR TKIs. How T790M affects the hypersensitivity of activating EGFR mutations is still not completely clear. Primarily, it was speculated, based on the crystallographic structure of the kinase domain of EGFR, that the bulkier methionine residue of the -gatekeeper T790M changed the ATP binding pocket of the kinase, therefore blocking the engagement of Erlotinib or Gefitinib[22]. However, more recently, it was demonstrated that T790M affected minimally the binding of Gefitinib to L858R-EGFR. Instead, L858R-T790M-EGFR had increased affinity to ATP when compared with L858R alone, which is predicted to decrease binding of Gefitinib and Erlotinib because these drugs are ATP-competitive kinase inhibitors[28]. These findings will certainly affect the development of the next generation of EGFR inhibitors with the ability to overcome T790M. In the original reports, preprogression samples lacked T790M, and it was thought that this abnormality was acquired only after exposure to Gefitinib or Erlotinib[22,29]. NSCLC with a mutation in the gene encoding epidermal growth factor receptor (EGFR) is susceptible to approved EGFR inhibitors, but resistance develops, mediated by the T790M EGFR mutation in most cases[30].

This article include docking of Erlotinib with EGFR receptor so that we can use the same dimension for docking of various proposed molecules with correct Lipinski's parameters. With all of this docking of other EGFR inhibitor AEE788 with wild type EGFR and T790M mutant EGFR support the preparation of new EGFR inhibitors which will act also in mutated conditions of first generation EGFR inhibitors.

MATERIAL AND METHODS

Molecular Docking Simulation on receptor with ligand

Moleular docking for Erlotinib and AEE788 were carried out using Autodock 4.2 as docking tool. The protein visualization for molecular docking studies were performed by means of Pymol, Chimera, DS visualizer and MMP Plus^{TM}.

Crystal structure of protein

The crystal structure of EGFR associated with bound ligand Erlotinib, wild type EGFR associated with bound ligand AEE788 and T790M mutant EGFR associated with bound ligand AEE788 were downloaded from RCSB Protein Data Bank portal with ID (1M17.pdb), (2JIU.pdb) and (2J6M) respectively. The bound ligands (Erlotinib, AEE788 and AEE788) were found within the receptor in its bioactive conformation in their crystal structure.

Receptor processing and ligand preparation-

The downloaded protein (1M17.pdb) had one chain A. Chain A of downloaded protein consist of bound ligand Erlotinib. The downloaded protein (2J6M.pdb) had one chain A. Chain A of downloaded protein consist of bound ligand AEE788. The downloaded protein (2JIU.pdb) had chain A and chain B. Chain A of downloaded protein consist of bound ligand AEE788. The downloaded proteins consist of bound ligands, which were separated by using software Chimera.

The ligand was separated from the receptor 2JIU.pdb by means of Chimera software.

Grid box

The regions of interest used by Autodock was defined by considering grid area by making a grid box around the binding sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box had 3 thumbwheel widgets which let us change a number of points in x, y and z dimentions. The spacing between grid points could be adjusted with another thumbwheel and x, y, z centers could be adjusted with another thumbwheel.

RESULTS AND DISCUSSION

Validation of Molecular Docking Simulation process

To validate the process of docking of Erlotinib, AEE788 and AEE788 with EGFR, wild type EGFR and T790M mutant EGFR respectively, was done by following parameters:

Binding energy of complexed structure

Binding energy of docked ligand should be in the range between -5 to -15Kcal/mol.

Binding energy of different complexes were found to be:

Overlay of docked and crystallized ligands

The docked conformation of ligands should be perfectly overlayed with the crystal structure ligands of downloaded protein. This testing of the Autodock docking algorithm with ligands (already within receptor as complex) was completed successfully and the docked conformation of ligands were perfectly superimposed with reference structure of respective ligands, i.e. its respective crystal structures. The re-docking of this ligands were successfully achieved to get final results.

Ligand-Protein Interactions

Similar interactions between the docked ligand and the receptor should be observed after docking. To that of interactions present in the crystallized structure of protein.

Interaction between EGFR and docked Erlotinib

Figure No.13 and Figure No.14 was compared, it was found that polar and hydrophobic interactions were same as shown in following Table No.3.

Interaction between wild type EGFR and docked AEE788

Figure No.15 and Figure No.16 was compared, it was found that polar and hydrophobic interactions were same as shown in following Table No.4.

Interaction between T790M mutant EGFR and docked AEE788

Figure No.15 and Figure No.17 was compared, it was found that polar and hydrophobic interactions were same as shown in following Table No.5.

Molecular dynamic simulation

Root-Mean-Square-Deviation (RMSD) for docked complex of wild type EGFR and AEE788

After the minimization of protein RMSD should be less than 1.5 A^0. After the minimization of protein RMSD value was found to be 0.8 A^0.

Root-Mean-Square-Deviation for docked complex of T790M mutant EGFR and AEE788 After the minimization of protein calculation are terminated, results are recorded in the form of RMSD in*.dcd file. After the minimization of protein RMSD value was found to be 0.8 A^0.

RMSD for both complexes were found to be near to 0.8, it means the difference between docked and pdb downloaded complex was only 0.8.

Table No.1: Grid box sizes taken for different three receptor

S.No	Receptor→		EGFR	Wild Type EGFR	T790M Mutant EGFR
1	No. of points	X dimention	42	42	40
		Y dimention	34	34	50
		Z dimention	42	56	50
2	Spacing A^0		0.381	0.381	0.381
3	X		21.727	-52.96	-7.955
	Y		-0.892	0.419	18.386
	Z		54.097	-20.255	29.516

Table No.2: Binding energy of various ligands after docking

S.No	Complex	Binding Energy(Kcal/mol)
1	EGFR With Docked Erlotinib	-6.44
2	Wild Type EGFR With Docked AEE788	-10.79
3	T790M Mutant EGFR With Docked AEE788	-11.05

Table No.3: Interaction between EGFR and docked Erlotinib

S.No	Ligand	Experimental K_i(µM)	Docked K_i(µM)	Polar interaction	Hydrophobic interaction
1	ERLOTINIB	0.3-0.4	2.32	MET769 THR766	LEU820 LEU768 LEU694 GLY772

Table No.4: Interaction between wild type EGFR and docked AEE788

S.No	Ligand	Experimental K_i(nM)	Docked K_i(nM)	Polar Interaction	Hydrophobic interaction
1	AEE788	0.89	12.35	MET793 THR854	THR790, LEU844 LEU718, LYS745 GLY796, ALA743

Table No.5: Interaction between T790M mutant EGFR and docked AEE788

S.No	Ligand	Experimental K_i(nM)	Docked K_i(nM)	Polar interaction	Hydrophobic interaction
1	AEE788	0.89	7.95	MET793 THR854	MET790, LEU844 LEU718, LYS745 GLY796, ALA743

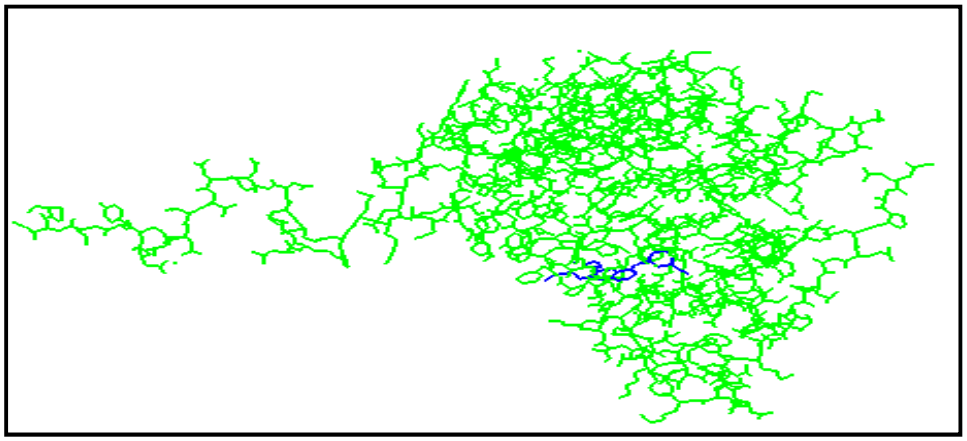


Figure No.1: Crystal structure of EGFR associated with ligand Erlotinib

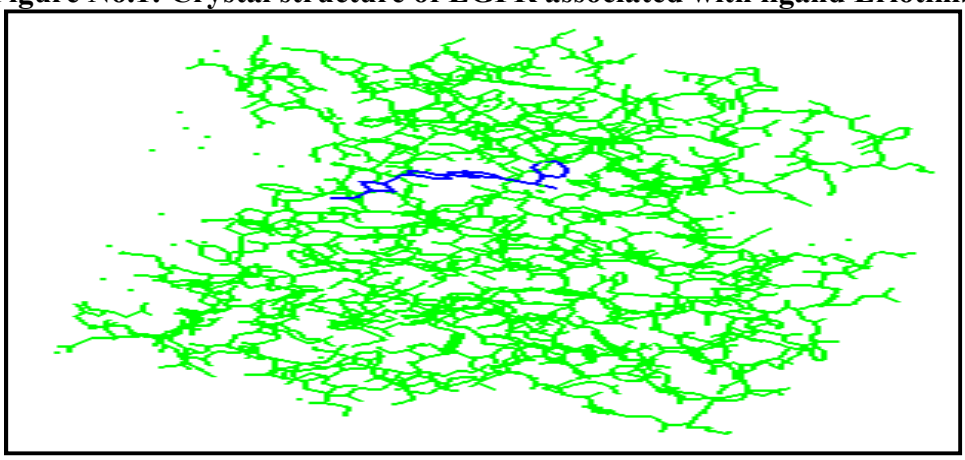


Figure No.2: Crystal structure of wild type EGFR associated with boundligandAEE788

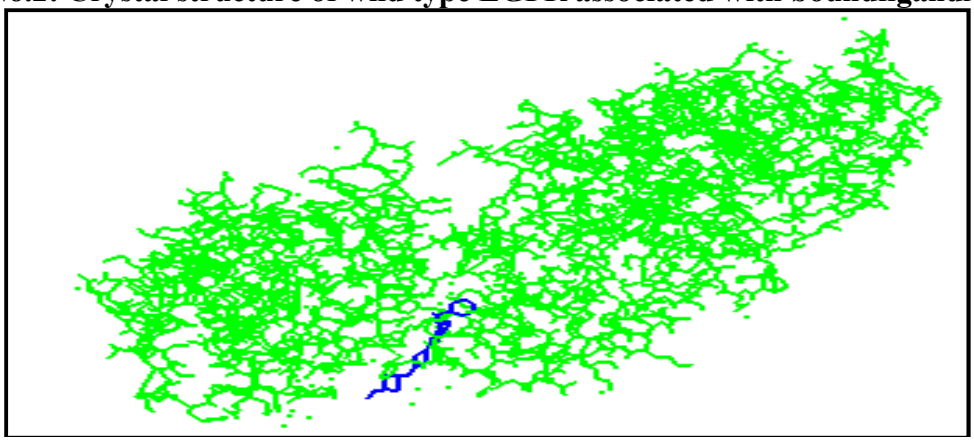
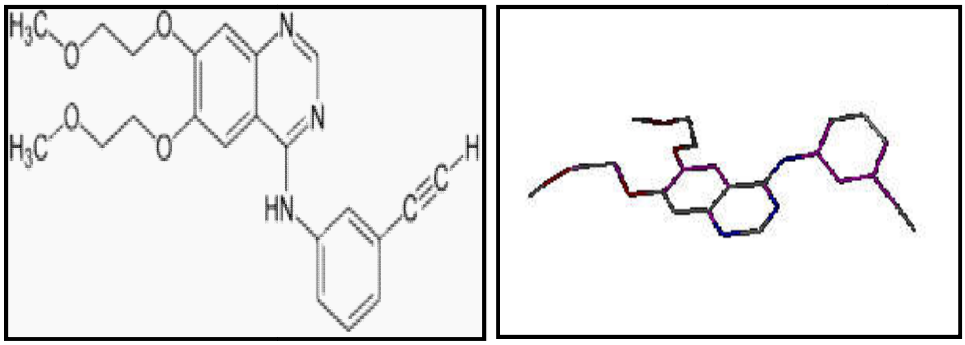
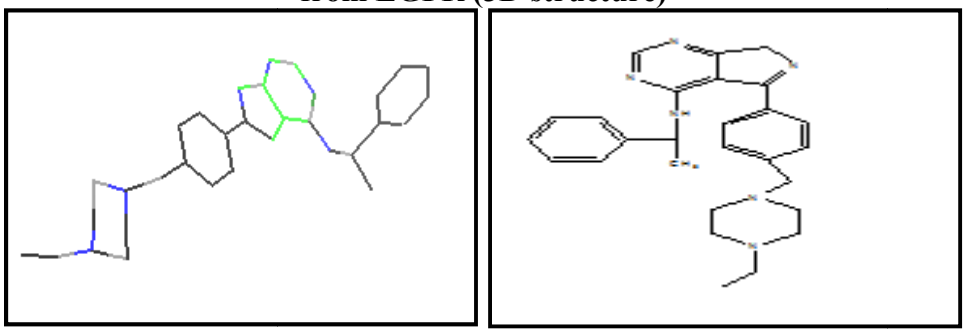


Figure No.3: Crystal structure of T790M mutant EGFR associated with bound ligand AEE788



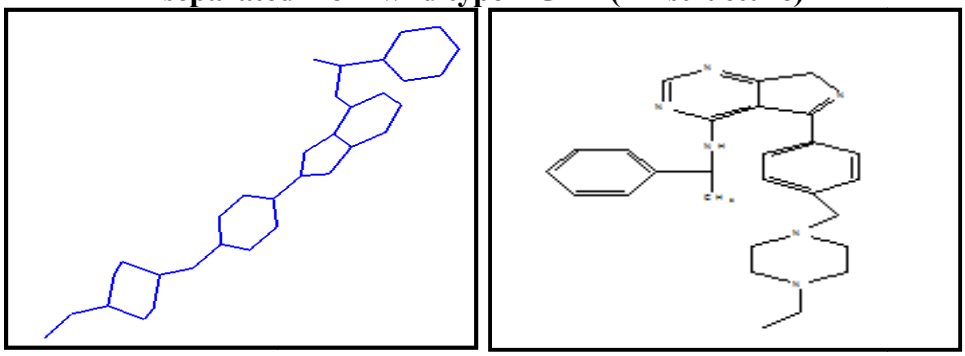
a **b**

Figure No.4(a): ligand Erlotinib separated from EGFR (2D structure) (b). ligand Erlotinib separated from EGFR (3D structure)



a **b**

Figure No.5(a): ligand AEE788 separated from wild type EGFR (3D structure) (b). ligand AEE788 separated from wild type EGFR (2D structure)



a **b**

Figure No.6(a): ligand AEE788 separated from wild type EGFR (3D structure) (b). ligand AEE788 separated from wild type EGFR (2D structure)

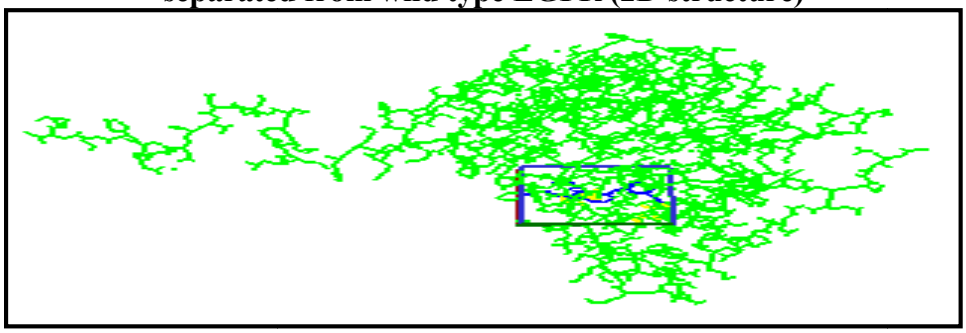


Figure No.7: Grid box covering all active sites in EGFR

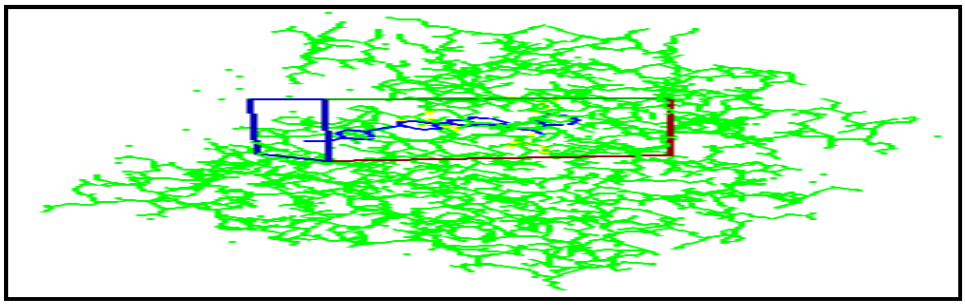


Figure No.8: Grid box covering all active sites in wild type EGFR

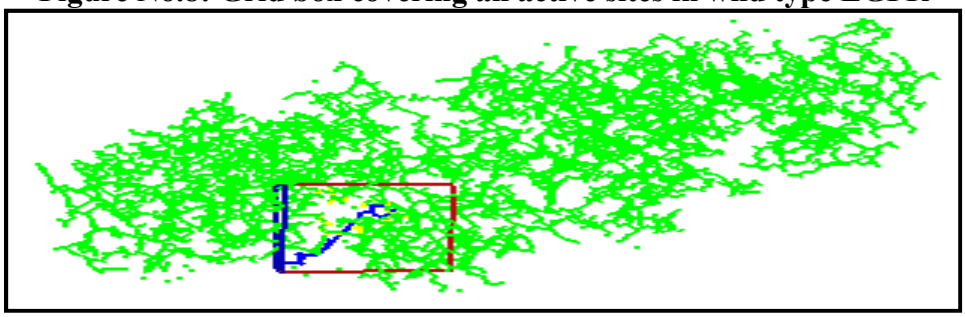


Figure No.9: Grid box covering all active sites in T790M mutant EGFR

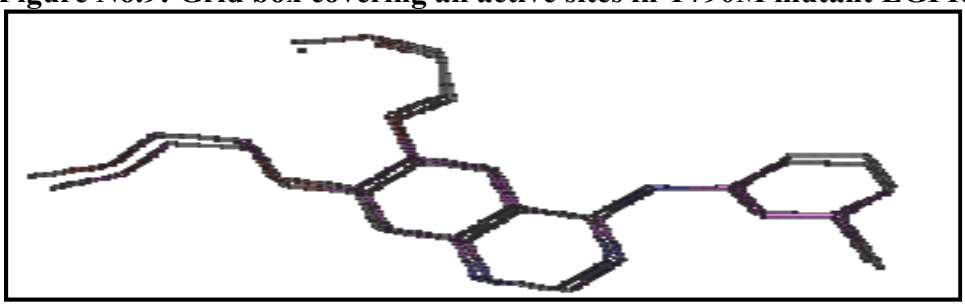


Figure No.10: Overlay of docked and crystallized Erlotinib

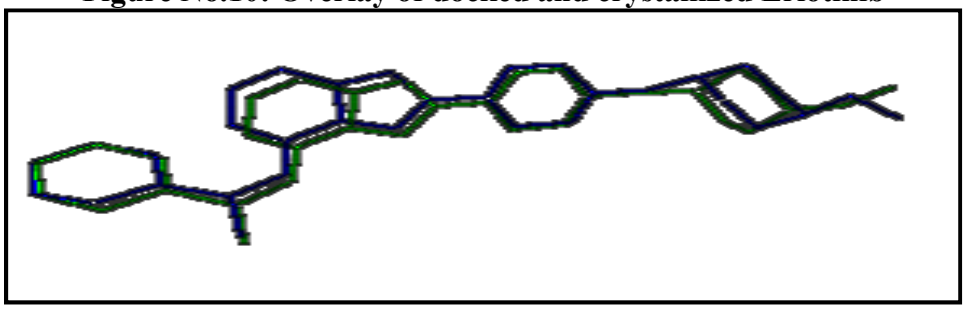


Figure No.11: Overlay of docked and crystallized AEE788 (wild type EGFR)

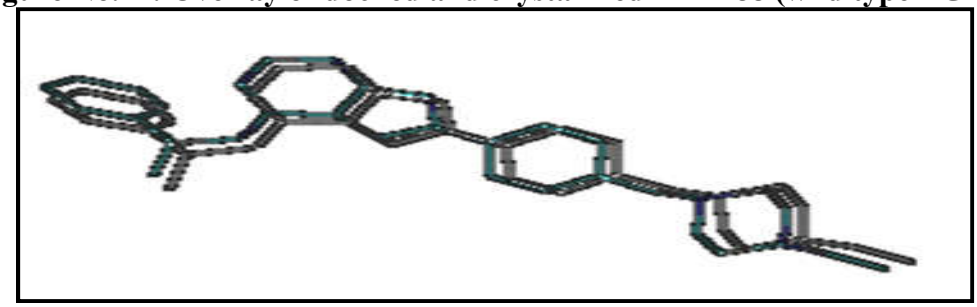


Figure No.12: Overlay of docked and crystallized AEE788 (T790M mutant EGFR)

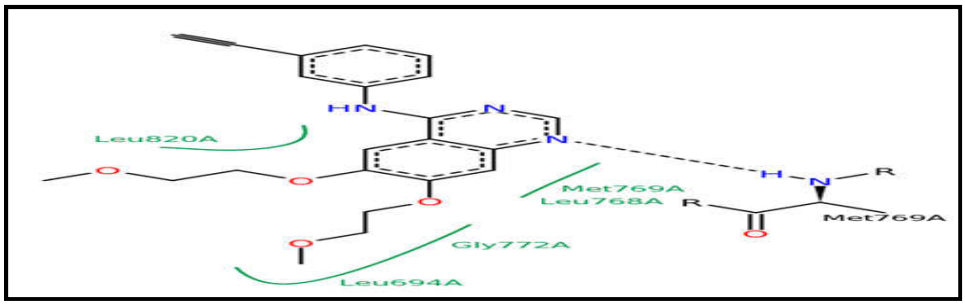


Figure No.13: Two-Dimentional interaction of EGFR with Erlotinib by pdb

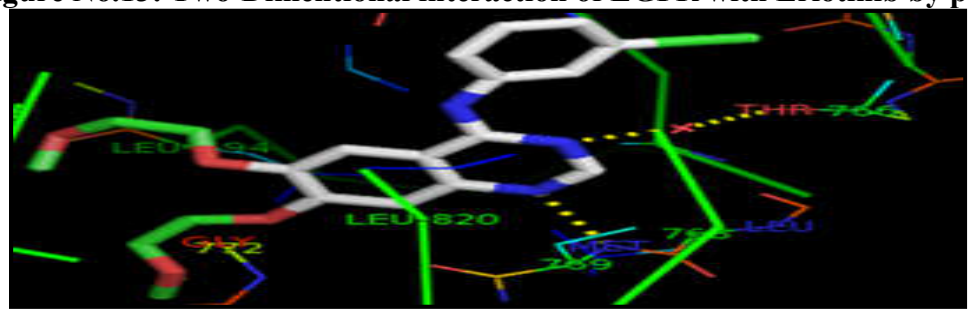


Figure No.14: Three -Dimentional interaction of receptor EGFR with ligand docked Erlotinib

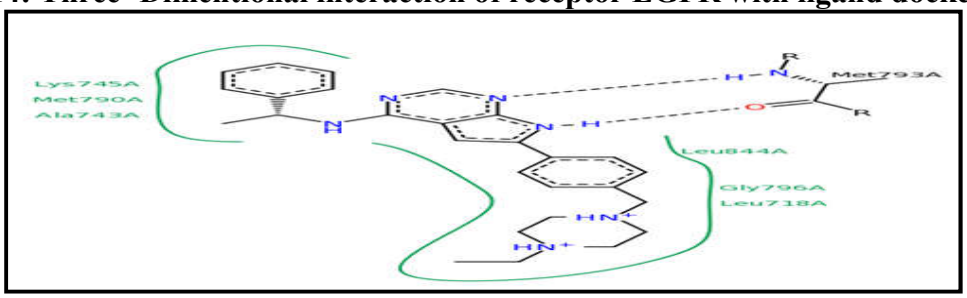


Figure No.15: Two-Dimentional interaction of receptor T790M mutant EGFR with ligand AEE788 by PDB

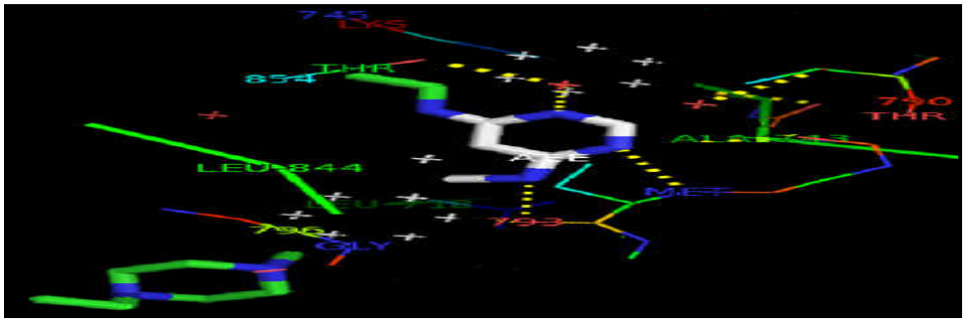


Figure No.16: Three- Dimentionalinteraction of receptor wild type EGFR with docked AEE788

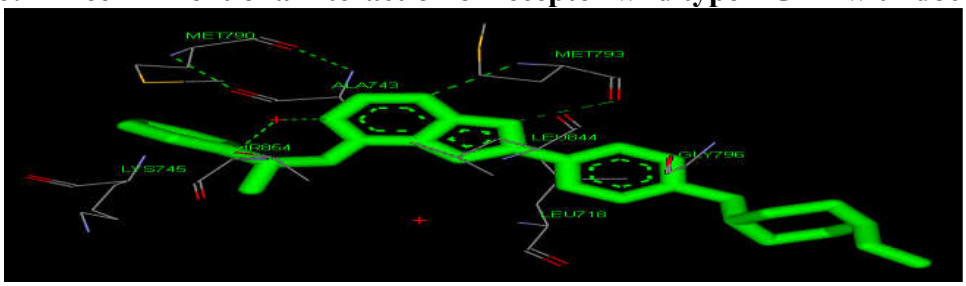


Figure No.17: Three-Dimentional Interaction of receptor T790M mutant EGFR with docked AEE788

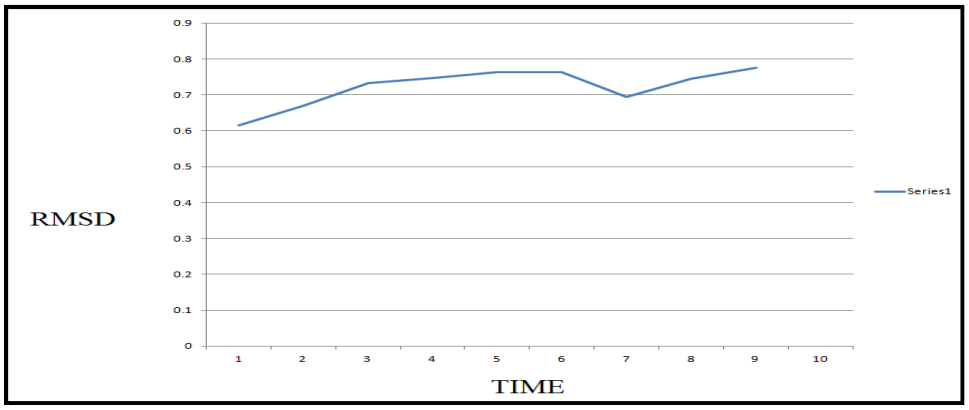


Figure No.18: Graph between RMSD and time

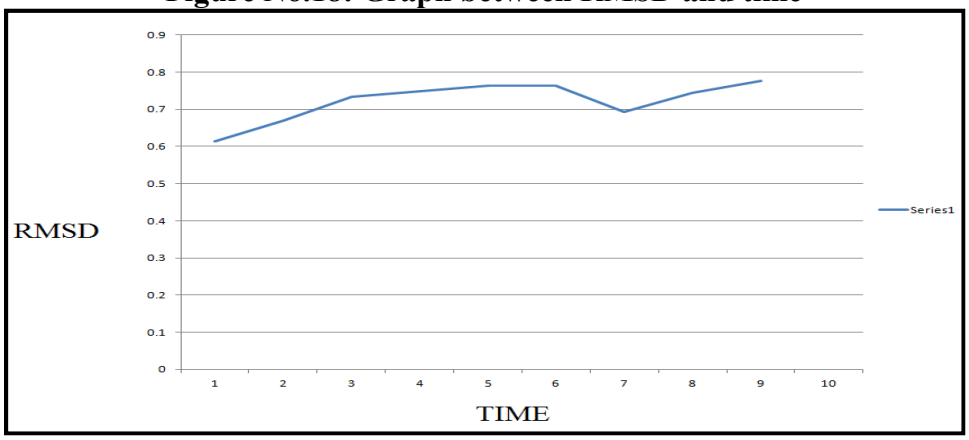


Figure No.19: Graph between RMSD and time

CONCLUSION

All such type of process which are based on software reduce our time and expenses for designing of new molecules. Without using synthesis and animal activity process we can find the activity of new molecules. EGFR TKIs have great importance to treat cancer. Erlotinib and AEE788 which are novel EGFR TKIs undergoes molecular docking simulation process. This overall study helpful to determine activity of newly designed molecule that they will act as good EGFR tyrosine kinase inhibitor or not.

All above study concluded that docking process which is used for docking of Erlotinib and AEE788 can be used for various EGFR TKIs to check their activity and binding to EGFR receptor. By using above information we can find that our newly designed molecule will properly fit into EGFR receptor and also act in T790M resistance condition.

FUTURE ASPECTS

We can design new molecules by using structural activity relationship (SAR) of various EGFR TKIs which have good anticancer activity. SAR based designed molecule can docked by using dimensions and process of Erlotinib and AEE788 docking to find out their importance as used as EGFR tyrosine kinase inhibitor to treat cancer.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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