Molecular modelling studies of diphenylquinoxaline derivatives as c-met kinase: A comparison of various docking softwares

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Abstract

In this work a total of twelve Quinoxaline derivatives was selected for molecular docking comparative studies. These molecules are selected based on synthetic compounds with inhibitory activity against c-met kinase. Autodock 1.5.6, patchdock and Igemdock were used for molecular docking comparative analysis of 12 Quinoxaline derivatives into the active site of c-met kinase obtained from x ray crystal structure 1r1w.pdb. It revealed that a number of sulfonamido quinoxaline derivatives have presented better energy values than the co crystallized ligand, Nilotinib and can interact with catalytic residues, thus making them possible catalytic inhibitors against c-met kinase.

Keywords: Molecular docking; Patchdock; Igemdock; Autodock; Quinoxalines; C met kinase; Anti-cancer.

INTRODUCTION

Inhibition of c- met kinase, which is expressed by the epithelial cells constitutes a promising class against cancer disease by reducing the cell scattering invasion, protection from apoptosis and angiogenesis and consequently suppresses the tumour development [1]. Bioactive components isolated from medicinal plants that are used as a traditional medicine often provide the lead structure for modern research and development strategies. There for much effort has been exhausted in the search for effective and safe drugs as as anticaner agents [2]. There are numerous TKIs aiming at various tyrosine kinase has been generated by the originators of these compounds and proven to be effective antitumour agents and anti-leukemic agents. Based on this work Imatinib was developed against chronic myelogenous leukemia and later gefitinib and erlotinib aiming at the EGF receptor Sunitinib an inhibitor of the receptors for FGF, PDGF and VEGF is also based on early studies on TKIs aiming at VEGF receptors. Cabozantinib, developed by Exelixis approved by the FDA in 2016 appears to be on its way to the standard of care in regards to TKIs [3]. Nilotinib approved for the treatment of imatinib-resistant chronicmyelogenous leukemia. Structurally related to Imatinib, it was developed based on the structure of the Abl-Imatinib complex to address Imatinib intolerance and resistance. It is benzamido derivatives linked to various heterocyclic compounds [4]. More attention is devoted to developing new c-met kinase inhibitors with Quinoxaline as a heterocyclic nucleus. Previous studies revealed that Quinoxaline nucleus has better c-met kinase inhibitory activity. In the present study, docking based screening protocol for Quinoxaline based compound library of 12 compounds towards c-met kinase inhibitors are presented. We postulated that comparison with various docking tools made us to get an accurate conclusion regarding the ligand receptor interaction.

MATERIALS AND METHODS

Target enzyme

Crystal structure of the tyrosine kinase domain of the hepatocyte growth factor receptor c-met was selected as tyrosine kinase target enzyme, which was retired from Protein Data Bank (PDB) at the
Research collaborator for structural Bioinformatics (www.rcsb.org). The selected pdb (1r1w) does not link to any type of legends has a resolution of 1.8 Å [5-6].

Ligand preparation
Various Quinoxaline derivatives were drawn in chemdraw software and checked whether they obey the Lipinski’s rule by using molinspiration software. Energy minimization was carried out by using PRODRG. The structure is saved in pdb format. This ligands in pdb extension is brought into different docking tools [7-8].

Autodock
The autodock 1.5.6 is used as one of the tools for docking purpose. The energy minimized protein in pdb format is modified in autodock tool by adding polar hydrogens, gasteiger charges and merging polar hydrogens. Finally the atoms are assigned as AD4 type and saved as pdbqt format. The ligand in pdb format is modified by giving torsions and saved in pdbqt. The receptor grids of enzymes were developed by using 60x60x60 grid points in xyz with grid spacing of 0.375Å. The Lamarckian genetic algorithm was used for all molecular docking simulations. Population size of 150, mutation rate of 0.02 and crossover rate of 0.8 were set as the parameters. Simulations were performed using up to 2.5 million energy evaluations with a maximum of 27,000 generations. Each simulation was performed 10 times, yielding 10 docked conformations. AutoDock 1.5.6 rank them according to their energies. The lesser the energy, the better the conformation, therefore best confirmation (i.e. Least energy) was selected [9].

Patchdock
It is a geometry-based molecular docking algorithm. It is aimed at finding docking transformations that yield good molecular shape complementarity. The PatchDock algorithm divides the Connolly dot surface representation of the molecules into concave, convex and flat patches. Then complementary patches are matched in order to generate candidate transformations. Each candidate transformation is further evaluated by a scoring function that considers both geometric fit and atomic desolvation energy. Finally, an RMSD (root mean square deviation) clustering is applied to the candidate solutions to discard redundant solutions. The main reason behind PatchDock’s high efficiency is its fast transformational search, which is driven by local feature matching rather than brute force searching of the six-dimensional transformation space. It further speeds up the computational processing time by utilizing advanced data structures and spatial pattern detection techniques, such as geometric hashing and pose clustering, that were originally developed in the field of computer vision as detailed [10].

iGEMDOCK
For the docking, virtual screening, and post-screening analysis. For post-screening analysis, iGEMDOCK can enrich the hit rate and provide biological insights by deriving the pharmacological interactions from screening compounds. The pharmacological interactions represent conserved interacting residues that often form binding pockets with specific physico-chemical properties to play the essential functions of the target protein. Experiment results show that the success rate of iGEMDOCK is 78 % (root-mean-square derivations below 2.0 angstrom) on 305 protein-compound complexes. For virtual screening, pharmacological interactions derived by iGEMDOCK often involve the biological functions and enrich the hit rates on three public sets We believe that iGEMDOCK is useful for understanding the ligand binding mechanisms and discovering lead compounds [11].

Consensus scoring and ranking
Generally, docking programs predict the protein - ligand complex structures with reasonable accuracy and speed. The ability to predict the binding mode of a ligand to differentiate poses is based on reliable scoring functions. However, combinations of various scoring functions would reduce the errors in single scoring schemes and improve the probability of identifying true hits. Thus, it has been demonstrated that consensus scoring is generally more effective than single scoring for molecular docking and represented an effective way in getting improved hit rates in various virtual database screening studies. In our study, we tested three different scoring functions such as Autodock 1.5.6, iGEMDOCK and Patchdock softwares. The scores generated by the programs are ranked by using the Tsar and generated 4 classes, of which, the compounds in class 1 is found to have top rank and considered to have the top score.
RESULTS AND DISCUSSION

Table 1. Comparative docking study of Quinoxaline derivatives with TKI’s by using three different docking softwares is underlaid below.

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Docking poses
In these the sticks in red colour indicates the ligand, blue colour shows protein and green coloured line represents the hydrogen bond. The ligand interacts with amino acids like ASP 122, TYR 1230, PHE 1089, ASP1228, ASP 1204, HIS 1202, ASP 1222, ARG 1203, PHE 1280, PRO 1246, LEU 1246. From the 10 confirmation the best confirmation is selected and its binding energy, inhibition constant are -8.04 and 1.28 µm respectively. This exhibits the confirmation with lesser inhibition constant shows better results.

Fig 1. The best pose of the standard drug nilotinib

The docking results reveal that the (E) -4-((2,3diphenyl quinoxaline-6-sulfonamide) methyl) benzene sulfonic acid NQ₁₁ exhibits more negative binding energy -8.13 Kcal/mol, than the standard synthetic drug nilotinib which is having a binding energy of only -8.07 Kcal/mol. This can be a breakthrough in the novel drug search. NQ₆ is having less negative binding energy that is -6.59 Kcal/mol

Fig 2. The best autodock poses of the designed lead Quinoxaline derivatives

The blue colour represents the protein chain and rose indicates the ligand, the 2 green line indicates 2 hydrogen bond interactions. NQ₁ have a binding energy of -8.04 Kcal/mol and inhibition constant of 1.28 um.

The binding energy and inhibition constant of NQ₁₀ is -8.01 Kcal/mol &1.34 µm respectively. Torsional energy is found to have 1.19. Vanderwalls hydrogen bond dissolving energy is -9.15.

The torsional energy is 1.19 and ligand efficiency is 0.21. Inhibition constant is -8.13 µm and binding energy is found to be 1.34 Kcal/mol. There is one hydrogen bond interaction.
Patch Dock

Fig 3. The best patchdock poses of Quinoxaline derivatives in patchdock

The ribbon structure represents the protein strands and stick form indicates our ligand molecule. Patchdock provides atomic contact energy (ACE) of 200 conformations. The confirmation that has a more negative ACE is considered to be the best confirmation. The ligand performs interesting intermolecular H-bond with catalytic residue. In the present study NQ_7, NQ_5, NQ_11 have the highest negative ACE value, -455.70, -451.52 and -424.87 respectively. Whereas the standard drug nilotinib have ACE value as -312.95 which is lesser effective than the synthesised scaffolds.

iGEMDOCK

Fig 4. iGEMDOCK poses of standard and best quinoxaline derivatves

In the igemdock, Vander wall interaction, hydrogen bond energy and electrostatic interaction are taken as the parameters. Among the designed series NQ_3, NQ_5, NQ_9 and NQ_11 have, the more negative energy, that is, -105.47, -105.43, -110.64 and -105.32 respectively. Standard drug nilotinib have energy -97.25 which is better that the synthesized compounds NQ_1, NQ_12, NQ_10. Taking a closer look into the residues in interaction with the docked pose, we could note that this pose interacted likely with the same manner as the original crystallographic ligand, through hydrogen bonds with the residues M-CYS-1308, S-GLN-1304, S-ASP-1310, S-GLU-1120, S-ASP-1310 and M-GLU-1306.

The Consensus scoring method is followed for ranking and scoring molecular docking results and represents an effective way in getting improved hit rates in various virtual database screening studies. By this method NQ5 and NQ11 have high scores that are 15 and NQ6, NQ10 scored the least, that are 9 and 8 respectively. Thus combinations of various scoring functions would reduce the errors in single scoring schemes and improve the probability of identifying true hits. Therefore methyl and sulfonic acid substituted designs are predicted to be better active. This can be taken into account for the further design and synthetic development of the anticancer drugs.
CONCLUSION
Molecular docking simulation approaches are commonly used in modern drug design process to take a closer look into ligand-receptor binding mode and provide guidance for future studies. In this, we have carried out a comparative docking study by using autodock, iGEMDOCK and patchdock to get an accurate score and thus identifying true hits. About 12 derivatives of quinoxaline are designed and results were compared. Among them methyl and sulfonic acid substituted diphenyl quinoxaline analogues were found to have better score in which scoring is done by consensus. The present work can be considered for the development of various derivatives of Quinoxaline as a c-met kinase inhibitors.

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CONFLICT OF INTEREST
No Conflict of Interest.

REFERENCES