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ORIGINAL ARTICLE

Identification of Inhibitors against Metastasis Protein "*Survivin*:" *In silico* Discovery Using Virtual Screening and Molecular Docking Studies

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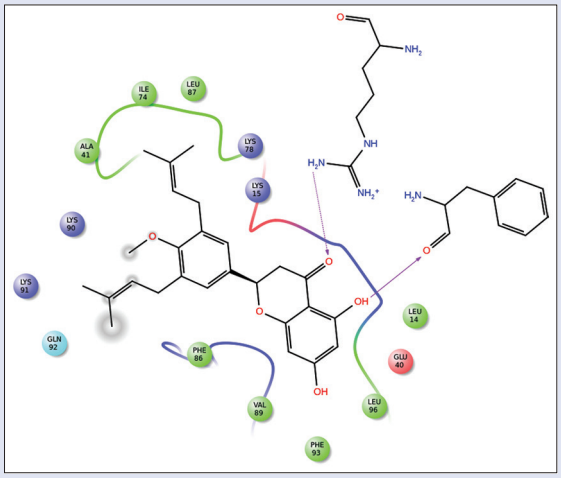
ABSTRACT

Background: In experimental therapy of cancer, survivin is considered to be one of the well-established targets. Studies have found that it is overexpression in most of the human tumors, but it is rarely found in normal tissues. It is having varied structural and functional role. It controls cell division and cellular stress response and also regulates metastasis and migration of cancerous cells. It has also been recognized as a biomarker which makes it unconventional drug target. In spite of being one of the centrally active components in metastasis and invasion, their clinical use is minimal. To increase the therapeutic efficiency of cancer and its various stages, it is important to survey novel reagents targeting the pathways and mechanism involving survivin. **Objective:** The aim of this study was to identify novel survivin inhibitor candidates using *in silico* screening. **Materials and Methods:** In this course of work, virtual screening on a dataset of natural compounds retrieved from ZINC and other libraries were performed. Comparative analysis of the protein was done by studying the binding affinity of inhibitors that are already available. The best interacting complex was set for molecular dynamics simulation for 25 ns to validate the stability of system. These molecules were checked for their toxicity and absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties using OSIRIS and pre-ADMET tools. **Results:** We discovered ten such candidates with better binding efficiency with survivin in comparison to marketed chemical against the same. Furthermore, these inhibitor candidates did not induce cell toxicity. Binding affinity of reference molecules was varied from −6.8 to −8.5 kcal/mol while that of top scoring compound ZINC00689728 is −9.3 kcal/mol binding energy. Good placement and strong bond formation of selected molecule was observed during course of work. It is also having permissible ADMET property. **Conclusion:** Considering all the parameters, the screened molecule can be considered as a potential lead compound for designing new drug against survivin. Further investigation and testing will be required to make it to the final stage.

Key words: Natural compounds, screening, simulation, survivin, toxicity

SUMMARY

- Survivin is one of the important protein of metastasis. Inhibiting survivin might led to the increased therapeutic efficiency of cancer. In this work we are screening library of natural compounds in view of finding some potent inhibitor against survivin.



Abbreviations used: MD: Molecular dynamics, LogS: Aqueous solubility, Acceptor HB: Hydrogen bond acceptor, Donor HB: Donor hydrogen bond donor, ADMET: Absorption, distribution, metabolism, excretion, and toxicity, RCSB: Research Collaboratory for Structural Bioinformatics, OPLS: Optimized potentials for liquid simulations, RMSD: Root-mean-square deviation.

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INTRODUCTION

Most of the cancer patient's undergone treatment has suffered from relapsing of infection in form of metastatic tumor. Metastatic process comprises cell invasion of tumor from the primary tumor, intravasion, arrest, and extravasation of the circulatory system which is followed by the growth at a distant site and angiogenesis.[1,2] There are various methods of measuring metastatic progression; one involves the measurement of size of large lesions on imaging and by indices of patient survival. Metastasis is a network of various proteins and pathways interweaved in a manner that they affect functioning of each other. There are various proteins that have not been explored as they were expected to be and have potency to be a target for secondary infection that is caused by metastasis. Expression of survivin has

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reported in almost all the tumors qualifying it as a biomarker of metastatic tumor.[3,4] In malignancies as well as in melanoma, the dual role of survivin has been studied and this includes both promitotic and antiapoptotic one.[5] In various studies conducted on animal model system, downregulation of the survivin or inactivation of its function has shown to inhibit tumor growth. It is evident that protein survivin is an unconventional target and earlier also various approaches had been applied to inhibit the same. These methods include survivin-specific immune response, interference from its expression, interaction, and inhibition with its binding pattern. Direct inhibition of protein through YM155 has also been tested.[6] Considering the importance of survivin in progression of the metastatic movement and considering the fact that there is few computational study on the interactions of natural compounds and survivin, it would be of interest to perform computational studies to screen some potent and effective herbal compounds against survivin. The number of encouraging examples signifies the importance and feasibility of the method. It involves steps that area "nonconventional" in current drug development protocols, but it is clearly worthwhile pursuing.

Apart from providing a beneficiary platform for searching a potent inhibitory molecule, this method also helps in screening of large library of chemicals in a very short span of time, which reduces the cost and energy of finding a new molecule to half of its original cost.

MATERIALS AND METHODS

Current work was conducted on a system with 8 GB RAM, Intel(R) Core(Tm), 2GB graphics, and i7-3220 CPU @ 2.30 GHz processor. Maestro suite of Schrödinger was used for screening and docking simulations. Desmond suite was utilized for molecular simulation studies (2015, Schrödinger, LLC, New York, NY, USA), absorption, distribution, metabolism, and excretion (ADME) analysis was performed on an online server pre-absorption, distribution, metabolism, excretion, and toxicity (ADMET) (https://preadmet.bmdrc.kr/), and for toxicity prediction, OSIRIS Property Explorer was used (http://www.organicchemistry.org/prog/peo/).

Selection and preparation of target

In this course of work, crystal structure of human survivin molecule was retrieved from Research Collaboratory for Structural Bioinformatics (RCSB) with PDB ID: 1F3H [Figure 1]. Refinement of protein structure was done through protein preparation panel of Schrödinger. Missing bond orders were added to the crystal structure of molecule. Bond orders were assigned, and constraint of root-mean-square deviation (RMSD) and optimized potentials for liquid simulation force field was used for restrained minimization. GLIDE v6.7 2015 Schrödinger, LLC, New York, NY, USA, was utilized for grid generation.

Preparation of ligand and virtual screening studies

Screening of libraries is a common trend in computational drug designing. Low-energy binding positions of drug candidates are searched through signifying a binding position. Virtual screening reduces the size of chemical compound repository to manageable size leading to synthesis of only few molecules to the subsequent screening against the chosen targets. Dataset of all the natural products from Zinc library[9] and dataset from Drugbank Drug were retrieved in SDF format and set for virtual screening GLIDE v6.7, 2015, Schrödinger, LLC, New York, NY, USA. Virtual screening by GLIDE is based on three layers of docking, i.e., high-throughput virtual screening (HTVS), standard precision (SP), and extra precision (XP). All compounds of the dataset were subjected for HTVS docking first and around 10% of the datasets move to SP docking and again precised amount of molecule further move to final XP docking. High-ranked top 11 compounds along with their binding affinity and other entities are mentioned in Table 1. Detailed two-dimensional (2D) structures of top 11 compounds are shown in Figure 2.

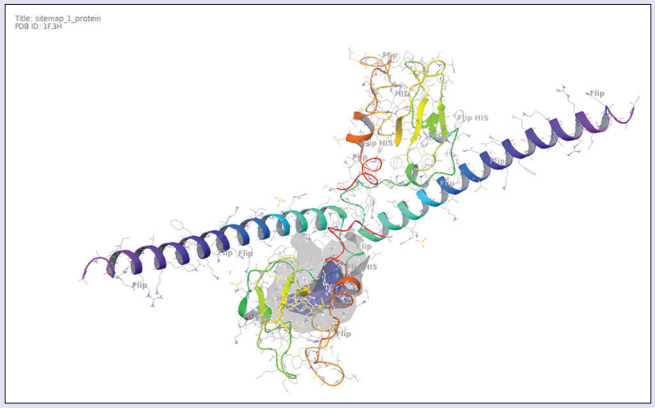


Figure 1: Three-dimensional structure of protein survivin with its active site

Table 1: Top eleven screened compounds with their database ID, Docking score, number of Interacting hydrogen bonds, interacting residues, and other possible interactions

Compounds ID	Binding affinity	No of hydrogen bonds	Residues interacting (For hydrogen binding, Pi-Pi interaction and Hydrophobic Interaction)
ZINC00689728	-9.3	2	PHE13,ARG10,ALA41,ILE74,LEU87,LEU14,LEU96,PHE93,VAL89,PHE86
ZINC77257204	-9	2	PHE93,LYS90,PHE59,LYS115
ZINC28462577	-9	2	CYS84,SER81,LYS122,GLN92
ZINC04245684	-9	1	LYS15,PHE86,PHE13,LYS13
ZINC01597393	-8.8	1	ARG106,GLU100,PHE93
ZINC38140514	-8.6	1	ASN112,LYS122,GLU126
ZINC03941105	-8.6	1	GLY83,LYS91,ARG18
ZINC00058188	-8.5	1	VAL89,GLN92,LEU104
ZINC03871358	-8.5	1	ARG108,ARG18,LYS15
ZINC18185774	-8.4	1	LYS15,ARG108,LEU14
ZINC06394172	-8.3	1	ARG18,LYS15,PHE13

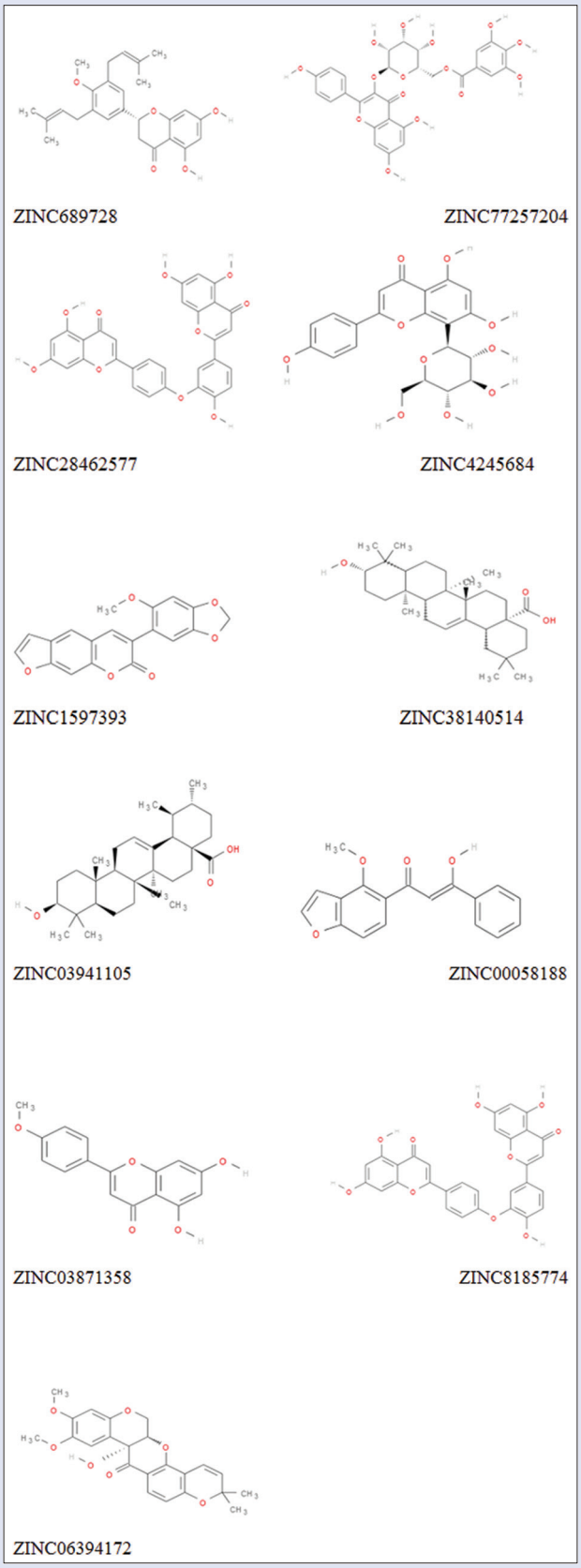


Figure 2: Two-dimensional structure of top 11 screened inhibitors (ZINC689728, ZINC77257204, ZINC28462577, ZINC4245684, ZINC1597393, ZINC38140514, ZINC03941105, ZINC00058188, ZINC03871358, ZINC8185774, and ZINC06394172)

Retrieving reference molecules

Various known inhibitors of survivin were downloaded from repositories, and their docking studies were performed with that of 1F3H on the same grid which was used for virtual screening, by GLIDE module of 2015, Schrödinger, LLC, New York, NY, USA.

Molecular dynamics simulation

Desmond suite of Schrodinger was used for molecular dynamics (MD) simulation, among all the 11 screened ligands, one with maximum binding affinity, maximum hydrogen bonds, and with allowed ADME, and toxicity values were chosen for MD simulations. Further, RMSD and root-mean-square fluctuation (RMSF) plot of protein–ligand complex was analyzed to ensure the stability and all other conformational changes of the setup or system during whole process of 25 ns simulation.

System building step through Schrodinger

Preprocessing of the complex was done through Protein Preparation Wizard of Maestro. It was done by modifying all the side chains of complex and through putting it for minimization processing before MD simulation. There are various missing atoms with complex, and during preparation of complex, these missing atoms were added (2015 Schrödinger, LLC, New York, NY, USA). Specific size of continuous repeating units (10 × 10 × 10) Å was chosen for orthorhombic box-shaped boundary.

Molecular dynamics simulation through Schrodinger

Once the process of system building was done, MD was performed. Bad contacts found in residues were removed through minimizing its energy with hybrid steepest descent method and the Limited-memory Broyden–Fletcher–Goldfarb–Shanno algorithms.

Prime MM/GBSA calculations

Prime/MM/GBSA module of the Schrodinger was used for calculating relative binding energy of the chosen ligands. XP output file pv.maegz was used for this study. Further, active site of the protein was set for the self-adjustment to itself up to 5 Å for ligand accordingly. The equation for the calculation of Delta G can be sum up as _ Gbind = Ecomplex (minimized) − [Eligand (unbound, minimized) + Ereceptor (unbound, minimized)].

Calculation of absorption, distribution, metabolism, and excretion property

Druglikeness characteristics of the top 11 screened compounds were analyzed by pre-ADMET to predict the pharmacokinetics, druglikeness, and biochemical properties. There is certain range which is acceptable for each of the property, and these features were justified over that range to categorize the leads druggable.

Toxicity prediction

OSIRIS is an online tool for predicting toxicity; it was used to explore the toxicity of the best 11 screened out compounds. Best scored 11 compounds were taken for these investigations. OSIRIS (http://www.organic-chemistry.org) gives information about various biochemical and biophysical properties of lead that helps in categorizing it under drug-like compound. These properties include druglikeness, drug score, mutagenicity, irritancy, reproductive effect, solubility, and ClogP.

RESULTS

Receptor and analysis of its active site

1F3H survivin was taken as a receptor and its 3D structure was retrieved from RCSB. Submitted structure was obtained from X-ray diffraction method with resolution of 2.58 Å. Active site of protein was determined through sitemap module of Schrödinger.[7] It consists of two chains A and B. Important residues consist of PHE13, LEU14, LYS15, ARG18, GLU40, PHE58, PHE59, PHE86, VAL89, LYS90, LYS91, GLN92, PHE93, LEU96, LEU104, THR48, GLU51, MET54, LYS62, GLU63, LEU64, GLU65, LYS115, ASN118, ASN119, LYS122, GLU123, and GLU126.

Reference molecules and its analysis

Binding affinity of reference molecules is varied from −6.8 to −8.5 kcal/mol [Tables 2 and 3]. Reference molecule processing has intended to select the most efficient binding site before conducting the virtual screening study.

Different molecular library used in screening

Dataset of all the naturally occurring molecules was taken from ZINC database. It comprises 139079 natural compounds. Apart from ZINC library, 7759 compounds were taken from drug database. In total, 146838 from various datasets were used for performing screening study against protein 1F3H. Cutoff range was fixed for better evaluation of the system. In this case, it was marked to −8.3.00 kcal/mol. Screened compounds were showing better score than either of the synthetic or natural reference compound. Further, top 11 ligands with higher binding affinity and score >−8.3 kcal/mol were chosen for the future analysis. Molecules with their detail interaction including interaction residues, hydrogen bond, and docking score have been mentioned in Table 1. Moreover, the interaction of best compound with that of protein is shown in Figure 3a (2D interaction) and Figure 3b (3D interaction).

Study of the interaction complex of protein and ligand

Top scoring compound ZINC00689728 is having -9.3kcal/mol binding energy with two hydrogen bonds,where PHE13 and ARG10 of protein is interacting with CH group of benzene ring; there is Pi-Pi stacking observed with ALA41, ILE74, and LEU87. Hydrophobic interaction will include LEU14, LEU96, PHE93, VAL89, and PHE86. Similarly, second-ranked compound in list is ZINC77257204 having binding score of 9 kcal/mol and forming two hydrogen bonds with LYS90 and LYS115 amino acid residues. The third compound in list is ZINC28462577 having binding affinity of −9 kcal/mol with two hydrogen bonds with the LYS122, GLN92 amino acid residues. Score function and all other interactions such as binding affinity and number of hydrogen bond of the all selected 11 compounds such as ZINC00689728, ZINC77257204, ZINC28462577, ZINC04245684, ZINC01597393, ZINC38140514, ZINC03941105, ZINC00058188, ZINC03871358, ZINC18185774, and ZINC06394172 are shown in Table 1.

Table 2: Known Reference molecules and their PubChem IDs, docking scores, and interacting residues

Reference molecules (Name)	Pubchem ID	Docking score	No of hydrogen bonds	Interacting residues(Hydrogen bonds, PI-PI interaction and Hydrobhopic interactions)
Terameprocol	476861	-7.2	1	ARG18,LYS15,LYS11
Sepantronium(YM155)	10126189	-6.8	1	VAL89,LYS15,GLN40

Table 3: Known Natural inhibitors of survivin from literature, and their pubChem ID,d ocking score, and their interacting residues

Reference molecules (name)	Pubchem ID	Docking score	No. of hydrogen bonds	Interacting residues (Interacting Residues (Hydrogen bonds, PI-PI interaction and Hydrobhopic interactions)
Ardisianone	442721	-8.5	1	ARG18,VAL89,PHE59,GLN92
Piperine	638024	-8.2	1	ARG18,PHE13,LYS15
Curcumin	969516	-8.5	2	LEU104,GLU40,PHE93,LYS15,ARG18

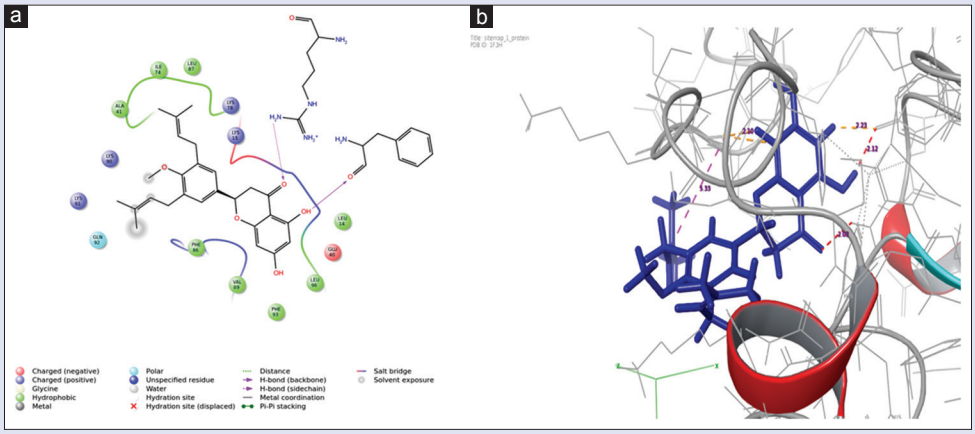


Figure 3: (a) Two-dimensional interaction diagram of ZINC00689728 with protein survivin, 6 hydrogen bonds are forming between chosen ligand and protein. Residues which are involved in bond formation are ARG18, LYS13, PHE93, LYS15, PHE86, and GLU40. (b) Three-dimensional interaction diagram of ligand and surviving

Molecular dynamics simulation studies

Studying the atomic level perturbation through MD simulation helps in understanding various biological aspects of molecule. These aspects include insights in structural makeup of complex or protein, conformational aspect of protein,[8] and search of unique molecules. A protein–ligand (ZINC00689728 and SURVIVIN) complex was set for MD simulation stability analysis. Once the system reaches its equilibrium stage, the production run was executed. After completion, it generated various interaction diagrams, simulation trajectory, and plots. These plots were put for an analysis for checking the stability of the interaction between ligand and protein. Simulation trajectory was found to behave stably and hence it confirms the appropriate docking of ligand and protein.

Analysis of root-mean-square deviation of protein–ligand complex

Movement of backbone and folding backbone inside the system defines the functional behavior of protein–ligand complex. Now, analysis of RMSD enables to detect the structural changes occurring in backbone of concerned protein and also in other residues of side chain of survivin protein through the complete process of 25 ns. Initially, sharp edges were observed in C-alpha, backbone of the protein converged after around 25 ns [Figure 4]. Later, it is getting stable when moving toward 25 ns and acts continuously till the end of simulation. Initial instabilities are showing that protein is going rigorous conformational changes over the period. Ligands RMSD and RMSF are showing consistent behavior during whole simulation period, which can be infer as stability of the complex.

Analysis of root-mean-square fluctuations of the protein

Deviation of various residues of protein in comparison to the chosen reference molecule is mainly analyzed by RMSF as shown in Figure 5.

Analysis of complex after simulation

Figure 3 is showing simulation analysis of protein survivin and ligand ZINC00689728 interaction. RMSD analysis of the complex confirms that the complex is structurally stable throughout the 25 ns simulation.

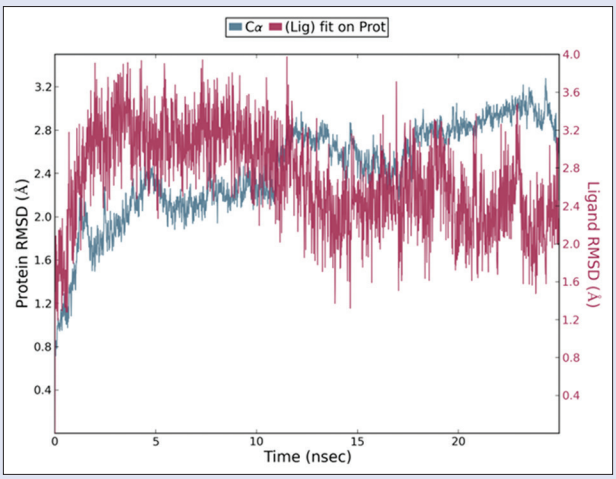
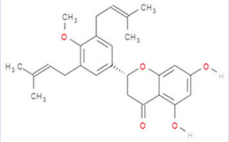
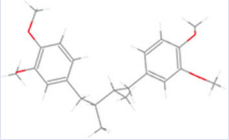
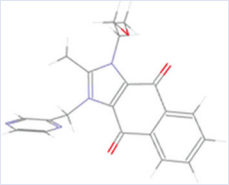
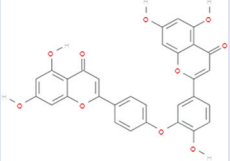
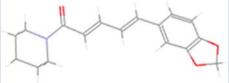
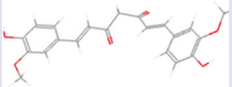


Figure 4: Root-mean-square deviation plot of C-alpha of protein and ligand at 25 ns. It is depicting the quality of the pose in respect to the time. Stability is being confirmed at the end of 25 ns simulation

Result of MM/GBSA calculations

Estimation of relative binding energy was done through implying MM/GBSA study. Prime module (Jacobson *et al*. 2004) of Schrodinger was used for the study. Molecules with best ranking score in XP mode were subjected for

Table 4: Two-dimensional structure of compounds along with their MM/GBSA score

Compound name	Compound structure	_Gbind (kcal/mol)
ZINC00689728		−118.623
Terameprocol		−113.512
Sepantronium (YM155)		−78.563
Ardisianone		−115.923
Piperine		−112.739
Curcumin		−116.604

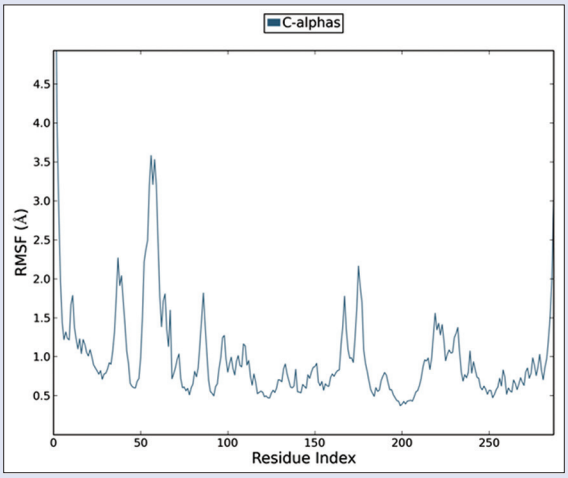


Figure 5: Root-mean-square fluctuation plot of residue number and C-alpha backbone of protein survivin at 25 ns simulation. It predicts the fluctuation of the backbone atoms; herein, the diagram protein is getting less fluctuating thus restoring the stability of backbone

the calculation. These studies were subjected to access the relative binding affinity of ligand toward receptor. Results are reported in Table 4.

Analysis of absorption, distribution, metabolism, excretion, and toxicity property

Top 11 molecules were put for pharmacokinetic descriptor calculation to evaluate the screened compounds on the parameter of druglikeness. A total of 10 descriptors were taken in account; ADME properties and other parameters for each inhibitor are given in Table 4. From analysis, it can be depicted that all the top 11 screened molecules are falling in adequate range of these ADMET descriptors.

Prediction of toxicity

No toxicity has been noticed for the selected compounds. Detail calculation of various parameters has been listed in Table 5 and 6.

DISCUSSION

At present, the standard treatment of cancer involves chemotherapy, radiation, and precise medicines. Although these treatments have been shown to be effective to a certain extent, it causes several side effects. Available drug targets specific protein which is beneficial to control the cancer but fails to restrict its movement to other parts. Treatment with surgery also poses problems of relapsing of the disease and formation of new lesions. Treatment with available herbal molecules has its own limitations in terms of efficiency and effectiveness. Taking these current issues into account, our primary goal was to identify a novel marker which expresses itself in diseased condition and can be targeted to localize the movement of cancerous cells. The second motive with which this work was proceeded was to identify novel chemical reagents which can restrict the target with better efficiency. Prior studies have identified one compound that targets the survivin, YM155. It is in its second phase of testing; YM155 is a first-in-class survivin inhibitor currently in phase I/II clinical trials as monotherapy or combination therapy for a variety of human malignancies.[9-14] Focusing on same our work has proposed more compounds against survivin with better efficiency than YM155.

Further, we simulated the docking process for survivin and best zinc compound obtained through screening and also calculated MM/GBSA energy. MM/GBSA energy is attractive approaches owing to their modular nature and that they do not require calculations on a training

Table 5: Principal descriptors, their acceptable ranges, and values of the selected inhibitory molecules: Eleven top molecule

Lipinski'sRule of 5											
ADME Descriptors	689728	77257204	28462577	4245684	1597393	38140514	3941105	58188	3871358	8185774	6394172
MW (g/mol)	329.78	600.4	396.8	542.46	336.29	393.47	443.31	428.47	455.5	418.91	410
XLogP3	2.8	1.29	3.5	5.7	3.89	1.9	5.5	3	3.3	4.6	3.01
Donor HB	2	9	1	1	0	0	0	6	0	1	1
Accept HB	3	8	5	6	6	7	6	6	6	5	7
Absorption											
Human intestinal absorption (HIA, %)	94.83	91.72	86.95	95.83	98.23	95.99	95.99	98.08	93.04	79.42	78.03
In vitro Caco-2 cell permeability (nm/sec)	38.1	12.09	6.77	12.014	43.8	22.23	22.2	43.43	12.79	4.53	10.05
In vitro MDCK cell Permeability (nm/sec)	0.0478	0.0489	0.048	0.054	3.83	0.437	0.0444	29.6	20.23	36.52	30.53
In vitro skin permeability (logKp, cm/hr)	-2.19	-3.971	-3.38	-3.91	-3.95	-2.61	-2.45	-2.91	-3.360	-4.28	-3.1
Distribution											
In vivo plasma protein binding (%)	100	99.22	100	92.12	90.97	100	100	92.34	90.91	99.71	92.15
In vivo blood-brain barrier penetration (Concentration in brain/ Concentration in blood)	5.99	0.0316	0.166	0.172	0.019	5.75	5.91	0.16	0.15	0.3675	0.26

HIA: Human intestinal absorption; ADME: Absorption, distribution, metabolism, and excretion; Hb: Hemoglobin; MW: Molecular weight

Table 6: Toxicity parameters of the selected compounds

Compounds ID	Druglikness	Solubility	ClogP	Reproductive effect	Irritant	Tumorigenic	Mutagenic
ZINC00689728	-0.1673	-4.832	6.47	NONE	NONE	NONE	NONE
ZINC77257204	.8088	-3.179	0.890	NONE	NONE	NONE	NONE
ZINC28462577	.28194	-6.689	4.75	HIGH	NONE	NONE	NONE
ZINC04245684	.3156	-4.23	4.62	NONE	NONE	NONE	NONE
ZINC01597393	-0.140	-5.215	3.24	HIGH	NONE	NONE	NONE
ZINC38140514	-0.154	-6.128	3.98	NONE	NONE	NONE	NONE
ZINC03941105	-2.040	-6.11	3.92	NONE	NONE	NONE	NONE
ZINC00058188	-0.015	-4.55	0.904	NONE	NONE	NONE	NONE
ZINC03871358	2.611	-3.17	0.403	NONE	NONE	NONE	NONE
ZINC18185774	7.010	-4.744	3.72	NONE	NONE	NONE	NONE
ZINC06394172	0.213	-4.34	3.52	NONE	NONE	NONE	NONE

set. MM/GBSA energy and docking simulation showed favorable docking stability.

CONCLUSION

The main purpose of this paper was to screen natural libraries against protein survivin. After implying all the tools, we propose that natural compounds are better in terms of binding affinity and compatible on parameter of ADMET and toxicity studies. Further studies of proposed inhibitors need to be carried out.

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Conflicts of interest

There are no conflicts of interest.

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