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Original Article

IN SILICO SCREENING BY MOLECULAR DOCKING OF HETEROCYCLIC COMPOUNDS WITH FURAN OR INDOLE NUCLEUS FROM DATABASE FOR ANTICANCER ACTIVITY AND VALIDATION OF THE METHOD BY REDOCKING

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ABSTRACT

Objective: This study aims to perform *in silico* screening of nine heterocyclic ligands containing furan or indole with oxygen in their structure selected from the compound database based on a literature review for predicting their anticancer activity on tyrosine kinase receptor receptors.

Methods: The receptor is complex with the ligand Gliteritinib and was downloaded from the protein database. The ligands used for this study were 5-fluoro-1H-indole-2-carboxylic acid,2(5H)-Furanone Furfuryl pentanoate, Furan-2,5-dicarbaldehyde, 2,5-Furandicarboxylic acid, Furan-2-yl(1H-indol-3-yl) methanone, Tert-butyl 3-formyl-1H-indole-1-carboxylate,7-Amino-5-fluoroindolin-2-one,7H-Furo[3,2-g]chromen-7-one. Pyrex molecular docking software was used to perform the analysis. The study was validated using a re-docking technique using the ligand Gliteritinib.

Results: A good docking score of (-7.8) was obtained for tert-butyl 3-formyl-1H-indole-1-carboxylate, leading to promising activity prediction. Furan-2-yl(1H-indol-3-yl) methadone and 7H-Furo[3,2-g]chromen-7-one also scored well with (-7.5) and (-7.3) respectively. The redocking process resulted in a score of (-9.2).

Conclusion: Values are comparable to the root primary square value, showing the reproducibility of this method. The finding gives insight into Insilco docking for anticancer activity and further exploration of phytochemicals for Insilco screening.

Keywords: Docking, Pyrex, Indole, Furan, Cancer, Redocking

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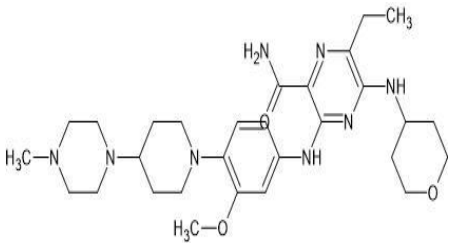
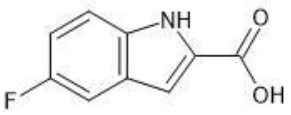
INTRODUCTION

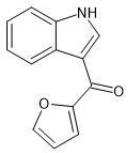
Furan-containing compounds have gained importance in medicinal chemistry since they have been used as chemotherapeutic agents. The C-2-substituted furan-containing compounds, anticancer, anti-inflammatory antioxidant, and anti-fungal agents are widely distributed in plants. Some are used for treating cardiac arrhythmias. Tetra hydro furyl moiety is a part of cardiac glycosides [1]. Furan-2 (5H)-one scaffold and its variations are present in various phytochemicals. Multiple derivatives can be synthesized by modifying the basic structure. Furan-2 (5H) one. It is of great interest because the five-membered ring offers a unique positioning of substituents by creating a scaffold to design a new compound. The commercially available inexpensive reactive forms of furan (5H)–one [2]. Oxygen-and sulfur-based heterocycles form the core structure of many anticancer, anti-inflammatory, anti-tumor, anti-bacterial, anti-malarial, and anti-fungal drugs. 'O' and 'S' bearing hetero compounds have paved the way for discovering new anticancer drugs. Among the other hetero compounds, oxygen and sulfur-containing heterocycles occupy an exceptional position in pharmaceutical drug development for anticancer compounds. Paclitaxel, a heterocyclic drug incorporating an oxygen-based structure featuring a combined oxetane ring, has been successfully employed in the treatment of ovarian, breast cancer, and sarcoma. Epoxide ring contains ether linkage, a fundamental structural unit of many anticancer drugs. Oxetanes are an essential element in altering metabolic pathways. Coumarinspossessanti-proliferative action. Flavanones are natural products that contain oxygen and exhibit numerous bioactivities like anti-bacterial, analgesic, anti-fungal, and antioxidant properties. Benzo furan derivatives have been reported as anticancer agents. Cancer is a complex disease; it is characterized by uncontrolled cell proliferation. However, with ongoing efforts and advancements in medical research, we can find better ways to prevent and treat it. The receptor tyrosine kinase plays a crucial role in cellular growth, motility, differentiation, and metabolism. They are subclasses of tyrosine kinases [3]. They share similar structures: an extracellular region and a carboxyl 'C' terminal. Dysregulation of RTK's signaling leads to many human diseases like Cancer [4, 5]. Molecular docking seeks to precisely anticipate the arrangement of ligands within the confines of a receptor's binding site, providing an accurate estimation of binding strength [6]. Critical advancements in this field include addressing receptor flexibility, incorporating solvation effects, fragment docking, and post-processing the docking results by integrating them into homology models and conducting comparisons [7]. PyRX is free open docking software by which we can dock multiple ligands in a single with a target protein. PyRX uses the Auto Dock Vina tool and Open Babel. Biovia Discovery Studio is used as a visualizer [8]. The study aims to provide valuable insights into the potential of heterocyclic compounds containing furan or indole nucleus as anticancer agents, validate the reliability of the molecular docking approach for virtual screening, and contribute to the identification of novel lead compounds for further experimental evaluation and development as anticancer drugs.



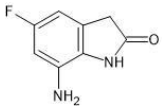
Gliteritinib



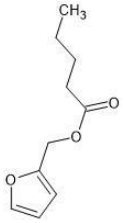
5-fluoro-1H-indole-2-carboxylic acid



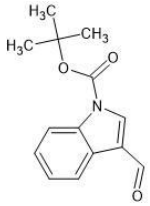
Furan-2-yl(1H-indol-3-yl)methanone



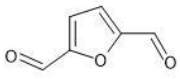
7-Amino-5-fluoroindolin-2-one



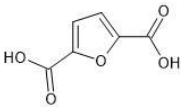
Furfuryl pentanoate



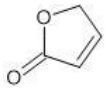
tert-butyl 3-formyl-1H-indole-1-carboxylate



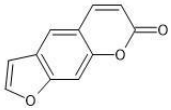
Furan-2,5-dicarbaldehye



2,5-Furandicarboxylicacid



2(5H)-Furanone



7H-Furo[3,2-g]chromen-7-one

MATERIALS AND METHODS

Protein preparation

The protein structure (6JQR) was downloaded from the RCSB protein data bank. The PDB file was opened, and the protein's binding site was determined from the available literature. The protein's crystal structure was purified with a ligand by eliminating HET atoms. The ligand groups were also removed. Removed the chains to avoid complexity and saved the file in PDB format [9].

Preparation of ligands

The protein and ligand must be in PDB format. The ligand was converted into PDB format using Biovia Discovery Studio. Biovia discovery studio was opened, and the ligand was selected and saved as PDB form [10].

PyRX software

Developed in Python programming language, is available for download and can be executed on any computer, meeting the required configuration and specifications. The hardware utilized for this purpose consisted of a Dell Intel Core i5 8th Generation system equipped with 8GB RAM, running Windows 10 software, and featuring HD Graphics.

Input files

Pub chem. The database was used to download the 3D structure of the sdf format of ligands. RCSB was used to download 6 JQR Receptor proteins.

Performing docking using PyRX

Auto dock vina was used for docking. It is provided in PyRX that can be docked using the Vina algorithm [11]. The protein and ligand were loaded. The protein and ligand were defined by clicking on protein and selecting make macromolecules. The ligand was defined by selecting make ligand. The PDBQT files were prepared. The grid box was established by choosing the protein and ligand and then proceeding by clicking forward. Once the grid box emerged, it was adjusted according to the docking requirements. Following the selection of the grid box, the level of docking exhaustiveness could be specified by entering the relevant numerical value. The docking process started by clicking the forward button. After forward docking, the poses and affinities can be obtained. The RMSD values were obtained. The PDB/PDBQT protein and vina output files were opened in PYMOL to analyze the result [12].

The redocking was also done using the same procedure, and binding affinity was obtained.

RESULTS AND DISCUSSION

The approach of molecular docking is widely used in research to determine potential binding modes of ligands with validated therapeutic proteins. It's a highly regarded method and has been successful in investigating the interaction of proteins with various ligands. In the present study, molecular docking was conducted using the X-ray crystal structure of FLT3, which is a receptor tyrosine kinase that plays a crucial role in hematopoiesis and is activated in various cancer types. FLT3 is complexed with the protein Gliteritinib, which has a Protein Data Bank (PDB) ID of 6JQR. According to literature reports, the 6JQR protein is widely distributed and is activated in tumor cells, where it promotes malignant progression, indicating its crucial involvement in the progression of cancer. FLT3 protein is a promising target for drug development due to its involvement in cancer progression and the fact that FLT3 mutations are commonly found in patients with acute myeloid leukemia. Therefore, it has the potential to be targeted for therapeutic intervention. The FLT3 inhibitor Gliteritinib is an excellent candidate for preventing FLT3 activation in these patients. Understanding the binding mode of Gliteritinib to FLT3 is of great significance for drug development and the treatment of AML. The molecular docking approach used in this study helps predict the potential binding mode of Gliteritinib to FLT3, which is an essential step in understanding the mechanism of action of FLT3 inhibitors and developing new drugs that target FLT3.

The study revealed that among the nine-oxygen-containing hetero compound of furan or indole heterocyclic compounds, auspicious activity was predicted due to good docking score for (-7.8) tert-butyl 3-formyl-1H-indole-1-carboxylate.,(--7.5) for Furan-2-yl(1H-indol-3-yl)methadone and (-7.3) 7H-Furo[3,2-g]chromen-7-one. When compared to the redocking score of Gliteritinib (-9.3). It can (-7.8) be considered a lead compound for anticancer activity and drug development. Indole core has continuously attracted the attention of researchers and has become a dynamic area of research due to its outstanding pharmacological activity [13]. It is substantiated by *in vivo* studies. The receptor 6JQR is the Tyrosine kinase receptor, FLT3, in complex with Gliteritinib. Defects in FLT3 can cause myelogenous leukemia. Acting as a cell surface receptor for the cytokine FLT3G,

thetyrosine–protein kinase plays a crucial role in governing the differentiation, proliferation, and survival of hematopoietic progenitor cells. Drugs like Gliteritinib act as inhibitors of FLT3. Therefore, a compound exhibiting favorable docking scores will likely possess FLT3 inhibitory activity, suggesting potential anticancer properties. Further studies using animal models and cell lines have to be conducted. Bioavailability and drug-like characteristics are comparable, and blood-brain barrier penetration is also predicted.

Table 1: Pyrex docking results

Ligand	*Binding affinity	Rmsd/ub	Rmsd/lb
Tert-butyl 3-formyl-1H-indole-1-carboxylate	-7.8	0	0
Furan-2-yl(1H-indol-3-yl)methanone	-7.5	0	0
7H-Furo[3,2-g]chromen-7-one	-7.3	0	0
5-fluro-I-H indole–2 carboxylic acid	-6.4	0	0
7-Amino-5-fluoroindolin-2-one,	-6.4	0	0
2,5-Furan dicarboxylic acid	-5.8	0	0
Furfuryl pentanoate	-5.4	0	0
Furan-2,5-dicarbaldehyde	-5.1	0	0
2(5H)-Furanone	-4.2	0	0
Gliteritinib	-9.2	0	0

*N=9

Table 2: Swiss ADME prediction

Ligand	Lipophilicity	Water solubility	Absorption	Drug likeliness	Synthetic accessibility
5-fluoro-1H-indole-2-carboxylic acid	Log P 1.22	Log S-2.92	GI-High BBB-Yes	Lipinski-0 Violation	1.43
7H-Furo[3,2-g]chromen-7-one	Log P 2.01	Log S-2.73	GI-High BBB-Yes	Lipinski-0 Violation	3.06
7-Amino-5-fluoroindolin-2-one	Log P 1.10	Log S-1.36	GI-High BBB Yes	Lipinski-0 Violation	1.70
Furan-2-yl(1H-indol-3-yl)methanone	Log P 1.88	Log S-3.42	GI-High BBB Yes	Lipinski-0 Violation	2.15
Gliteritinib	Log P 4.15	Log S-5.08	GI-High BBB Yes	Lipinski-2 Violation	4.73

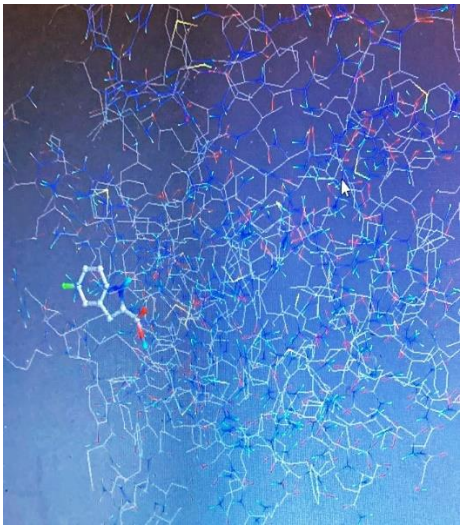


Fig. 1: Docked image of gliteritinib with 6JQR target

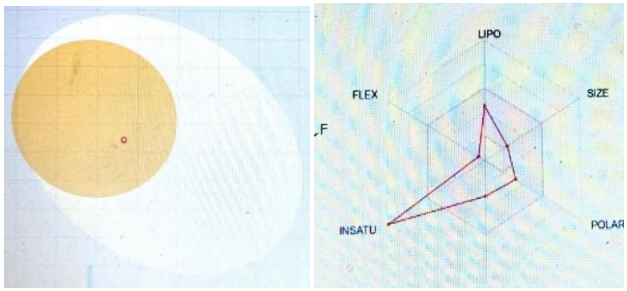


Fig. 2: Bioavailability boiled egg and radar of tert-butyl 3-formyl-1H-indole-1-carboxylate

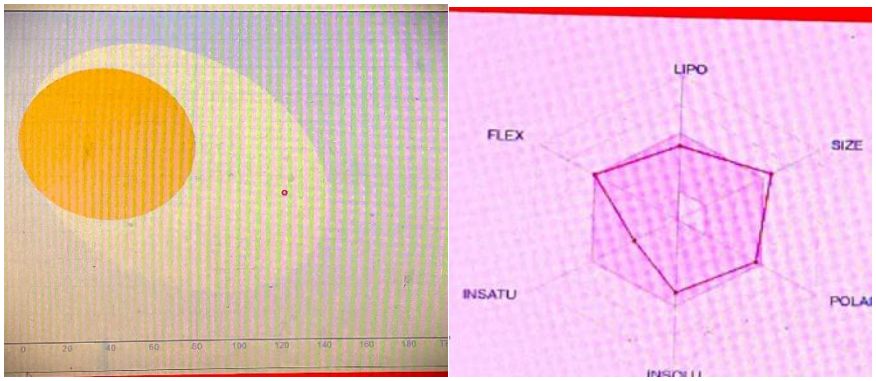


Fig. 3: Bioavailability boiled egg and radar of Gliteritinib

The scoring was analyzed to identify potential lead compounds. The binding affinities were compared with known anticancer drugs. Gliteritinib. The interaction analysis between ligand and protein active site residue identified vital interactions. The structure-activity relationship was done by comparing the compound's chemical structure with predicted activity. Virtual ADME analysis was done using ADME software, and the values were compared.

CONCLUSION

The current study revealed that the heterocyclic compound (-7.8) tert-butyl 3-formyl-1H-indole-1-carboxylate.,(--7.5) for Furan-2-yl(1H-indol-3-yl)methadone and (-7.3) 7H-Furo[3,2-g]chromen-7-one which have oxygen atoms in their chemical structure predicted to have suitable anticancer–anti-tumor property based on their docking scores. They act as FLT3 tyrosine Kinase inhibitors. The Swiss ADME prediction also proves their drug likeliness and acceptability with fair blood-brain barrier penetration than standard drugs. Further *in vivo* and *in vitro* studies and modification of their chemical structure using QSAR studies can be done to produce more potent anticancer compounds. Any new chemical entity that cures a deadly disease like Cancer is a milestone in medical therapeutics.

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AUTHOR CONTRIBUTION

Thomas Kurian made a total contribution to this work

CONFLICT OF INTERESTS

There is no conflict of interest

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