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Identification of potential targets and Screening for common signature in novel anticancer inhibitors in human

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Abstract :-Cancer remains a basic burden to public health despite substantial efforts aimed at developing effective chemotherapeutics. The goal of the project is to screen for common signature in novel drug targets and identification of potential lead molecules by analysis and prediction of its ADMET properties with high specificity. In the present study we have screened all 11,000 entries for Human Cancer Proteins available in PDB and retrieved 12 hits classified according to space group, accessible/buried surface area, and free energy of dissociation and further considered for the analysis of cation-pi interactions study results showed that high exposed percentage for Lys and Arg due to their hydrophilic properties and having high accessible surface area. Phe was having low percentage of exposed compared to other residues due to its hydrophobic nature. Ligands were screened through HitsGen by Inventus software, which is a standalone software that performs ADMET screening for ligands through six assays namely CACO, efflux, BBB, FDP,VDSS and finally 8 ligands that are being satisfied through all the screening results which are further analysed by docking studies using NOVODOCKER. We have observed that Tyr,Thr,Asp residues have significantly involved in donor /acceptor interaction, Though there is no significant PPI is observed among all the targets. After screening 216 hits and performing protein -ligand interaction studies revealed that Leucovorin and Morphine are potential ligands among 216 hits which can be further analysed for In vivo studies.

Keywords: *Molecular Docking, Drug Targets, Novodocker, Accessible/Buried Surface Area.*

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1. Introduction:

Cancers are a large family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. They form a subset of neoplasm. A neoplasm or tumour is a group of cells that have undergone unregulated growth, and will often form a mass or lump, but may be distributed diffusely. Cancer, also known as a malignant tumour or malignant neoplasm, is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Not all tumours are cancerous; benign tumours do not spread to other parts of the body.

With increasing evidence that the interaction and network between genes and proteins play an important role in investigation of cancer molecular mechanisms [1]

Many tumors consist of mixtures of subclones containing different sets of mutated, overexpressed and silenced genes. This heterogeneity makes the process of identifying good molecular targets very challenging. Most overexpressed genes and mutated genes may not represent good molecular targets because resistant subclones are present. The best target is a 'red dot' gene whose mutation occurs early in oncogenesis and dysregulates a key pathway that drives tumor growth in all of the subclones. Examples include mutations in the genes ABL,HER-2,KIT,EGFR,and probably BRAF, in chronic myelogenous leukemia, breast cancer, gastro-intestinal stromal tumors, non-small-cell lung cancer and melanoma, respectively[2]. Effective development of therapeutics requires identification of red-dot targets, development of drugs that inhibit the red-dot targets, and diagnostic classification of the pathways driving the growth of each patient's tumor [3].

In the present study we have screened all 11,000 entries for Human cancer proteins available in PDB[4] and retrieved 12 hits classified according to space group, accessible/buried surface area, and free energy of dissociation. Ligands were screened through Inventus software, which is a standalone software that performs ADMET screening for ligands through six assays namely CACO, efflux, BBB, FDP,VDSS and finally 8 ligands that are being satisfied through all the screening results which are further analyzed by docking studies using NOVODOCKER[5]. We have observed that Tyr,Thr,Asp have significantly involved in donor /acceptor interaction, Though there is no significant PPI is observed among all the targets,

2. Materials and methods:

2.1 Target screening and identification: The cancer targets having three dimensional structure are screened and identified through PISA software [6] which is an interactive tool for the exploration of macromolecular interface and essentially screens the targets for multimeric state, symmetry number, space group, accessible/buried surface area, free energy of dissociation, presence/absence of salt bridges and disulphide bonds etc. In PISA we have screened all 11,000 entries for Human cancer proteins

available in PDB and retrieved 12 hits (1GS4, 1WCH, 1X2J, 1X2R, 2B7F, 2RKB, 3G5K, 3G5P, 3HG1, 3IE3, 3S7S, 4B3Z.) classified according to space group, accessible/buried surface area, and free energy of dissociation.

PocketDetectorTM - Module has been used for discovering active site in respective protein targets. Active sites are given in ranking order and used as per user analysis and these cavities were further analyzed for ligand interaction with targets.

2.2 Screening and ADMET property analysis for Ligands:

PharmoPredictaTM is a comprehensive predictive ADME software system developed and validated to predict relevant pharmacokinetic and ADME characteristics of potential drugs. pk ExpressTM is bought from US based company G2 Research Inc. The system can be deployed as a PC desktop application or as an ADME compute engine in a larger cheminformatics system. Inventus pkEXPRESS includes the following: • Physiological Absorption Model , Physiological Metabolism Model , Physiological Distribution and Elimination Model. Out of 50 ligands that we have retrieved from Pubchem [7] as well as Drugank [8] we have obtained 8 ligands which have satisfied through all the screening results.

2.3 Docking Studies:

NovoDocker Molecular docking is a computational procedure that predicts the non-covalent binding of macromolecules or, more frequently of a macromolecule (receptor) and a small molecule (ligand) efficiently. It is an all-atom energy based Monte Carlo docking procedure [9] tested on a dataset of 226 proteinligand complexes. Average root mean square deviation (RMSD) from crystal conformation was observed to be 0.53 Å. The correlation coefficient (r2) for the predicted binding free energies calculated using the docked structures against experimental binding affinities was 0.72. Docking is performed with 12 targets and 8 ligands. The target protein structures such as 1GS4, 1WCH, 1X2J, 1X2R, 2B7F, 2RKB, 3G5K, 3G5P, 3HG1, 3IE3, 3S7S, 4B3Z are docked with selected lead molecules (Carmustin, Eloxatin, Exemestane, Hydroxyurea, Leucovorin, Morphine, Azithromycin) using NOVODOCKER which is a computational procedure that predicts the non-covalent binding of macromolecules or, more frequently of a macromolecule (receptor) and a small molecule (ligand) efficiently. The key characteristic of a good docking program is its ability to reproduce experimental binding poses of ligand. To test this ability the ligand is taken out of X-ray structure of its protein-ligand complex and docked back into its binding site. The docked binding pose was compared with the experimental binding pose, and a root mean square (RMSD) between the two is calculated, if the calculated RMSD between these two poses were under 2Å a then the prediction of binding pose was considered as successful for a particular protein-ligand complex.From this, the lowest energy conformations were regarded as the best binding conformations.

3. Results and discussions:

3.1 Target screening and identification: PDBePISA is an interactive tool for the exploration of macromolecular interfaces.Structural and chemical properties of macromolecular surfaces and interfaces probable quaternary structures (assemblies), their structural and chemical properties and probable dissociation patternwe have screened all 11,000 entries for Human cancer proteins available in PDB and retrieved 12 hits (1GS4, 1WCH, 1X2J, 1X2R, 2B7F, 2RKB, 3G5K, 3G5P, 3HG1, 3IE3, 3S7S, 4B3Z.) classified according to space group, accessible/buried surface area, and free energy of dissociation

Hit	PDB id	Mm size	Sym.num	Space group				ASA sq.A	BSA SQ.A	Delta G Kcal/mol
1	2B7F	3	1	C	1	2	1	11298	6129.5	36.2
2	3G5P	4	4	C	1	2	1	31272.2	13673.5	20.3
3	3G5K	4	4	C	1	2	1	31196.5	14464.3	20.2
4	3IE3	2	2	C	1	2	1	17722.4	5400.2	11.5
5	4B3Z	2	2	P	1	21	1	32309.2	2326.9	8
6	2RKB	2	2	C	2	2	21	23754.5	3293.5	3.6
7	3HG1	5	1	P	43	37503.8	11407.6	3.5	0	0
8	1X2R	2	1	P	61	12320.8	2544.8	3	0	0
9	1X2J	1	1	P	61	11851.1	0	0	0	0
10	1WCH	1	1	C	1	2	1	14774	0	0
11	3S7S	1	1	P	32	2	1	19787.4	0	0
12	1GS4	1	1	P	21	21	21	11688.8	0	0

Table1: Summary of PDB IDS and respective accessible surface area (ASA), Buried surface area (BSA) & Delta G values.

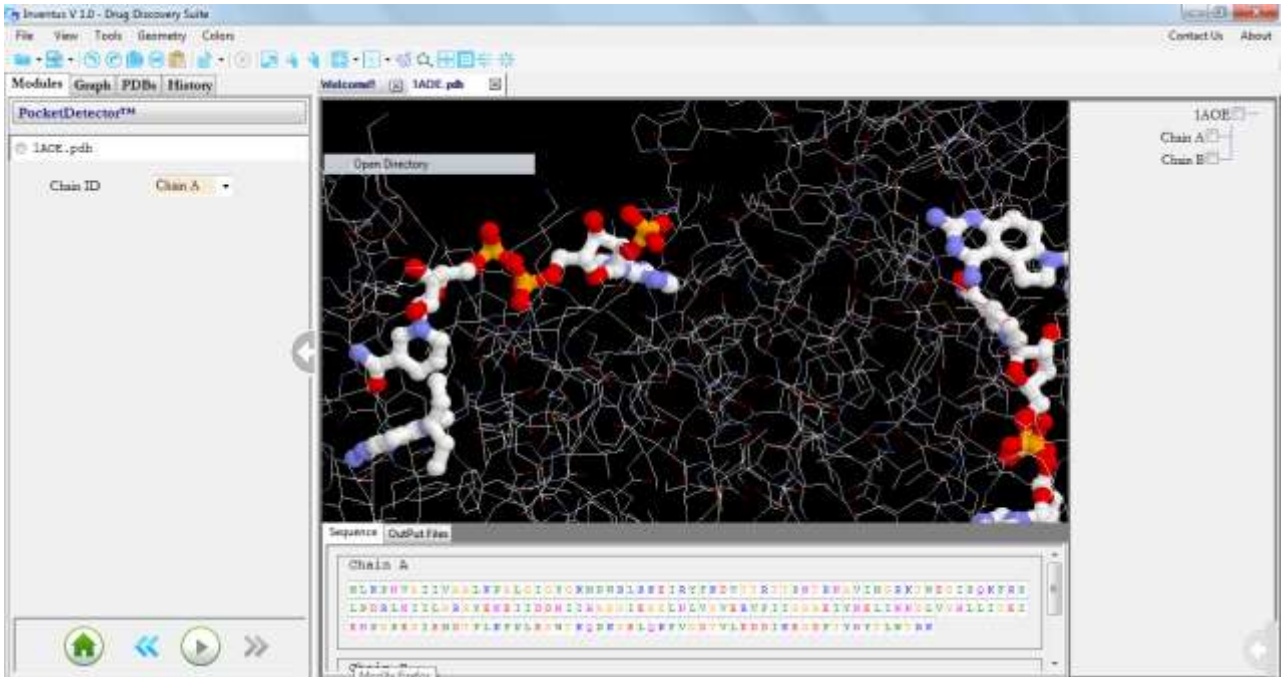

Fig1: Represents target cavity prediction from PocketDetectorTM Module

3.2 Screening and ADMET property analysis for Ligands:

de novo design supports drug discovery projects by generating novel pharmaceutically active agents with desired properties in a cost- and time-efficient manner[10] In this study Anticancer ligands were collected from Pubchem and Drugbank with the Keyword "Anticancer and Human". These ligands were screened through Inventus software, which is a standalone software that performs ADMET screening for ligands through six assays namely CACO, efflux, BBB, FDP,VDSS . Out of 50 ligands that we have retrieved from Pubchem as well as Drugank we have obtained 8 ligands which have satisfied through all the screening results.

3.3 Docking Studies: Molecular docking. The target proteins such as 1GS4, 1WCH, 1X2J, 1X2R, 2B7F, 2RKB, 3G5K, 3G5P, 3HG1, 3IE3, 3S7S, 4B3Z with selected reference lead molecules along with their pharmacological similar compounds is used for molecular docking. The overall results shows all the compounds Morphine compound along with their pharmacological similar compound Leucovorin , Hydroxyurea and Carmustine are strongly interacts with target protein and these compounds can be used for further clinical investigations.

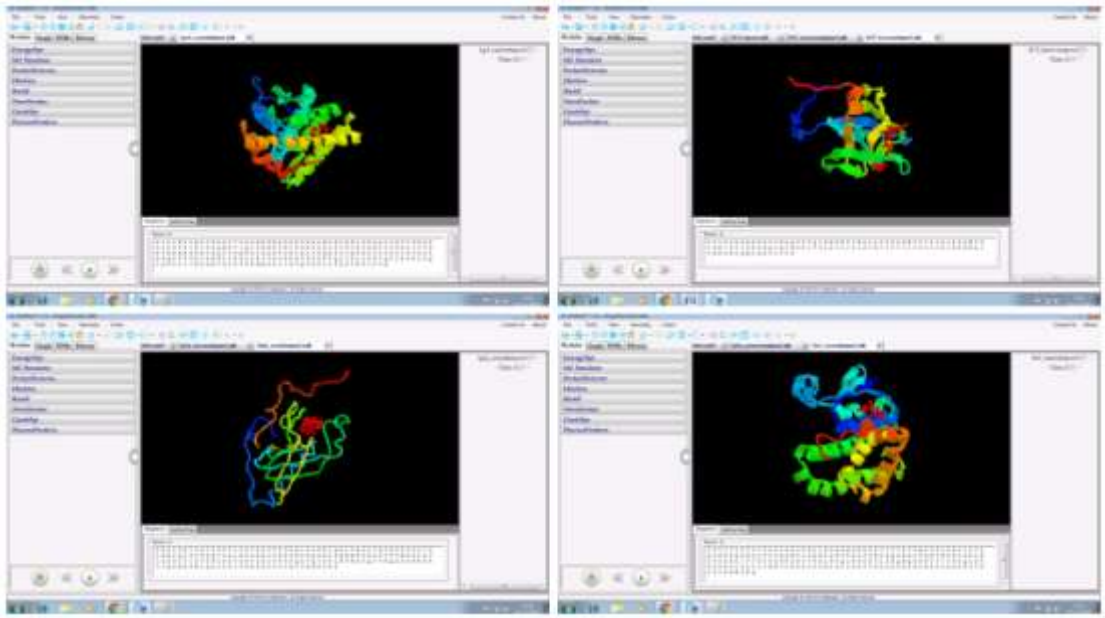

Fig2: Docking results of best poses using Novodocker tool.

TARGET	Ligand	E kcal/ mol	RADIUS	Thr	Thr	Tyr	Tyr	Asp	Asp
				DONAR	ACCEPTOR	DONAR	ACCEPTOR	DONAR	ACCEPTOR
1X2J	Carmustine	-4190.11	2.98188	OG1	OG1	OH	OH	ND2	OD1
1X2J	Exemestane	-4190.11	3.50104	OG1	OG1	OH	OH	ND2	OD1
1X2J	Leucovorin	-4190.11	5.91081	OG1	OG1	OH	OH	ND2	OD1
1X2J	Morphine	-4190.11	3.2725	OG1	OG1	OH	OH	ND2	OD1
1X2J	Hydroxyurea	-4190.11	1.83302	OG1	OG1	OH	OH	ND2	OD1
1X2J	Pemetrexed	-4190.11	4.2096	OG1	OG1	OH	OH	ND2	OD1
1GS4	Carmustine	2059.28	2.98198	OG1	OG1	OH	OH	ND2	OD1
1GS4	Exemestane	2059.28	3.50101	OG1	OG1	OH	OH	ND2	OD1
1GS4	Leucovorin	2059.28	5.91082	OG1	OG1	OH	OH	ND2	OD1
1GS4	Morphine	2059.28	3.27248	OG1	OG1	OH	OH	ND2	OD1
1GS4	Hydroxyurea	2059.28	1.83309	OG1	OG1	OH	OH	ND2	OD1
1GS4	Pemetrexed	2059.28	4.2096	OG1	OG1	OH	OH	ND2	OD1
3HG1	Carmustine	7.0124	2.98187	OG1	OG1	OH	OH	ND2	OD1
3HG1	Exemestane	7.0124	3.501	OG1	OG1	OH	OH	ND2	OD1
3HG1	Leucovorin	7.0124	5.91076	OG1	OG1	OH	OH	ND2	OD1
3HG1	Morphine	7.0124	3.27246	OG1	OG1	OH	OH	ND2	OD1
3HG1	Hydroxyurea	7.0124	1.83299	OG1	OG1	OH	OH	ND2	OD1
3HG1	Pemetrexed	7.0124	4.20953	OG1	OG1	OH	OH	ND2	OD1
3G5P	Carmustine	-2352.08	2.98196	OG1	OG1	OH	OH	ND2	OD1
3G5P	Exemestane	-2352.08	3.50112	OG1	OG1	OH	OH	ND2	OD1
3G5P	Leucovorin	-2352.08	5.9108	OG1	OG1	OH	OH	ND2	OD1

3G5P	Morphine	-2352.08	3.27241	OG1	OG1	OH	OH	ND2	OD1
3G5P	Hydroxyurea	-2352.08	1.833	OG1	OG1	OH	OH	ND2	OD1
3G5P	Pemetrexed	-2352.08	4.20962	OG1	OG1	OH	OH	ND2	OD1

Table: Represents Donoar /acceptor and stability of the protein ligand complex

4. Conclusion

PDBePISA is an interactive tool helped us to screen the target proteins based on Structural and chemical properties of macromolecular surfaces and interfaces and we finally obtained 11 hits which are significantly involved in cancer, Dataset of 11 proteins considered for the analysis of cation-pi interactions results showed that high exposed percentage for Lys and Arg due to their hydrophilic properties and having high accessible surface area. Phe was having low percentage of exposed compared to other residues due to its hydrophobic nature. later pocket detector tool predicted best cavities in targets respectively we have analysed and screened ADMET properties of ligands followed by molecular docking studies revealed that Tyr,Thr,Asp residues have significantly involved in donor /acceptor interaction, Though there is no significant PPI is observed among all the targets.Final screened lead molecules (Leucovorin and Morphine) can be further studied for in-vivo. It needs lot of computational analysis to examine targets and ligand interaction. A systematic computational medicinal chemistry approach aids in cancer biology research.

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6. Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper

References:

[1] Wu D, Rice CM, Wang X. Cancer bioinformatics: A new approach to systems clinical medicine. *BMC* Bioinformatics. 2012;13:71.
[2] Richard Simon. Bioinformatics in cancer therapeutics—hype or hope? . Nature Clinical Practice Oncology (2005) **2**, 223.
[3] Reimand J, Bader GD. Systematic analysis of somatic mutations in phosphorylation signaling predicts novel cancer drivers. *Molecular Systems Biology*. 2013;9:637.
[4] H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne The Protein Data Bank, Nucleic Acids Research, (2000) 28: 235-242.
[5] Novodocker: http://www.novoinformatics.com/molecule-discovery-centre.html
[6] E. Krissinel and K. Henrick (2007). *'Inference of macromolecular assemblies from crystalline state.'*. J. Mol. Biol. 372, 774--797.
[7] Sunghwan Kim, Paul A. Thiessen et al.PubChem Substance and Compound databasesNucleic Acids Res. 2015
[8] Wishart DS, Knox C, Guo AC, et al. DrugBank: a knowledgebase for drugs, drug actions and drug targets. *Nucleic Acids Research*. 2008;36
[9] Lorenzen S, Zhang Y. Monte Carlo refinement of rigid-body protein docking structures with backbone displacement and side-chain optimization. *Protein Science: A Publication of the Protein Society*. 2007;16(12):2716-2725..
[10] Gisbert Schneider . Uli Fechne , Computer-based de novo design of drug-like molecules.Nature Reviews Drug Discovery . 2005, 649-663.