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In Silico Screening and Docking Analysis of a Few Drugs against Proteins Expressed in Colon Cancer

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Abstract: ***Colon cancer claims the third rank in the list of most common cancers diagnosed in the United States. Literature findings suggest that certain proteins are highly expressed in a specific type of cancer. Therefore, there is a need to discover drugs that are specific against specific proteins in colon cancer. However, most of the anti-cancer drugs in the market are known to exhibit severe side effects. Hence new molecules with maximal efficiency of binding towards proteins expressed in colon cancer would be an advantage. In this study, a novel approach has been implemented to screen the existing drugs in the market versus highly expressed proteins in colon cancer and apoptosis. This study revealed five drugs, such as Olmesartan, Verteporfin, Ritonavir, Telmisartan, and Eprosartan respectively as probable anti-cancer agents based on the molecular dock scores obtained when compared with bounds ligands of each protein.***

I. INTRODUCTION

A. *Protein Data Bank (PDB)*

The RCSB PDB (Figure-1) provides a variety of tools and resources for studying the structure of biological macromolecules and their relationship to sequence, function, and disease. The RCSB is a member of the www.PDB whose mission is to ensure that the PDB archive remains an international resource with uniform data. This site office is used for browsing, searching, and reporting that utilize the data resulting from ongoing efforts to create a more consistent and comprehensive archive. The PDB database was used for the presence of 3D structure and this resulted in one structure hit. Table 1 given below was constructed based on experimental method, resolution, ligands, etc.

B. *Criteria To Select Protein For Analysis*

1) Protein should be determined by X-ray Diffraction method.
2) It should contain a bound ligand.
3) Resolution should be between 2-3 A°

C. *Molegro Virtual Docker*

An integrated platform for predicting protein–ligand interactions. Molegro Virtual Docker was used to perform docking. The protein and ligand molecules present in the PDB or Mol2 formats were imported into the workspace of the Molegro Virtual Docker software. The molecules were prepared after being imported into the workspace of MVD. The cavities present in the protein can be detected by the Detect Cavities option and the large cavity was selected as the binding site for the ligand while performing docking. The docking was performed using the docking wizard. Molegro Virtual Docker is an integrated platform for predicting protein-ligand interactions. Molegro Virtual Docker handles all aspects of the docking process from preparation of the molecules to determination of potential binding sites of the target protein, and the prediction of binding modes of the ligands. Molegro Virtual Docker provides the user with high-quality docking based on a novel optimization technique combined with a user interface experience focusing on productivity and usability. Molegro Virtual Docker (MVD) has been shown to yield higher docking accuracy than other state-of-the-art docking products (MVD: 87%, Glide: 82%, Surflex: 75%, FlexX: 58%).

Table 1: Proteins Selected from Protein Data Bank

PDB ID	EXPERIMENTAL METHOD	RESOLUTION (Å)	LIGANDS	TITLE	CHAINS	LENGTH OF SEQUENCE

1GFW	X-RAY DIFFRACTION	2.80	1-methyl-5-(2-phenoxymethyl-pyrrolidine-1-sulfonyl)-1h-indole-2,3-dione	The 2.8 angstrom crystal structure of caspase-3 (apopain or cpp32)in complex with an isatin sulfonamide inhibitor	A	147
1UA2	X-RAY DIFFRACTION	3.02	adenosine-5'-triphosphate	The crystal structure of human cdk7 and its protein recognition properties.	A, B, C, D	346
1UNH	X-RAY DIFFRACTION	2.35	(z)-1h,1'h-[2,3']biindolylidene-3,2'-dione- 3-oxime	Structural mechanism for the inhibition of cdk5-p25 by roscovitine, aloisine and indirubin.	A, B	292
1UV5	X-RAY DIFFRACTION	2.80	6-bromoindirubin-3'-oxime	Glycogen synthase kinase 3 beta complexed with 6-bromoindirubin-3'-oxime	A	350
2AZ5	X-RAY DIFFRACTION	2.10	6,7-dimethyl-3-[(methyl{2-[methyl({1-[3-(trifluoromethyl)phenyl]- 1h-indol-3-yl}methyl)amino]ethyl}amino)methyl]- 4h-chromen-4-one	Crystal structure of tnf-alpha with a small molecule inhibitor	A, B, C, D	148
2UZO	X-RAY DIFFRACTION	2.30	4-{5-[(z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]furan-2-yl}benzenesulfonamide	Crystal structure of human cdk2 complexed with a thiazolidinone inhibitor	A	298
3BLR	X-RAY DIFFRACTION	2.80	2-(2-chloro-phenyl)-5,7-dihydroxy-8-(3-hydroxy- 1-methyl-piperidin-4-yl)-4h -benzopyran-4- one	Crystal structure of human cdk9/cyclint1 in complex with flavopiridol	A	331
3GOE	X-RAY DIFFRACTION	1.60	N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro- 2-oxo-1,2-dihydro-3H-indol-3-ylidene)methyl]- 2,4-dimethyl-1H-pyrrole-3-carboxamide	Kit kinase domain in complex with sunitinib		

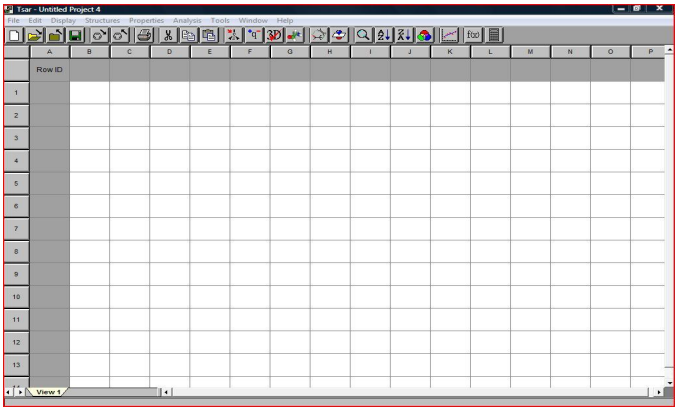
II. METHODOLOGY OF DOCKING

Molegro Virtual Docker was used to perform docking. The steps involved in docking were:

1) Importing the molecules or ligands
2) Preparing the molecules
3) Template Creation
4) Docking

a) *TSAR software: 2D to 3D Conversion:* The drawn 2D structures of the anticancer compounds, and inhibitors from the article were converted to 3D form by using TSAR Software tools.

b) *TSAR (Tools for Structural Activity Relationship) software:* TSAR was used to study properties and structures, performing statistical analysis, and predicting properties from structures. It is an integrated analysis package for interactive investigation. The TSAR Home page was shown below.



The steps for the conversion of 2D to 3D were done by using three options:

- Corina – Make 3D for converting 2D to 3D.
- Charges2 – Derive charges to derive charges.
- Cosmic – Optimize 3D energy optimization.

III. RESULTS

Apoptosis-Related Proteins:

S.NO	PDB ID	Mol Dock Score (kcal/mol)			Average Mol Dock Score (kcal/mol)	Average RMSD
		Run 1	Run 2	Run 3		
1	1GFW	-34.5183	-34.9730	-33.0932	-34.1948	0.523056
2	1UA2	-152.07	-151.550	-151.257	-151.626	0.539925
3	1UNH	-113.906	-113.906	-111.981	-113.264	0.855887
4	1UV5	-117.86	-116.780	-117.092	-117.244	0.768791
5	2AZ5	-101.003	-100.2775	-101.314	-100.865	0.822837
6	2UZO	-124.94	-120.70	-124.75	-123.463	1.392083
7	3BLR	-114.193	-114.283	-117.094	-115.19	0.447854
8	3G0E	-132.695	-132.907	-133.569	-133.057	0.426807

	Name of the Protein							
Name of the Drugs	2CBZ	3HRC	1UNH	1UV5	2AZ5	3G0E	3H0E	1GFW
Pentagastrin	170.44	157.17	176.88	130.28	110.15	164.17	126.87	86.98
Verteporfin	181.25	189.49	144.89	146.64	116.49	134.34	174.92	75.84
Ritonavir	125.57	170.4	143.93	140.46	114.72	142.32	148.19	98.69
Telmisartan	127.1	147.76	153.14	147.8	93.16	144.08	137.92	65.15
Montelukast	126.64	123.7	163.35	161.37	80.07	149.66	155.09	59.8
Glimepiride	131.31	133.45	144.14	124.59	98.05	146.69	114.51	42.25
Cefpiramide	129.27	145.8	134.23	108.25	90.69	143.77	115.65	84.85
Eprosartan	126.22	145.03	160.4	136.13	100.97	130.62	169.17	73.09
Latanoprost	109.22	120.43	135.41	138.07	88.31	123.76	116.17	38.51
Olmesartan	158.2	179.94	162.61	164.17	109.53	156.81	155.41	105.73

In consensus scoring, all the scores of best drug molecules obtained finally a total of 8 apoptosis-related were converted into positive values and imported into TSAR.

S. No	Drug Name
1	Olmesartan (Benicar)
2	Verteporfin (Visudyne)
3	Ritonavir (Norvir)
4	Telmisartan (Micardis)
5	Eprosartan (Teveten)

IV. CONCLUSION

Screening studies of 3500 drugs obtained from the drug bank database are docked against eight apoptosis proteins using Molegro Virtual Docker (MVD) software resulting in 20 drugs with few drugs such as Olmesartan, Verteporfin, Ritonavir, Telmisartan, and Eprosartan obtained as best compounds in more than one case. Further to filter the number of drugs obtained against apoptosis proteins, consensus docking and scoring were employed which reveal the top five drugs such as Olmesartan, Verteporfin, Ritonavir, Telmisartan, and Eprosartan respectively. Finally, this study states that novel compounds can be screened with high affinity against a specific target with few computational efforts.

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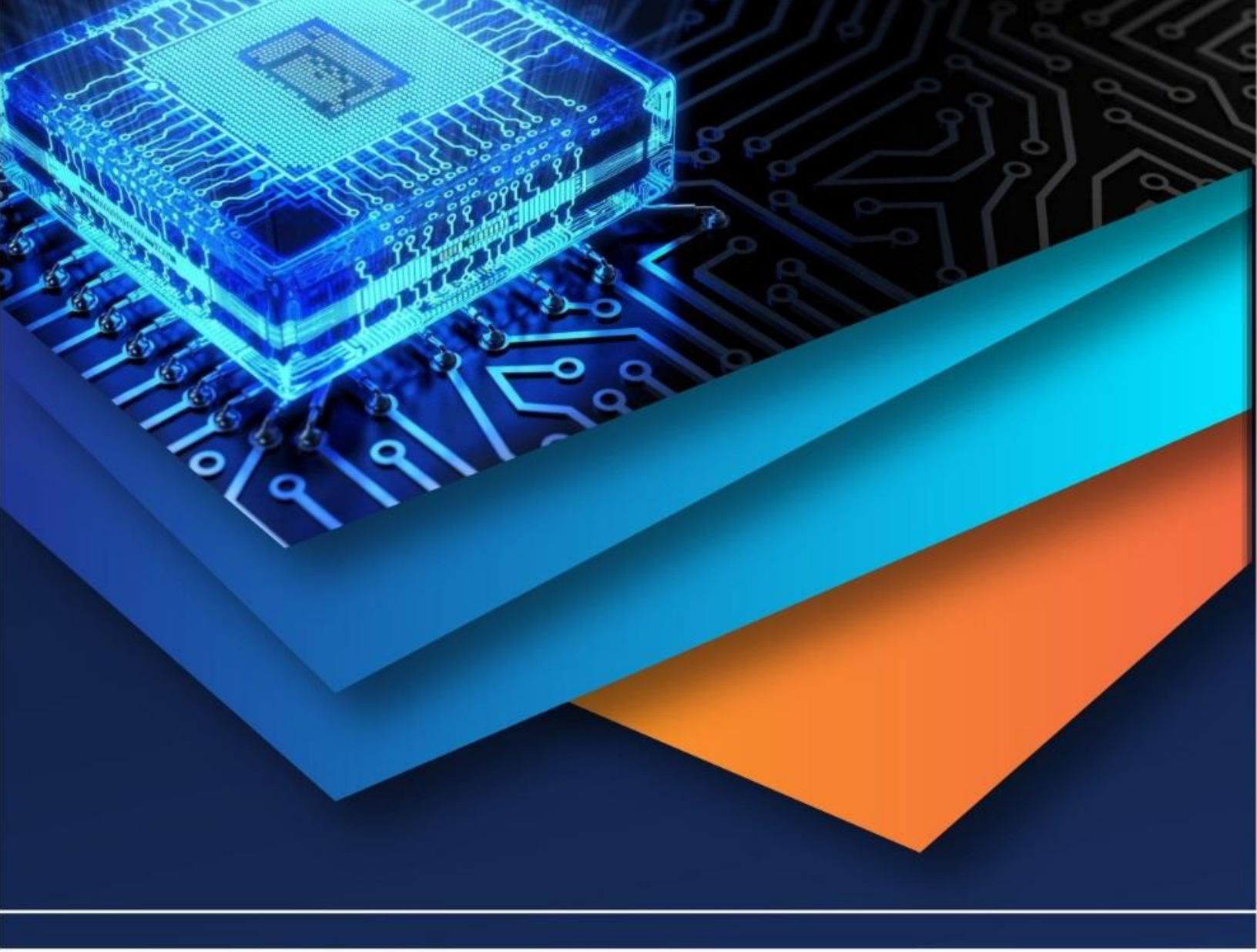

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