HOMOLOGY MODELING AND VIRTUAL SCREENING: A FAST TOOL FOR DRUG DESIGN

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Abstract: Breast cancer is the most common persistent cancer and the second main cause of cancer death in women.Sgk3 protein is serum glucocorticoid inducible kinase-3 belonging to AGC family kinase protein. It is also called as CISK (cytokine independent survival kinase). Sgk3 works as an estrogen receptor and endorses estrogen-mediated cell survival causing breast cancer. The present work involves identification of leads against sgk3 protein. The 3D structure of sgk3 protein is built using homology modeling techniques. Molecular dynamics simulation is carried out using NAMD for energy minimisation of the protein .Validation is performed by Ramchandran plot, proSA and errat. Further, active site is determined using different servers, Site map and literature studies. Grid is generated using active site residues and Asinex ligand molecules are docked at the binding region. Based on the scoring functions and ADME properties new chemical entities are identified. Synthesis of new analogues will be carried out, which inhibits cell proliferation to prevent breast cancer.

Keywords: Homology modeling, Molecular dynamics, validation, virtual screening, ADME properties.

1. INTRODUCTION

The mainstream of the human breast cancer starts with estrogen dependent protein kinase and activation of the estrogen receptor [1]. Estrogen is group of similar hormones estrogen, diol and triol.These hormones are uniquely responsible for the growth and development of female characteristics and reproduction. Estrogen is produced in the ovaries, adrenal glands and fat tissues. In women estrogen circulates in the blood stream and binds to ER (estrogen receptor) cells in target tissues. Estrogen plays a crucial role in development and progression of ER- positive breast cancer through ERα. These ERα consist two ER binding regions at the sgk3 locus. Promoter analysis exposed that ERα stimulates the activity of SGK3 promoters by interaction [2].SGK3 protein is the part of SGK family Kinase. The family contains three isoforms SGK1, 2 and 3 proteins. These are dependent on PI3-K, serine threonine kinases [3]. SGK family genes involve in distinct functions in Mammals. Those isoform functions show similar functions like v-AKT in cell proliferation, growth and cell survival. In this process SGK3 plays an important role in oncogenic signaling pathway. In Breast cancer progression P I3K is activated by growth factor receptor (RKT) [4], Which in downstream activates and phosphorylates PDK1 [5]. PDK1 protein is further involved in activation and phosphorylation of sgk3 protein in T-loop motif at Thr320 residue [6]. In this way Bcl-xL protein(B-cell lymphoma-extras'large) levels increase and inhibits the pro-apoptotic proteins Bcl-2 protein BAD (Bcl-2 antagonist of cell death (Bad) and forkhead boxO3 (FOXO3) proteins [7, 8, 9, 10]. Sgk3 further Phosphorylates its co-activator flight less-I (FLII) which is also involved in ER positive breast cancer cell survival [11, 12]. All these pathways suggest overexpression of sgk3 protein involved breast cancer leading to tumour progression. SGK3 is novel target which actively participate in breast cancer.

The present study involves inhibition of SGK3 protein and the design of new lead molecules through virtual screeing of asinex database, prioritized by binding interation and ADME properties.

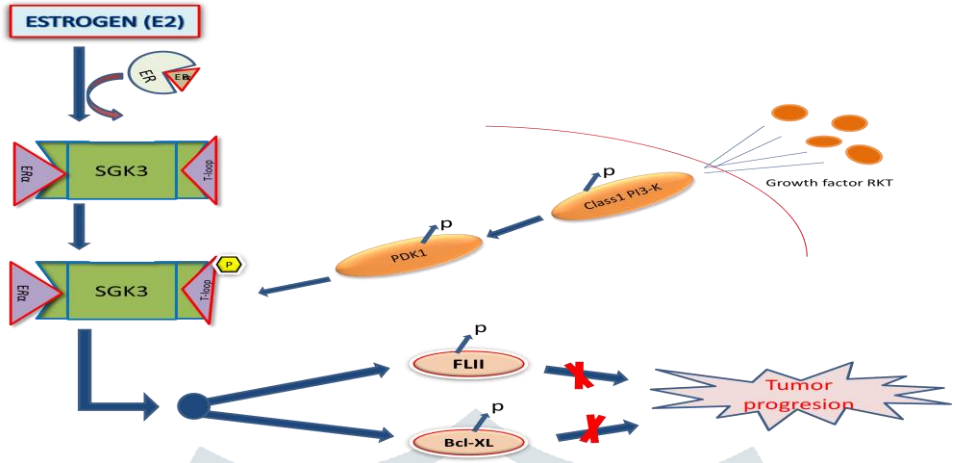


Fig1: Biological pathway of sgk3 protein.

SGK3 is induced by estrogen via estrogen receptor transcriptional mechanism, Growth factor receptor activates class PI3-K which leads to phosphorylation of PDK1, subsequently activation and phosphorylation of sgk3. This activated sgk3 up-regulates Bcl-xL expression, phosphorylating Flightless I (FLII), which are causes breast cancer progression.

2. MATERIALS AND METHODS

2.1. Homology modelling

The structure of sgk3 protein is not reported in the protein data bank. The 3D structure is built using comparative modeling technique based on the known 3D structures of its Closest homologue called as template taken from BLAST server [13, 14].Template Selection is based on query coverage, sequence similarity and statistical E value, The pairwise sequence alignment between the target and the template protein sequences is carried out using ClustalW server [15, 16]. Twenty structures have been built from Moeller 9.13 server [17]. Out of 20, 3D dimensional homology models generated the model with least modeller objective function is taken out for further work.

2.2. Molecular Dynamics

Molecular dynamics simulations are subjected to forces, and their motions at various temperatures and pressures are tracked in computer simulations, The refinement of 3D model of SGK3 protein is carried out by NAMD server [18]. Energy minimisation was done to adjust the structure to the Force field, the segment provided in the system to generate lowest energy to do the simulation studies [19]. Molecular Dynamics for SGK3 protein is carried out by using NAMD_2.9-win32-multicore to reduce the steric clashes that may occur in the system. The solvation of the system was carried out in a cubic solvation box (62.2Å x 62.2Å x 62.2Å) using periodic conditions which is containing water molecules. The fully solvated system was further minimized by using conjugate gradient method. Molecular dynamics simulation of SGK3 protein was performed using CHARMM with all atoms CHARMM 22 force field to provide the lowest energy model of SGK3 protein [20].

2.3. Protein preparation

Protein preparation wizard module of Schrodinger Suite was used to prepare the protein structure (Schrodinger LLC, 2010, New York, NY). from this structure water molecules and hetero atoms removed and hydrogen atoms are added. The complex was minimized to relieve steric clashes using the OPLS 2005 force field [21]. until a stage where a Root Mean Square Deviation (RMSD) of 0.3 Å, which is default cutoff value is reached for the model.

2.4 .Validation of 3D model

Energy minimized 3D model of sgk3 protein is validated using PROCHEK program which gives the information regarding the stereo chemical quality of the given protein Structure in Ramchandran plot which gives dihedral angles φ against ψ of possible conformations of amino acid of protein structure [22]. Further validation process is carried out with ProSA [23]and ERRAT [24, 25]to check the potential errors of the Protein.

2.5. Active site

Active site of sgk3 protein was predicted from SiteMap in Schrodinger tool [26]. This server gives active regions or pockets of protein which are also called cavities revealing potential binding capacity with ligands such as hydrogen bond acceptor, hydrogen bond donor, metal bond regions and hydrophilic regions.

The binding residues of template protein 2R5T and ligand phosphor aminophosphonic acid-adenylate (C10H17N6O12P3) are taken from PDBSum [27].These binding active residues of 2R5T of template are correlated to residues of sgk3 protein in Clustal Omega [28]to generate active site residues

2.6. Virtual Screening

Virtual Screening study [29, 30] is a hopeful tool for identifying new ligand molecules. A library of asinex database molecules are used as ligand molecules for ligand preparation in the ligprep module of the Schrodinger suite (LigPrep version 5.6, Schrödinger, LLC, New York, NY, 2010) [13]. These ligand Molecules are converted to 3D structure in OPLS 2005 force field and minimized to obtain different conformers which are having low energy, tautomeric forms, stereo isomers and ionization states [31]. a grid is generated at the active region of the protein from the Schrodinger suite (Glide, version 5.6, Schrödinger, LLC, New York, NY, 2010) For inhibition of SGK3 protein to enable docking. The ligands are subjected to dock at the active site of SGK3 protein and grid is generated using active site residues in schrodinger suite. The ligand molecules are passed through the various filtering processes. such as high throughout virtual screening HTVS, standerd precision SP and Extra precision XP modes [32,33]. In Each stage top molecules are picked up for filtration, and finally ligand- protein docked complexes are obtained in xp mode which are considered as lead molecules

2.7. Free energy calculations

Prime MM-GBSA formulation, the binding free energy of a ligand (L) to a protein (P) to form the complex (PL) is obtained from Schrodinger server [34]. SGK3 protein and ligand strain energies with good precision are given for a set of ligand molecules and the protein receptor. Below equation shows calculation of the binding Energy of complex.

$$\Delta Gbind = G(PL) - G(P) - G(L)$$

The free energy of each of the three molecular systems P, L, and PL is given by the expression:

$$G(X) = EMM(X) + Gsolv(X) - TS(X)$$

ΔEmm = The difference in the minimized energy between the receptor - ligand complex and the sum of the energies of the free receptor and the free ligands.
ΔGsol = The difference in the GBSA solvation energy between the receptor - ligand complex and the sum of the energies of the free receptor and the free ligands.
ΔGSA= The difference in the surface energy between the receptor - ligand complex and the sum of the energies of the free receptor and the free ligands.

2.8. ADME properties prediction

The ligand molecules obtained from xp outfile, are subjected to ADME (adsorption, distribution, metabolism and elimination) properties using Qikprop module of Schrodinger software suite (QikProp version 3.3). These molecules have drug like properties, and lead a Promising way to identify NCE'S [35].

3. RESULTS AND DISCUSSION

The 3D structure of SGK3 protein is not reported in Protein Data Bank, hence the 3D model was built for sgk3 protein using homology modelling technique based on sequence similarities with template protein. This similarity is identified based on E value, query coverage by using different servers, Which are shown in table1, Different servers are used for The template selection such as NCBI BLAST and J PRED [36].

Table 1: SGK3 protein template selection was carried out by different web servers.

S.No	Name of The Tool	Parameters	Template PDB IDs	e-value
1	BLAST	Sequence position	2R5T A	0-0
2	J-PRED	Secondary structure prediction	2R5T A	e-153

Conserved domain of SGK3 protein obtained from BLAST server indicates the active site region of protein SGK3 show in fig-2.

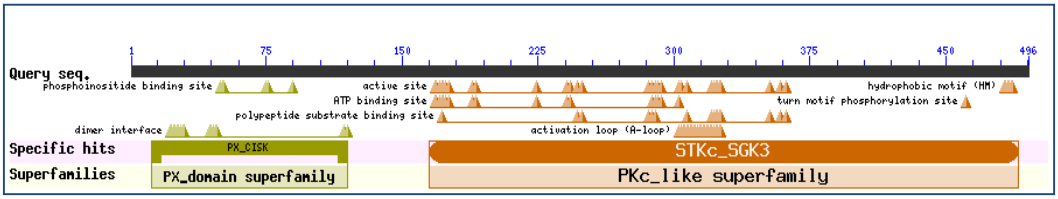


Fig-2: The Conserved domains of sgk3 protein indicating from 160 to 363 amino acid residues as active site region Retrieved from BLAST server.

Selected template 2R5T-A used to build 3D model of SGK3 protein by homology modelling twenty models were generated from Modeler 9.13 server. Among these 20 models, Model with least energy model taken out subjected to further process. Pair wise sequence alignment of SGK3 protein with sgk1 template is carried out by CLUSTAL-W server shown in fig-3.

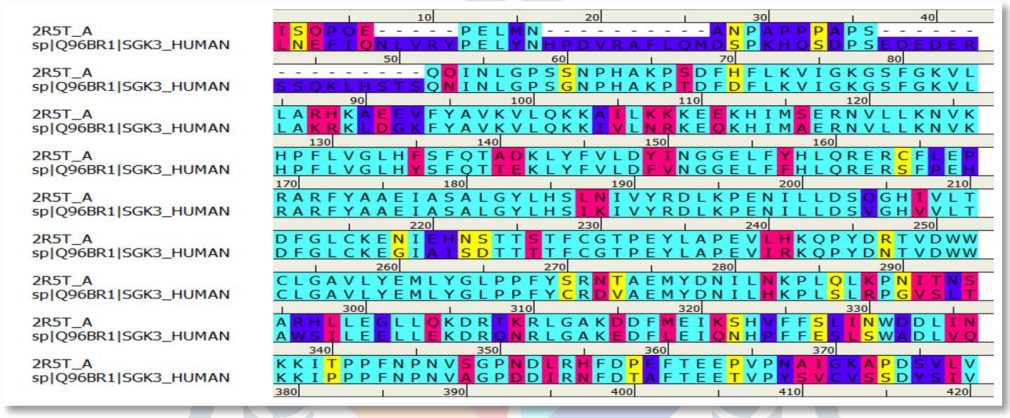


Fig- 3: Pair wise sequence alignment of sgk3 sequence with 2R5T sequence is generated from CLUSTAL OMEGA server. Identical residues are represented cyan color. Strongly similar residues are pink color, weakly similar residues are in yellow color, and non similar residues are blue in color.

Molecular dynamics (MD) simulations is a useful tool for structure-based drug design. Molecular Dynamics and Simulations studies were performed from NAMD_2.9-win32-multicore.All non-hydrogen atoms were harmonically controlled with a force constant of 30 K.Cal/mol which is decreased to 10 K.Cal/mol during minimisation. Number of time steps in each cycle is 20. Nonbonded interactions were calculated by cut off at an atom pair distance of 10 Å with a 2 Å switching region with one lakh interaction at NTP 298K/1atm. Smooting fuctions for both electrostatic and vanderwal forces were applied by switching technique shown in fig-4.

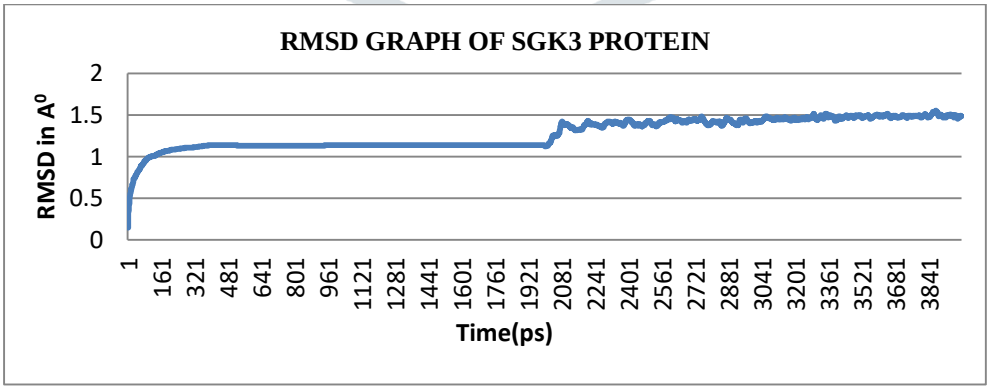


Fig-4: RMSD graph of SGK3 protein drawn by taking RMSD values on Y-axis in Å and simulation time in picoseconds on X -axis. The RMSD deviation was observed 1.1 Å.

Given above RMSD graph indicates stability of the protein. The initial stage of RMSD value is very less (about 0.3 Å) which indicate protein position are fixed during the simulation around the Protein area by water molecules. During RMSD running process

values are gradually increased upto 1.1Å. This process relieves of loose surrounding atoms like hydrogen. These RMSD 1.1Å values are relatively good for maximum protein simulation carried between 977 to 1953 picoseconds getting stability of protein in this region. This resulting minimized protein further validated.

The minimized protein is validated by Ramchandran plot, errat and ProSA. Ramchandran plot obtained from PROCHEK analysis indicates 98.9% Residues having in the favoured region. This indicates good stereo chemical quality of the protein after energy minimisation shown in fig-5.

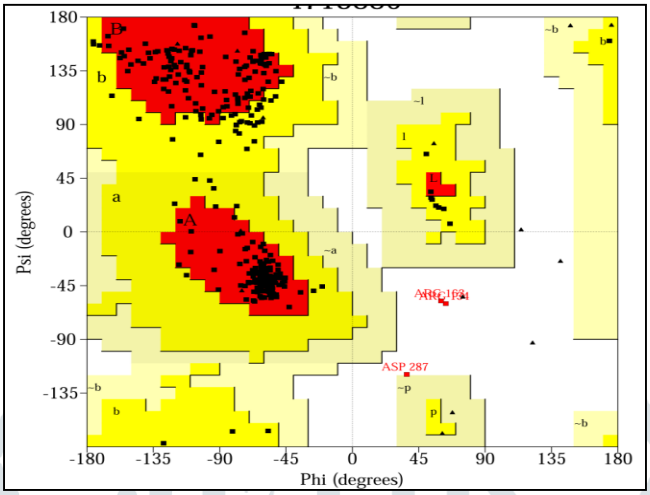


Fig- 5: Stereo chemical analysis and of SGK3protein by Ramachandran contour plot using PROCHECK server.

Statistics Of Ramchandran Plot	No. of residues	percentage
Most favoured regions [A, B, L]	225	80.50%
Additional allowed regions [a, b, 1, p]	34	18.4.9%
Generously allowed regions [~a, ~b, ~1,~p]	5	0.0%
Disallowed regions [XX]	1	1.1%
		98.9%
Non- glycine and non- proline residues	265	
End –residues (excl Gly and Pro)	1	
Glycine residues	16	
Proline residues	13	
	295	

Fig-5: Stereo chemical analysis and of SGK3protein by Ramachandran contour plot using PROCHECK server. The red color in the plot indicates the most favorable region. Yellow represents additionally allowed region. The Ramachandran contour plot for sgk3 protein is showing amino acids in most favoured region as 91.0%, additionally allowed region 7.9%% , generously allowed region 0.4% and disallowed region 0.7%.

Dimension of structural error for each residues in 3D structure model was analysed by ERRAT server from SAVES. Non- bonded interactions between different atoms was explained by ERRAT,resulting in overall model quality 81.935, indicating the model is stable shown in fig-6.

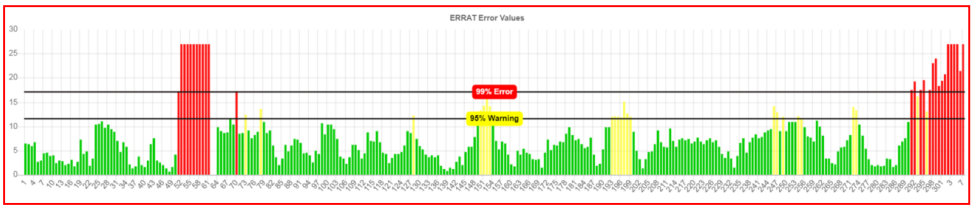
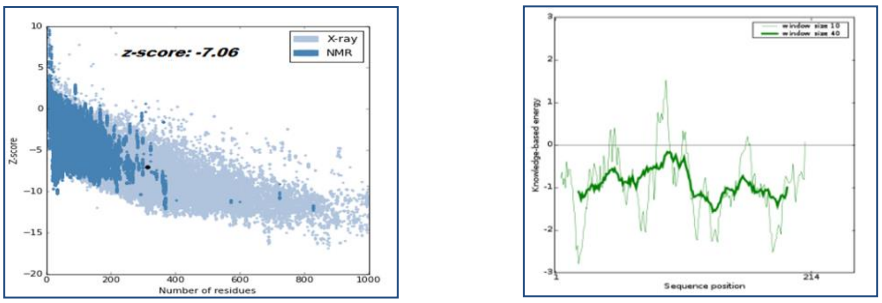


Fig- 6: ERRAT of SAVES servers given 81.935 overall quality factor of SGK3 protein.

ProSA consist of two models ie overall model quality and local model quality of protein. In overall model quality (Fig-A) -7.06 Z-score indicates stability of the protein which is represented as block spot. Local model quality graph (fig-B) is correlated between amino acid residues vs energy showing all the amino acid residues of sgk3 protein fall in negative region indicating good quality model. shown in fig- 7.



(A) Overall model quality (B) Local model quality

Fig- 7:

{Fig-A}: Overall Model Quality of ProSA-web z-score of all protein in PDB determined by X-ray crystallography (light blue) and by NMR spectroscopy (dark blue).The black spot corresponds to SGK3 protein. Z-Score = -7.06.
{Fig-B}: Local model quality of SGK3 protein evaluated from ProSA energy plot with respect to amino acid sequence.

3D structure of sgk3 protein consists of 13 helix- helix interactions, 20 beta turns,2 sheets, 14 helics,5 beta bulges,7 strands, in this C-terminal region yellow in color N-terminal region purple color, conserved domain indicates light brown shown in fig-8.

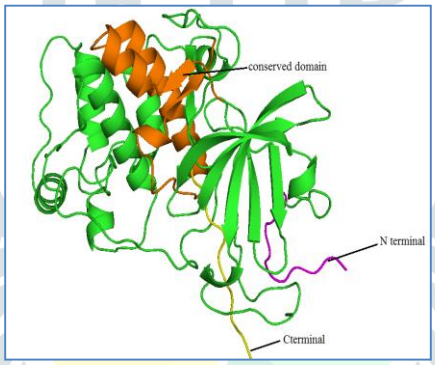


Fig-8: 3D model of SGK3 protein. N-terminal amino acids and C-terminal amino acids shown in brown and blue colors respectively.

Table 2: 14 α-helices of SGK3 protein secondary structure with their starting, ending amino acids, sequence of residues and length.

No	Start	End	No.resid	Length	Sequence
1	Pro95	Asp97	3	-	PSD
2	Lys131	Ala133	3	-	KKA
3	Leu184	Glu191	8	12.32	LFYHLQRE
4	Glu196	Ser215	20	29.93	EPRAREYAAEIASALGYLHS
5	Pro225	Asn227	3	-	PEN
6	Lys245	Asn247	3	-	KEN
7	Pro266	Leu269	4	6.68	PEVL
8	Thr277	Tyr292	16	24.09	TVDWWCLGAVLYEMLY
9	Thr302	Asn311	10	14.33	TAEMYDNILN
10	Asn322	Leu331	10	15.24	NSARHLLEGL
11	Arg336	Lys338	3	-	RTK
12	Phe346	Lys350	5	8.01	FMEIK
13	Val353	Phe355	3	-	VFF
14	Trp360	Lie364	5	7.84	WDDLI

Length of S.No 1, 2, 5,6, 11, 13 are not indicated as one helix turn requires more than 4 amino acids. . Fig-9 shows the Interaction diagram between template 2R5T with its ligands. This diagram taken from PdbSum is used to identify active site residues of SGK3 protein shown in fig-9

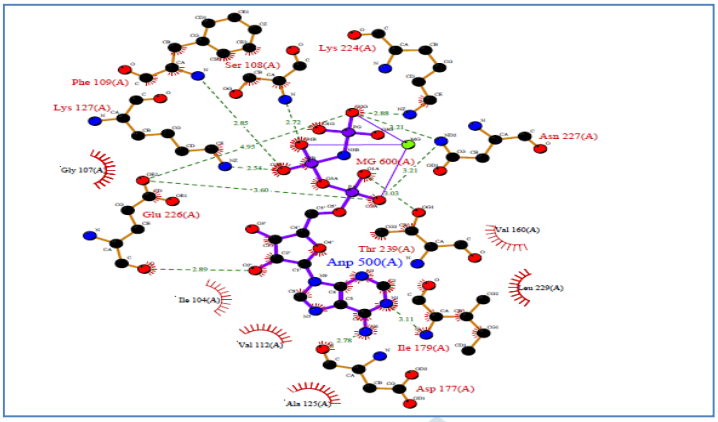


Fig-9: Active site residues of 5R2T protein are identified from ligand interaction diagram LigPlot in PDBSum.

Identified residues of 5R2T templet protein is manually correlated with SGK3 protein using Clustal Omega. The identified residues of SGK3 are I104, G107, S108, F109 V112, K127, V160, D177, I179, L224, E226, N227, L229, T239, A500 shown in fig-10.

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sp|O00141|SGK1_HUMAN      VKTEAAKGT--LTYSRMRGMVAILIAFMKQRRMGLNDFIQKIANNSYACKHPEVQSILKI
sp|Q96BR1|SGK3_HUMAN      LKKQFPAMALKIPAKRIFG-DNFDPDFIKQRRAGLNEFIQNLVRYPELYNHPDVRAFLQM
                          :*.:    :  :  .*: *   :   *:**** ***:***::..     :**:*:::*::
                                                          104 107 108 109 112
sp|O00141|SGK1_HUMAN      SQPQEPELMN-----ANPSPPPSPSQQINLGPSSNPHAKPSDFHFLKVLGKGSFGKVLLA
sp|Q96BR1|SGK3_HUMAN      DSPKHQSDPSEDEDERSSQKLHSTSQNINLGPSGNPHAKPTDFDFLKVIGKGSFGKVLLA
                          ..*:. .  .    . .    * **:******.******:**.****************
                                   127                              160
sp|O00141|SGK1_HUMAN      RHKAEEVFYAVKVLQKKAILKKKEEKHIMSERNVLLKNVKHPFLVGLHFSFQTADKLYFV
sp|Q96BR1|SGK3_HUMAN      KRKLDGKFYAVKVLQKKIVLNRKEQKHIMAERNVLLKNVKHPFLVGLHYSFQTTEKLYFV
                          ::* :  ********** :*::**:****:******************:****::*****
                          177 179                                224 226 227 229
sp|O00141|SGK1_HUMAN      LDYINGGELFYHLQRERCFLEPRARFYAAEIASALGYLHSLNIVYRDLKPENILLDSQGH
sp|Q96BR1|SGK3_HUMAN      LDFVNGGELFFHLQRERSFPEHRARFYAAEIASALGYLHSIKIVYRDLKPENILLDSVGH
                          **::******:******.* * ******************::*************** **

sp|O00141|SGK1_HUMAN      IVLTDFGLCKENIEHNSTTSTFCGTPEYLAPEVLHKQPYDRTVDWWCLGAVLYEMLYGLP
sp|Q96BR1|SGK3_HUMAN      VVLTDFGLCKEGIAISDTTTTFCGTPEYLAPEVIRKQPYDNTVDWWCLGAVLYEMLYGLP
                          :********** *  ..**:*************::*****.******************
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Figure 10: Prediction of active site of human SGK3 protein with SGK1 template protein
The active site residues of SGK3 and SGK1 residues shown green and pink respectively.

Grid is generated using the active site residues. The same residues were found in putative active site prediction servers SiteMap,Q-site.The ligand binding activesite having different Volumes.

The active site domain contains hydrogen bond donors, hydrogen bonds Acceptor, hydrophilic and the hydrophobic regions identified by SiteMap gives an idea about nature of the binding site region. Among three volumes generated from Sitemap, SiteMap1,2 and 3 are having high Site score, and D score. The calculation is based on the hydrophobicity of the pocket for the druggability and expresses in terms of numerical values 0-2. Below numerical values indicates bonding site nature of the protein completely fit for docking ligands, shown in table-3.

\Table 3): Active site regions produced in Sitemap for SGK3 protein.

Site map site	Site score	Size	Dscore	Volume (Å)	Hydro phobic	Hydro philic
1	1.057	101	1.076	165.326	1.021	1.002
2	1.021	113	0.964	486.031	0.229	1.267
3	0.893	82	0.904	174.930	0.251	0.992

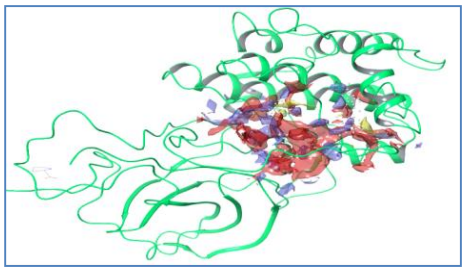


Fig-11: Active site domain of the sgk3 protein identified from sitemap in schrodinger tool Red color depicting the hydrogen donor, light blue indicate hydrogen acceptors, hydrophilic and hydrophobic are showed spring green and yellow respectively.

Asinex database was used to Identify new chemical entities for inhibiting the activity of sgk3 protein. Based on structure based virtual screening new molecules with different conformations were produced. 10,000 ligand molecules were subjected for lig prep which produced 19188 molecules with different conformations. The resulting output molecules were subjected for virtual screening module of Schrodinger suite. This process consists of three filtration process which are mainly High through put virtual screening (HTVS) mode, standard precession (SP) mode and the extra precession (XP) mode. Under each process top molecules are filtered by flexible docking of conformers. This process generates 140 molecules in HTVS, which are subjected to SP mode. This further produced 10% molecules which generated 43 molecules, these are further subjected to XP which resulted in 13 molecules the ligand molecules are prioritized based on glide score and glide energy and the ligand molecules good affinity with protein shown in table-4.

Table-4: Chemical structures glide scores and glide energies of top scoring ligands docked against SGK3 Protein

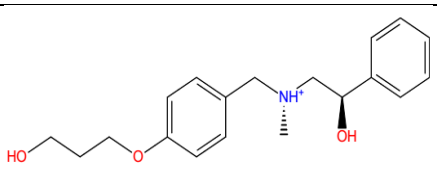
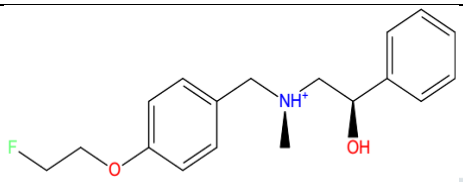
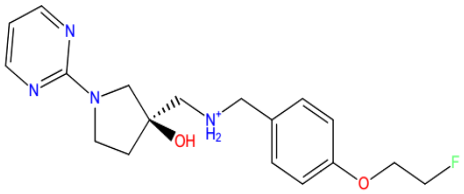
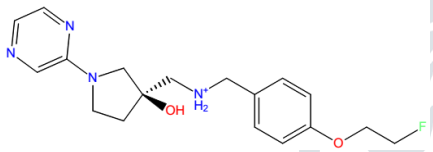
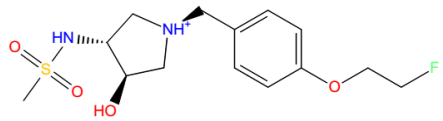
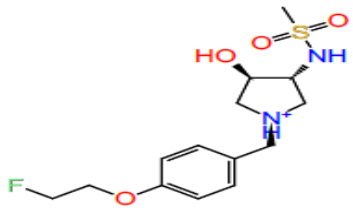
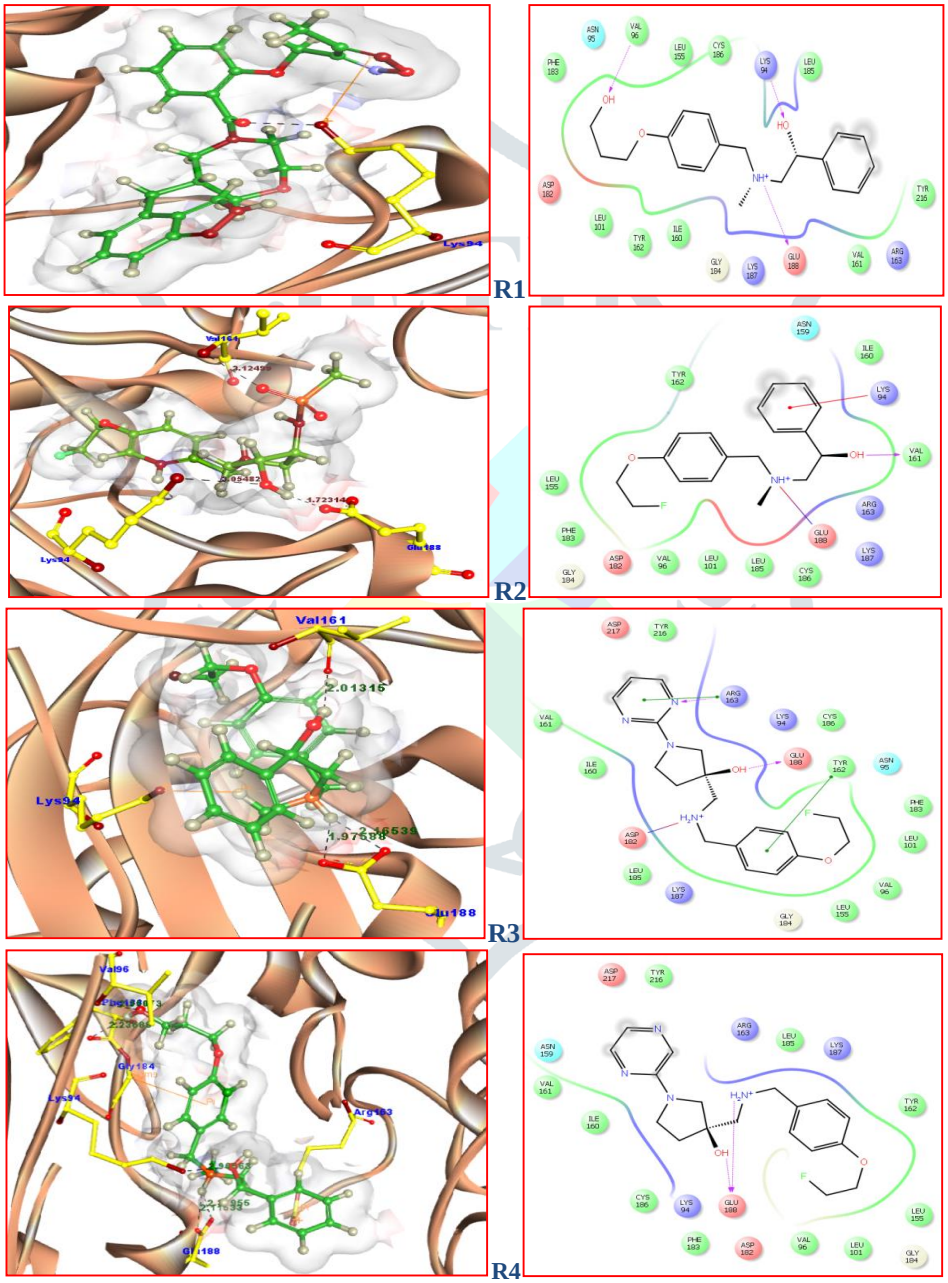
S.No	Structure	Glide score	Glide energy	Intermolecular interactions	Bond distance
R1		-8.076	-42.736	LYS94:N-39:09 VAL96:N-39:021 R1:H45-PHE183:O R1:H49-GLU188:OE1 R1:H49-GLU188:OE2 Pi-cation interactions R1-ARG163:NH1 R1-ARG163:NH2 Pi-sigma interaction R1-P:GLY184:CA	2.96563 2.95073 2.23689 2.37955 2.11533
R2		-7.288	-38.294	R2:H40-VAL161:O R2:H45-GLU188:OE1 R2:H41-GLU188:OE2 Pi-cation interactions R2-P:LYS94:NZ	2.0136 2.16539 1.97588
R3		-6.710	-42.246	R3:H41-P:GLU188:OE2 VAL96:N-41:F11 ARG163:NH1-41:N17 Pi-cation interactions R3-P:GLY184:A	1.79111 2.76621 3.09589
R4		-6.685	-38.871	R4:H41-GLU188:OE2 R4:H49-GLU188:OE1 LYS94:N-R4:O20 LYS184:N-R4:F11	1.86538 2.04293 2.50677 3.14521
R5		-6.448	-38.493	R5:H32-GLU188:OE2 LYS94:N-R5:O10 VAL161:N-R5:O7	1.72313 3.05482 3.12499
R6		-6.406	-34.921	VAL96:N-:UNK:F21 ARG163:NH1-:UNK:7 UNK:H32-GLU188:E	2.66777 2.68934 1.56555

Table 5: Prime MMGBSA OF SGK3-LIGAND complex energy calculation

S.no	ligand	Prime MMGBSA DG bind [dG (1)]
1	M1	-42.47
2	M2	-64.98
3	M3	-62.23
4	M4	-53.92

dG (1) indicate strain energy of receptor with ligand.

MMGBSA prime table obtained from Schrodinger suite to know binding free energies of protein-ligand complex.



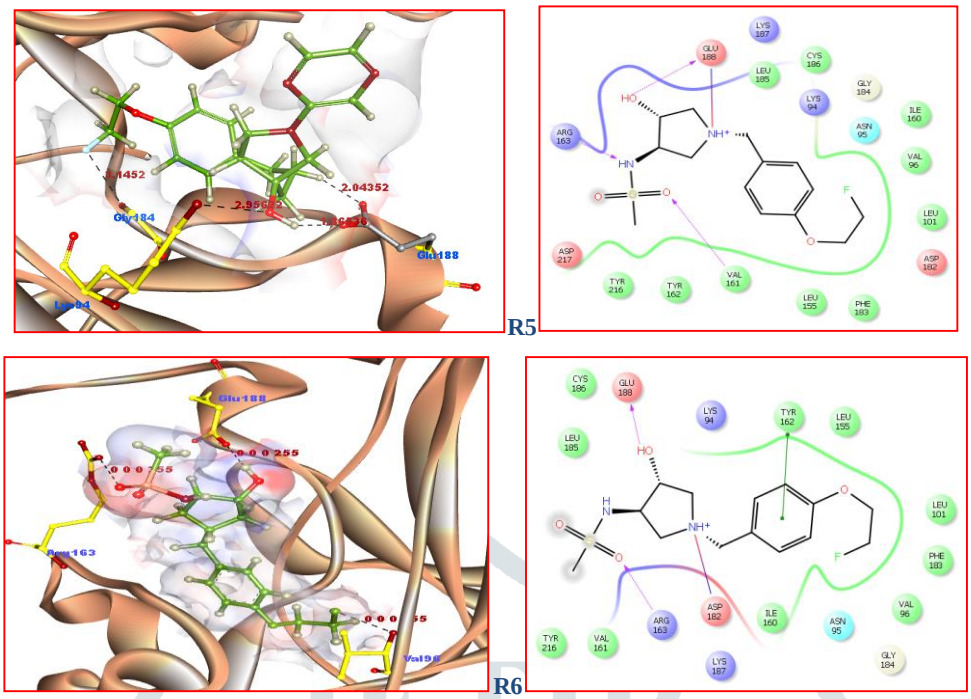


Fig- 12: Docked pictures of top prioritised ligand molecules with protein amino acid residues. In which red color Indicate ligand molecule. Amino acid brown color and hydrogen bond interactions between ligand molecules and protein indicate black color.

Table 6): ADME properties of highest Glide score and Glide energy ligand molecules predicted from QikProp module of Schrodinger

S.No	CNS	Mol.wt	DonarHB	AceptorHB	Qplog po/w	QplogBB	%Human oral Absorption	Rule of three	Rule of five
R1	1	315.41	2	6.15	2.93	-0.66	89.32	0	0
R2	1	303.37	1	4.45	3.48	0.23	100.00	0	0
R3	1	346.40	2	5.50	3.70	-0.03	92.53	0	0
R4	1	346.40	2	6 .02	3.70	-0.25	70.81	1	0
R5	0	332.38	2	8.95	1.15	-0.76	70.81	0	0
R6	0	332.38	2	8.95	1.1	-0.76	70.81	0	0

The permissible ranges of ADME properties are CNS: -2 (inactive) +2(active); Mol.Wt (130-725); Donor HB: (0.0-6.0); Accept HB: (2.0-20.0); QPlogP0/w (-2.0-6.5); QPlogBB: -3.0-1.2); %Human oral absorption: >80%high, <25% low; Rule of three (3); Rule of five (4); Total solvent accessible volume in Cubic angstroms [volume]; 500.0-2000.0; predicted apparent caco-2 cell(model for gut blood barrier) permeability in nm/s[QPPCaco]; < 25 poor, > 500 great, -3.0 -1.2number of likely metabolic reactions[Meta]; 1-8, human oral absorption[Human Oral A ; 1 low,2 medium, 3 high; number of Nitrogen's and Oxygens [N & O]; 2-15.

Above given ADME ranges shows good drug development properties. Top selected active ligand molecules are engaged in binding at SGK3 active site, preventing the activity of SGK3 protein. Among top 6 docked complexes, M2 and M3 shows high range human oral absorption and lowest binding energy prime MMGBSA, this indicate two ligands completely fitting into active region and SGK3 protein causeing complete inhibition of SGK3 protein function progression.

These two ligand molecules (R2, R3) are constantly binding to GLU188 indicating that this amino acid responsible for SGK3 protein inhibition show in fig-13.

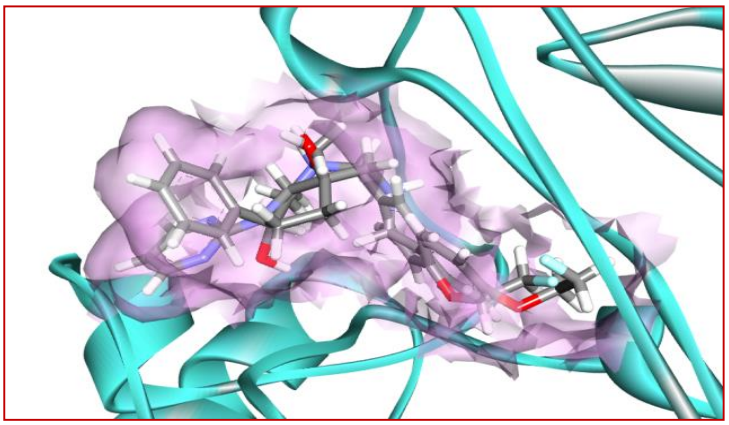


Figure 13: Ligands R2, R3 are binding with the same aminoacid resideues of SGK3 protein superimposed in the binding cavity.

APPLICATION

Identification of lead compounds for the protein SGK3 causing breast cancer which is playing major role during the metastasis staging of the breast cancer.

CONCLUSION

SGK3 protein belong to AGC family protein kinase, it is involved breast cancer progression. The structure of SGK3 protein obtained from homology modelling technique based on 2R5T Template selection, the resulting protein is validated, active site region is identified. New chemical Entities were obtained from virtual screening from ASINEX database. This screened top docked ligands binding with amino acid residues Glu188,Lys94,Val96,Val161, are mainly responsible for inhibition of the SGK3 function and arrest the mechanism of the protein responsible for cell proliferation .

Acknowledgements

The Author Muddagoni Narasimha is thankful to the University Grants Commission (UGC) India for financial support under the junior research fellowship (JRF) (Roll NO: 123647, REF. NO:21/12/2014(ii) EU-V: Sr,NO.2121410086). thankful to the Head, Department of Chemistry and the Principal, of the Nizam College, Osmania University, Hyderabad for providing the facilities to carry out this work.

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