In-silico molecular docking study of novel derivatives of erlotinib in glioma

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Abstract. Gliomas are primary brain tumours arises from the glial cells. Gliomas associated risk factor depend upon its degree of stage and grade. Erlotinib is a quinazoline derivative and antineoplastic agent that capacities as a Protein Kinase Inhibitor for Epidermal growth factor receptor (EGFR) related tyrosine kinase and widely used for treating non-small cell carcinoma. Erlotinib, (a tyrosine kinase inhibitor) has been found in the glioblastoma. ErbB (EGF family receptor tyrosine kinase) established to control cell survival, proliferation, migration, and differentiation. The ErbB receptor accounts for the restricted and redundant functions in the maintenance of tissues in adult mammals. Newly discovered drug targets and personalised treatments could be used to identify the characteristics of any individual's tumorigenesis. To see the binding mode of deferent classes of erlotinib carefully chosen based on the structural comparison, we employed simulated screening and molecular docking based on the theory of evolution. The study consists of a simulated screening of around 3200 molecular derivatives of erlotinib and their molecular docking using a Lamarckian genetic algorithm. Molecular docking results showed binding energy ranging from -12.15 kcal/mol to -1.17 kcal/mol. Top 10 best-docked proteins were analyzed using UCSF Chimera and finding discovered the complicated atomic-scale properties between ligand and the target protein. Further wet lab study requires to study the actual binding as binding mode provided. To identify new inhibitors of EGFR with higher potency and specificity, additional information is needed for future designs molecules.

Keywords: Molecular docking, EGFR, erlotinib, glioblastoma

INTRODUCTION

Cancer has been established as a major health problem globally, which impacts more than 8 million death annually (Ferlay *et al.*, 2012). Brain tumours nearly represent 2% among all type of cancer and 90% of the central nervous system (Board PATE, 2019). On an estimate, gliomas represent almost 70% among all brain tumours and shown a high incident in adults (Ostrom *et al.*, 2014). Glioblastoma multiforme (GBM) is known as a rapid growing glioma represents about 55% of total gliomas and 20% of whole-brain tumours (Urbańska, *et al.*, 2014). GBM falls under the fifth

grade most invasive and deadly tumours. Surgery and radiation are commonly known as treatment strategies (Stupp *et al.*, 2006). GBM generally found to be highly chemo resistive in nature, so the therapeutic intervention is confined and majorly restricted (Villano *et al.*, 2009). There is a high demand to finds out new drug opportunities for a better cure. Widely accepted transmembrane tyrosine kinase receptor accomplishes the critical role in glioma neoplasia, upon activation the receptor transduces the signal for the cell proliferation and survival. To create a new

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therapeutic approach signalling cascades for this receptor should be obstructed. Most importantly, Raf/Ras/Mek/Erk and mTOR/Akt/PI3K pathways are having the decisive role for the signalling cascade.

EGFR was primarily sequenced receptor that possesses amino acid enzyme activity (Wells, 1999). ErbB/HER belongs to the receptor tyrosine kinases family consisting of EGFR/ErbB1/HER1, ERBB2/HER2, ERBB3/HER3 and ERBB4/HER4 (Ferley *et al.*, 2008; Stupp *et al.*, 2006). EGFR overexpression has been identified in many cancers like breast, lung, pancreas, and glioblastoma. However, HER2 has been found overexpressed in breast and ovarian cancers (Hudis 2007; Citri & Yarden 2006; Davies & Samuel 2010). EGFR overexpression can be seen in non-small-cell lung cancer; moreover, a mutation in these EGFR will help develop targeted cancer therapy (Hudis 2007; Bowers *et al.*, 2001; Paez, 2004; Gharwan & Groninger, 2016). HER2 copy number has been amplified in 20%-30% breast carcinoma (Hudis, 2007). Long exposure of erlotinib could lead to downregulate the EGFR expression along with its molecular invasion effectors in brain tumour cell line culture (Lal *et al.*, 2002). The last phase II clinical trial of erlotinib was well accepted in glioblastoma therapy and showed a modest undeniable control above placebo (Wen *et al.*, 2014). The capability of erlotinib is highly characterised in other cancer cell lines and found to obstruct cell cycle by initiating G1/S phase arrest (Moyer *et al.*, 1997; Quatralle *et al.*, 2011).

In pre-clinical trials, erlotinib showed striking impression by repressing anchorage-independent development in tumor cells lines (Halatsch *et al.*, 2004). According to previous research, outcomes underscore the thought that distinctions in tissue-explicit science as well as the signalling system coupled to EGFR incredibility impact TK1 adequacy. So, we draw the attention to identify new inhibitors of EGFR with higher potency and specificity to tackle receptor tyrosine kinase.

MATERIALS AND METHODS

Ligand generation

2D equivalent structural derivatives of N-(3-Ethynylphenyl)-6, 7-bis (2-methoxy ethoxy) quinazoline-4-amine were acquired from PubChem. By using inbuilt similarity fingerprinting search, we selected the molecule which got the highest score of 0.68. This search provides a total of 3200 ligands in which only 500 ligands were tested on the basis of their chemoinformatics analysis. The software Chem Sketch was utilized for generating and sketching MDL Molfile (v2000) molecules; then the ligands were changed into protein databank formats (PDB) using Open Bebel software.

Target or receptor protein

PDB crystal structure of EGFR tyrosine kinase domain with novel inhibitor downloaded from RCSB (<http://www.rcsb.org>) using PDB ID: 5JEB. The devoted ligands were separated and energy minimisation implemented by the optimized protocol of Swiss PDB viewer (Gueux & Peitsch 1997).

Docking setup

Docking studies of protein and ligand had been performed by utilising Auto Dock software version 4 (Moris *et al.*, 2009) which shows binding energy analysis through grid and energy potential using various search algorithms to find out exact binding characteristics on given super molecule. Polar hydrogen molecules are added to the ligand by using AutoDock hydrogen module. A standard procedure was used for the distribution of the Kollman united partial atom charges which involved at random places with the population size of 150.

The result was the clustered rendering 1 Å root mean square deviation standard with exact ten docking runs. The grid size -12.352* 104.011* 22.946 points and grid positioning of 40 Å was selected. The Chimera UCSF was utilized for viewing the coordinates of the docked structure within the range of 5 Å of the molecule-protein interaction. UCSF Chimera can be found at the following URL (www.cgl.ucsf.edu/chimera). The molecules which are displaying least binding energies were assessed for drug-likeness using

“Rule of five” (RO5) for the detection of possible pharmacokinetics. All molecules are subjected to the study of molecular properties and drug likeness scores.

RESULTS AND DISCUSSION

Different derivatives of erlotinib were docked using a Lamarckian Genetic Algorithm. Merging an utterly unique algorithm rule for binding site identification and assessment of picturing tool has provided an efficient means to exploit unrevealing the characteristic of binding cavity. Total of 100 molecules were adequately screened on the origin of the structural resemblance of erlotinib. Scoring functions are the mathematical methods used to predict the strength of the non-covalent interaction. In the fields of computational chemistry and molecular modelling scoring functions are fast approximate mathematical methods used to predict the strength of the non-covalent interaction (also referred to as binding affinity) between two molecules after they have

been docked. Most commonly, one of the molecules is a small organic compound such as a drug and the second is the biological target such as a protein receptor (Tables 1 & 2).

For the evaluation of a scoring function, an experimentally observed protein-ligand complex can be used. In structure-based drug design, the RMSD is a measure of the difference between a crystal conformation of the ligand and a docking prediction. Hence for stability, we always look for minimum values.

Typically, if a ligand binds to a protein, the enthalpic term decreases due to favourable intermolecular interactions and the formation of intermolecular bonds. This means whatever molecules giving minimum energy are favourably binding to the active site of the target. In the world of chemical transformations, chemicals always want to minimize their Gibbs free energy. What this means is that chemicals will tend to transform into other states or chemicals that have less Gibbs free energy. For example, Ice will always convert to water when the temperature is above 0 degrees Celsius.

Table 1. Chemical properties of the top 10 molecules out of 500 molecules with the minimum binding energy.

No.	PubChem ID	Compound IUPAC name	Minimum binding energy	Run
1	87471879	N-[3-(2-deuterioethynyl)phenyl]-6,7-bis(2-methoxyethoxy) quinazolin- 4 -amine	-13.13	2
2	59772909	6-butoxy-N-(3-ethynylphenyl)-7-(2-methoxyethoxy) quinazolin - 4 – amine	-13.60	9
3	49849306	N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy) quinazolin-4-amine hydrochloride	-12.67	6
4	44609731	Icotinib Hydrochloride	-12.24	6
5	25204422	N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy) quinazolin-4-amine hydroiodide	-12.22	9
6	16045651	N-(5-ethynyl-2-methylphenyl)-6,7-bis(2-methoxyethoxy) quinazolin-4-amine	-11.72	1
7	11452930	N-(3-ethynylphenyl)-6,7-bis(3-methoxypropoxy) quinazolin-4-amine	-11.52	2
8	118919167	N-(3-ethynylphenyl)-5-iodo-6,7-bis(2-methoxyethoxy) quinazolin-4-amine	-11.41	9
9	91350798	N-[3-(3-ethoxy-3-methylbut-1-ynyl)phenyl]-6,7-bis(2-methoxyethoxy) quinazolin-4-amine	-11.38	7
10	89265293	2-[6-(2-cyanoethoxy)-4-(3-ethynylanilino) quinazolin-7-yl] oxyethyl cyanate	-11.37	4

Table 2. Chemical structure of the top 10 molecules.

1.	2.
3.	4.
5.	6.
7.	8.
9.	10.

CONCLUSIONS

The development of the unique biologically active compounds is the necessary need for the developing world. In this study, we successfully docked EGFR protein with erlotinib derivatives to give new insight for drug interaction study. Based on this molecular docking study, we found ten potent molecules consisting of minimum binding energy with having at least one hydrogen bond with the receptor protein. These types of approaches can play a more serious role in the ongoing race of the development of a new drug molecule for hitting new molecular targets. The scope of this work gives the pivotal the binding mode via in-silico practice. Furthermore, it remains highly required to generate such results in wet lab modes to test the new drugs in reality for understanding their better specificity and metabolism.

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