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Research Article

Identification of Potent Lead Molecules for Furin Receptor Through HTVS and Molecular Docking

Harsha Vardhan P, Vikas Reddy V, Mourya Reddy Ch, Rathi Suganya P*

Department of Genetic Engineering , School of Engineering & Technology, SRM University, kattankulathur, Tamil Nadu, India.

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ABSTRACT

Objective: Furin is the family of proprotein convertase and localized in Trans Golgi Network (TGN) and cell surface. It is the major processing enzyme of the secretory pathway. Furin inhibitors are known to be therapeutic agents since it is involved in viral and bacterial activation, alzimer's disease and cancer. Furin is the family of proprotein convertase and localized in Trans Golgi Network (TGN) and cell surface. It is the major processing enzyme of the secretory pathway. Furin inhibitors are known to be therapeutic agents since it is involved in viral and bacterial activation, alzimer's disease and cancer. In this study, High Throughput virtual screening is used to screen natural and synthetic compounds and the short listed compounds are taken for checking the ADMET property. Methodology: The crystal structure of furin protein target was obtained from RCSB protein data bank (PDB Id: 4RYD) and protein preparation is done. Ligand from Zinc database are downloaded and prepared and taken for HTVS. Then the short listed compounds were taken for studying the ADMET property. Results: ZINC19799372, ZINC20411483, ZINC20412114, ZINC20411616 has highest docking score when compared with other small molecules. The drug-likeness and pharmacokinetic properties and other descriptors such as molecular weight, H-bond donors, H-bond acceptors, logP (octanol/water) and human oral absorption for the screened hits were predicted by Qikprop. The selected screened compounds ZINC19799372, ZINC20411483, ZINC20412114, ZINC20411616 has satisfactory percentage of oral absorption of >80% and are known to be potential lead compounds. Conclusion: In this study, we have screened the dataset of 1000 natural compounds and predicted the drug-likeness properties to identify the potent inhibitors against furin, and were also able to visualize the interactions of protein-ligand complex.

Keywords: Furin, inhibitors, HTVS, ADME.

INTRODUCTION

Furin is an important member of proprotein convertase (PCs). This is a calcium dependent serine endoprotease encoded by FURIN gene[1]. It is generally found in the secretory, endocytic pathways and cell surface. Furin is vastly expressed in Golgi apparatus and the main fuction is to cleave other proteins making them active by cleaving consensus motif (Arg-X-(Arg/Lys))[2]. Substrates of Furin include blood clotting factors, serum proteins and growth factor receptors such as the insulin-like growth factor receptor. At the cell surface, pathogens like HIV, influenza, dengue fever, Ebola, Marburg virus, pseudomonas exotoxin, and papillomaviruses are cleaved by furin to become active and attain functional form[3,4]. Furin is a one of the important protein, which plays a major role in many diseases; therefore, it can be targeted for development of therapeutic agents.

Here we focus on identifying the potential inhibitors against the target protein furin to inhibit the expression level of furin. High Throughput Virtual Screening (HTVS) of 1000 natural compounds was carried out. Binding energy and ADME properties of the selected hits were analyzed. The flowchart for the study is given in figure.1.

MATERIALS AND METHODS

Schrodinger Module used for the study are Protein Preparation Wizard[5], Ligprep[6], QikProp[7], Virtual screening and Molecular Docking[8-10] are the Schrödinger modules used for this study. All modules were attained via Maestro graphical interface[11]. The workflow is shown in Figure 1.

Preparation of small molecules

A set of 1000 compounds were prepared for the screening using the Ligprep module of the Schrödinger Suite v10.2 (http://www.schrodinger.com/). In Ligprep, the 2D structures of small molecules were imported to a process that adds hydrogen atoms, removes molecules with inappropriate properties, generates low energy conformers and optimizes geometries. The minimized ligprep output file was used for further analysis.

Preparation of target protein

The crystal structure of furin protein target was obtained from RCSB protein data bank (PDB Id: 4RYD). One furin chain from crystal structure was used for protein preparation Wizard since biological assembly is known to

*Author for Correspondence: rathisuganya.p@ktr.srmuniv.ac.in

Table 1: Top 10 hits of screened compounds based on docking score and glide energy.

Title	Docking score (Kcal/mol)	Glide gscore (Kcal/mol)	Glide emodel	Glide energy (Kcal/mol)
ZINC19799372	-5.751	-5.91	-62.425	-41.083
ZINC20411483	-5.642	-5.722	-60.12	-40.534
ZINC20412114	-5.568	-5.65	-62.169	-40.468
ZINC20411616	-5.504	-5.576	-61.546	-39.984
ZINC54313361	-5.469	-5.642	-61.643	-44.333
ZINC54313359	-5.429	-5.617	-61.342	-44.721
ZINC20591190	-5.58	-6.181	-55.601	-41.137
ZINC22854473	-5.48	-6.393	-78.542	-53.28
ZINC20411602	-5.278	-5.327	-60.719	-43.001
ZINC54313357	-5.245	-5.443	-64.354	-43.799

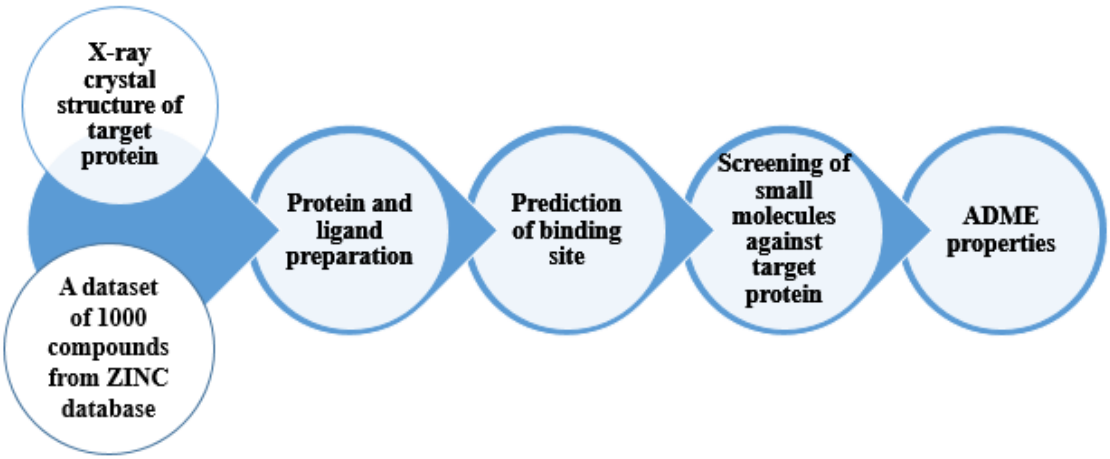

Figure 1: Flow chart for identifying potential inhibitor against furin.

be monomer. In this process, charges and bond orders were assigned, hydrogens were added, waters were removed and protein structure was refined and optimized at neutral pH. Force field OPLS 2005 was used for minimization.

Receptor Grid Generation

After protein preparation, receptor grids were generatedby specifying the binding site with a 3D cubic box. SiteMap was used to estimate the location of the active site by searching regions near the protein surface, generating hydrophobic and hydrophilic contour maps of the protein, and calculating energy potentials. Enclosing box of x:-39.84, y:--8.58, z:-2.61 was placed depending upon SiteMap prediction. Based upon the fact that the binding site is not shallow, the nonpolar atoms were slightly scaled back, by choosing the van der Waals radius scaling factor of 0.75 for non-polar parts, so that nonnative ligands would dock to the receptor better. Rotation of all receptor hydroxyl and thiol groups within the grid was allowed.

Virtual Screening of small compounds

High throughput virtual screening (HTVS) is typically done to test a large compound collection for potential activity against the chosen target. Here Structure-based screening is done to find the binding mode of the protein target. The compounds from the zinc database are taken and screened with target protein based on Qikprop and Lipinski rule of five. It screened the compounds by considering Physiochemical properties and drug like properties such as MW<500, Hydrogen bond donor<5, hydrogen bond acceptor <10 and logP <5. The hit compounds can be marked and ranked according to the fitness score which should be in range from 0 to 3 and docking score was calculated.

Prediction ADME properties

The QikProp program was employed to obtain ADME properties of the compounds. These physically significant descriptors, such as partition coefficient, van der Waals surface, aqueous solubility, and pharmaceutically relevant properties for small molecules. All of the compounds were neutralized before being used by QikProp. The program was processed in normal mode and predicts physiochemical properties and principal descriptors, along with a detailed analysis of log *P* (octanol/water), QP%, SASA, %oral absorption and log HERG. It also checks the acceptability of the compounds based on Lipinski's rule of five, which is crucial for rational drug design.

RESULTS

Screened result of small molecules with target protein

Small molecules of 1000 natural compounds were downloaded from ZINC database was screened against target protein based on pharmacokinetic properties and Lipinski's rule of 5. The binding orientation and docking score relative to the target receptor were determined and

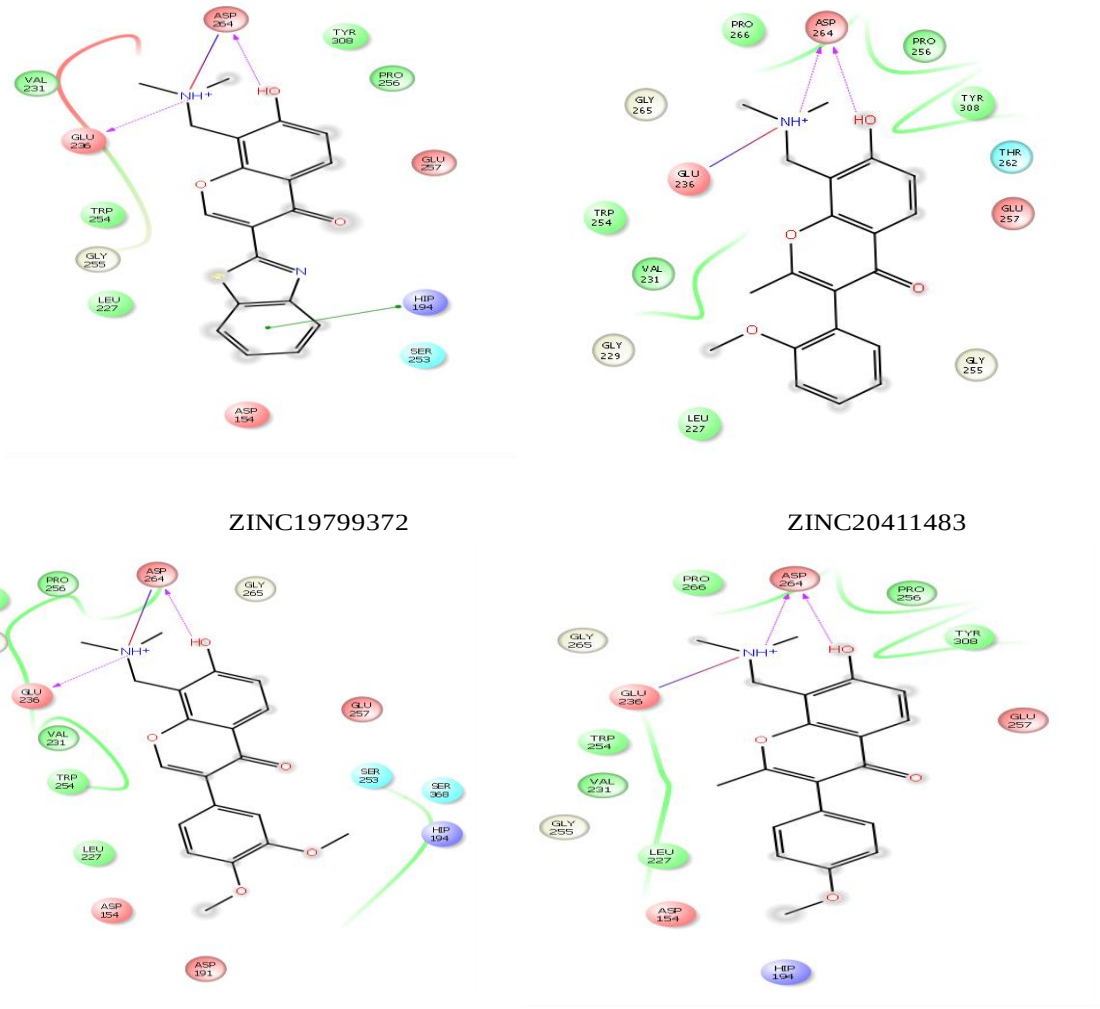

Figure 2: Protein- Ligand interaction of screened hits with active site of target protein.

Table 2: Prediction of ADME properties for selected hits.

Title	Molecular Weight (KDa)	Donor HB	Acceptor HB	% Human Oral Absorption
ZINC54313359	400.433	0	7	100
ZINC54313361	414.46	0	7	100
ZINC54313357	400.433	0	7	100
ZINC20411602	395.454	1	6.75	95.461
ZINC20412114	339.39	1	6	92.535
ZINC20411616	339.39	1	6	91.417
ZINC20411483	355.39	1	6.75	90.352
ZINC19799372	352.407	1	6.75	86.739
ZINC22854473	414.5	1	8	77.417
ZINC20591190	400.492	2	8.95	62.098

it was varied from -5.91 Kcal/mol to -1.83 Kcal/mol. Table 1 shows the best 10 ligands and their corresponding docking score with receptor furin. It was observed that the compound ZINC19799372, ZINC20411483, ZINC20412114, ZINC20411616 has highest docking score when compared with other small molecules. The best interaction with active site was shown in Figure 2.

The best glide gscore was obtained for compound ZINC19799372 which gave a score of -5.91 Kcal/mol and glide energy of -41.08Kcal/mol. It had H-bond interaction with side chain residue ASP 264 and GLU 236. The compound ZINC20412114 gave glide gscore of -5.65 Kcal/mol and glide energy of -40.46 Kcal/mol with H-bond interaction with side chain residue ASP 264. The compound ZINC20411483 gave glide gscore of -5.722 Kcal/mol and glide energy of -40.534 Kcal/mol with H-bond interaction with side chain residue ASP 264, GLU 236. The compound ZINC20411616 gave glide

gscore of -5.576 Kcal/mol and glide energy of -39.984 Kcal/mol with H-bond interaction with side chain residue ASP 264.

Predicted Drug-likeness property

The drug-likeness and pharmacokinetic properties and other descriptors such as molecular weight, H-bond donors, H-bond acceptors, logP (octanol/water) and human oral absorption for the screened hits were predicted by Qikprop. The selected screened compounds ZINC19799372, ZINC20411483, ZINC20412114, ZINC20411616 has satisfactory percentage of oral absorption of >80% and are known to be potential lead compounds. Table 2 shows the ADME properties of selected small molecules.

CONCLUSION

Furin is a type I transmembrane protein which can be transported through secretory pathway. Furin cleaves precursor protein to render them into active form. It activates both host and pathogen proteins at Trans Golgi Network and cell surface respectively. Here the small molecules of 1000 natural compounds from ZINC database were screened based on QikProp and Lipinski's rule of five. Based on glide gscore and ADME properties, chemical compounds ZINC19799372, ZINC20411483, ZINC20412114, and ZINC20411616 are known to show good binding energy and drug-likeness properties

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