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Modern approaches for drug validation on behalf of computer aided drug designing for Adenocarcinoma

Abstract

In this research our team working on drug validation on behalf of CADD for Adenocarcinoma. We modified some drugs which are already available in market for chemotherapy of Adenocarcinoma. Lung cancer can cause certain changes in the DNA of lung cells. These changes can lead to abnormal cell growth and, sometimes, cancer. In this research we updated well known drug of Adenocarcinoma treatment via computational platforms and we found this drug via protein ligand interaction with favorable statical & structural (Tables Below) computation platforms.

Keywords: Adenocarcinoma, CADD (computer aided drug designing), DNA, drugs

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Introduction

By definition, invasive lung Adenocarcinoma is a malignant epithelial tumor with glandular differentiation, and with either mucin production or pneumocyte marker expression.[1] Pulmonary Adenocarcinoma has become the most prevalent histological type of primary lung cancer accounting for almost half of all lung cancers. It is also the most histologically variable and heterogeneous form of lung cancer. This makes it a major focus of research to improve lung cancer patient survival.[2] According to the Finnish Cancer Registry, 36% of the histologically confirmed lung cancers in 2007–2012 were reported as Adenocarcinoma, 27% as SCC, and 19% as SCLC Only two decades earlier, SCC was the most common histological type in an epidemiological lung cancer study representing the general population of Northern Finland with a prevalence of 40%, while the prevalence of Adenocarcinoma and SCLC was 26% and 24%, respectively.[3] The etiological factors influencing the shift in the relative proportions of pulmonary Adenocarcinoma vs. SCC are complex and not clearly understood.[4] In the literature, the emerging predominance of Adenocarcinoma since the 1960s has been strongly related to three smoking-associated factors. First, the change in cigarette manufacturing with the rise of filtered, lower tar- and nicotine containing cigarettes leading to deeper inhaling and a more peripheral distribution of tobacco smoke in the lung.[5] This together with the increase in tobacco-specific N-nitrosamines in the manufactured cigarettes has been said to promote a shift from central tumors, including SCC and SCLC, to peripheral tumors, i.e., Adenocarcinoma.[6] Second, the risk of SCC and SCLC increases more rapidly with increasing smoking duration than the risk of Adenocarcinoma, causing Adenocarcinoma to appear later.[7] Third, the risk of SCC and SCLC decreases more rapidly after smoking cessation than for Adenocarcinoma There is also evidence that non-smoking related factors have influenced the changes in the prevalence of Adenocarcinoma It is estimated that 10–15% of lung cancer deaths are accounted for by factors other than active smoking.[8] The improvements in the imaging and detection of peripheral pulmonary nodules as well as changes in the histological classifications 37 of lung tumors and in the pathological techniques may have influenced time trends in the adenocarcino.[9] Yet the temporal and geographical patterns and trends observed suggest genuine changes in the prevalence rates Among women, however, Adenocarcinoma rates have always been higher than SCC rates regardless of the smoking status, and the differences have widened over time.[10]

Cisplatin is similar to the bifunctional alkylating agents. It covalently binds to DNA and disrupts DNA function. After cisplatin enters the cells, the chloride ligands are replaced by water molecules. This reaction results in the formation of positively charged platinum complexes that react with the nucleophilic sites on DNA. These platinum complexes covalently bind to DNA bases using intra-strand and inter-strand cross-links creating cisplatin-DNA adducts thus preventing DNA, RNA and protein synthesis.[6] This action is cell cycle phase-nonspecific. Cisplatin also has immunosuppressive, radiosensitizing, and antimicrobial properties. Nephrotoxicity is a major concern when prescribing cisplatin. Renal dysfunction due to cisplatin may manifest as renal insufficiency, hypokalemia and hypomagnesemia. The risk for these adverse effects is related to the dose and interval of cisplatin and may be minimized by adequate hydration.[11] Vinorelbine is a semisynthetic vinca alkaloid derived from vinblastine. Vinca alkaloids such as vincristine and vinblastine are originally derived from periwinkle leaves (vinca rosea). Vinorelbine inhibits cell growth by binding to the tubulin of the mitotic microtubules. Like other mitotic inhibitors, vinorelbine also promotes apoptosis in cancer cells. In vitro vinorelbine shows both multidrug and non-multidrug resistance. Mild to moderate peripheral neuropathy (paresthesia, hypesthesia) is the most frequently reported neurologic toxicity and usually reversible on discontinuation of vinorelbine. Cisplatin does not appear to increase the neurotoxic effects of vinorelbine. However, prior treatment with paclitaxel may result in cumulative neurotoxicity.[12]

Materials and methods

Database NCBI (National Center for Biotechnology Information).[13] PDB (Protein Data Bank).[14] Drug Bank.[15] Tools: BLAST (Basic Local

Alignment Search Tool).[16] Model validation: SAVES (Structural Analysis and Verification Server)[17] Model visualization: Chimera, Rasmol, Pymol, discovery studio, Binding site analysis: Qsite Finder, Pocket Finder.[18,19] Dockingtool: Auto Dock, hex, PATCHDOCK, (hexserver.loria.fr/)Automated Docking Server: Online different type of docking server, The first step in methodology is collection of sequences data from NCBI. Sequence alignment: The protein sequences of Adenocarcinoma (>AAG28523.1 Adenocarcinoma antigen ART1 [Homo sapiens]) were obtained from NCBI/PDB after that the homology modeling of sequence is done then selection of the best model is done with the help of core region and model validation a binding site is also predicted via online tools then go for docking for identification of potential ligand with minimum energy for validation of selected Drugs. Expectation Value=0.002 , Search Tool = blast, Mask Low Complexity=yes) via BLASTP .this blast mainly use for protein the results of Computer Aided Drug Designing to find the potential drug candidate for Adenocarcinoma based on different type potential parameters Homology modeling, also known as comparative modeling of protein, refers to constructing anatomic-resolution model of the "*target*" protein formats amino acid sequence and an experimental three-dimensional structure of a related homologous protein. In this project homology modeling completed with Geno3D & Phyre it is an automatic web server for protein molecular.

Results and discussion

The results analysis base on Sequence of Adenocarcinoma antigen ART1 [Homo sapiens]

>AAG28523.1 Adenocarcinoma antigen ART1 [Homo sapiens]

MNLQRYWGEIPISSSQTNRSSFDLLPREFRLVEVHDPPLHQPSA
NKPKPPTMLDIPSEPCSLTIHTIQLIQHNRRLRNLIATAQAQNQQ
QTEGVKEESEPLPSCPGSPPLPDDLLPLDCKNPNAPFQIRHSDP
ESDFYRGKGEPVTELSWHSCRQLLYQAVATILAHAGFDCANES
VLETLTDVAHEYCLKFTKLLRFAVDREARLGQTPFPDVMEQ
VFHEVGIGSVLSLQKFWQHRIKDYHSYMLQISKQLSEEYERI
VNPEKATEDAKPVKIKEEPVSDITFPVSEELEADLASGDQS
LPMGVLGAQSERFPSNLEVEASPQASSAEVNASPLWNLAHV
KMEPQESEEGNVSGHGVLGSDVFEEPMSGMSEAGIPQSPDDS
DSSYGSHSTDSLMGSSPVFNQRCKKRMRKI

Expectation Value=0.002, Search Tool = blast, Mask Low Complexity=yes) via BLASTP .this blast mainly use for protein the results of Computer Aided Drug Designing of *drug validation* to find the potential drug candidate for Adenocarcinoma based on different type potential parameters Homology modeling, also known as comparative modeling of protein, refers to constructing anatomic-resolution model of the "*target*" protein formats amino acid sequence and an experimental three-dimensional structure of a related homologous protein. In this project homology modeling completed with Geno3D & Phyre it is an automatic web server for protein molecular selected model templates analysis via previous step submission ion Geno 3d server (Figure 1) (Tables 1-4).

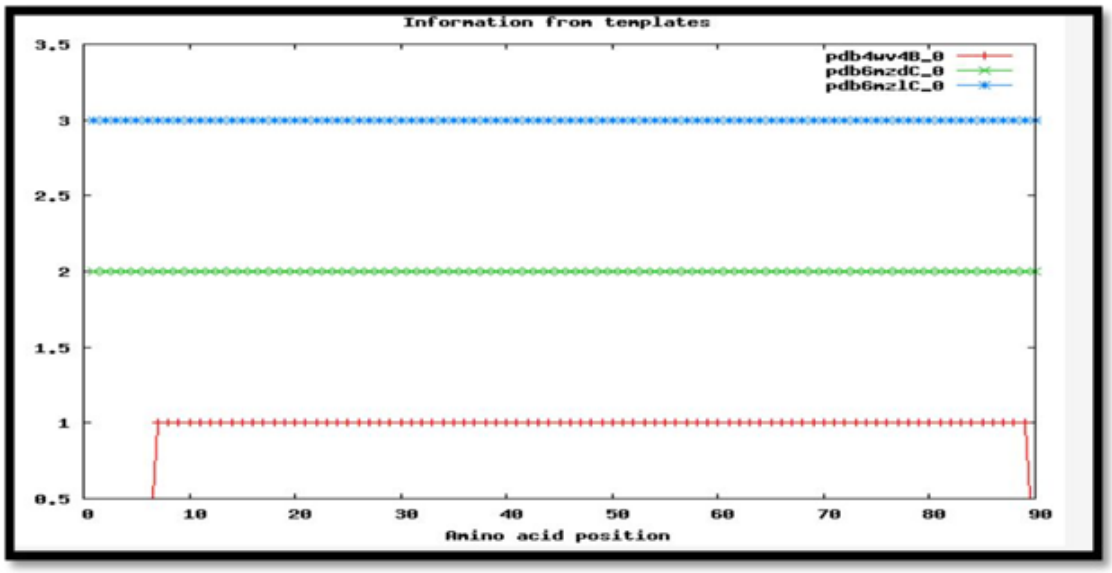


Figure 1 Information of amino acid positions as selected templates.

Table 1 This table explains about the selected template identity information

Name of template	Secondary information	Identity
pdb4wv4B_0	78.4 %	25.6
pdb6mzdC_0	98.4 %	23.6
pdb6mzlC_0	94.9 %	23.6

Table 2 This table explains structure of statical deviations

Deviation between templates on this chain (Angstrom)			
Name of templates	**4wv4B**	**6mzdC**	**6mzdC**
4wv4B	0.00	1.15	1.15
6mzdC	1.15	0.00	0.00
6mzlC	1.15	0.00	0.00
Mean deviation : 0.767372			

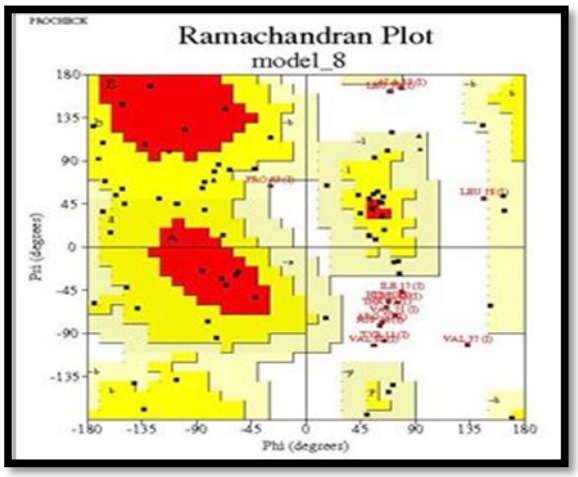
Citation: Srivastava V, Agrawal SP, Kalra SJS, et al. Modern approaches for drug validation on behalf of computer aided drug designing for Adenocarcinoma. *MOJ Toxicol.* 2019;5(1):53–60. DOI: 10.15406/mojt.2019.05.00153

Table 3 This table explains the energy and core of each predicted models

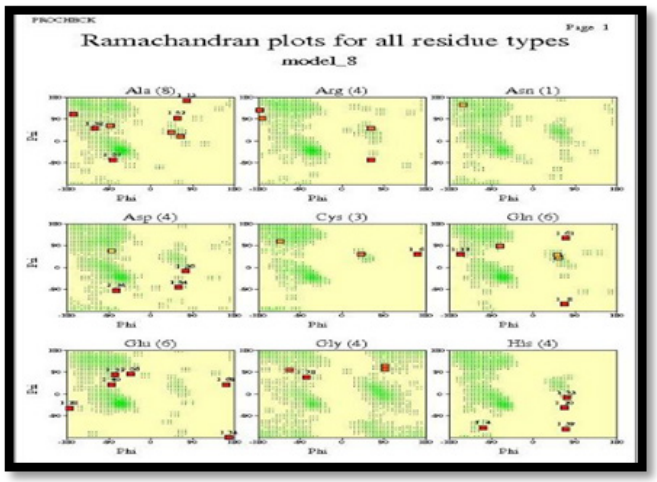
Model number	Models energy (kcal/mol)	Core	Allowed	Generously	Disallowed
Model 1	8244.74	80.2%	16.0%	3.7%	0.0%
Model 2	-3567.42	80.2%	16.0%	1.2%	2.5%
Model 3	-3486.13	90.1%	4.9%	2.5%	2.5%
Model 4	-3519.33	80.2%	17.3%	2.5%	0.0%
Model 5	-3597.54	87.7%	11.1%	1.2%	0.0%
Model 6	-3536.62	82.7%	13.6%	2.5%	1.2%
Model 7	-3319.28	86.4%	9.9%	2.5%	1.2%
Model 8	-2316.14	17.3%	44.4%	22.2%	16.0%
Model 9	-3393.46	82.7%	12.3%	2.5%	2.5%
Model 10	-3509.73	88.9%	8.6%	1.2%	1.2%

Table 4 This table explains the structures of selected parameters model number 1

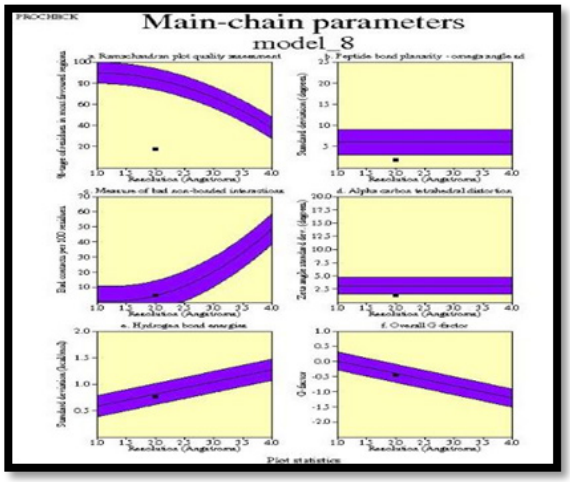
Ramachandran plot amachandran plot



Ramachandran plots for all residue types



Main-chain parameters



Side-chain parameters

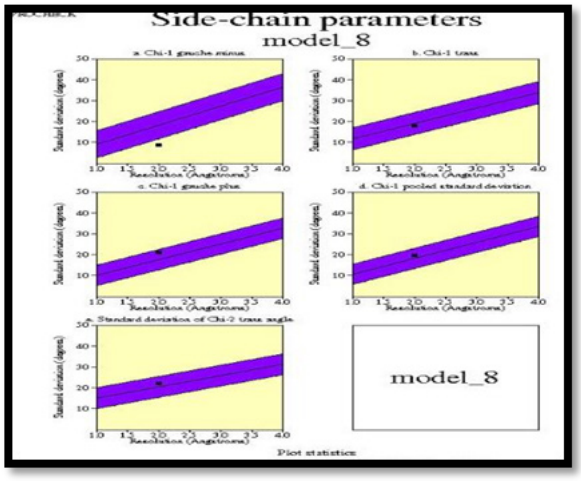


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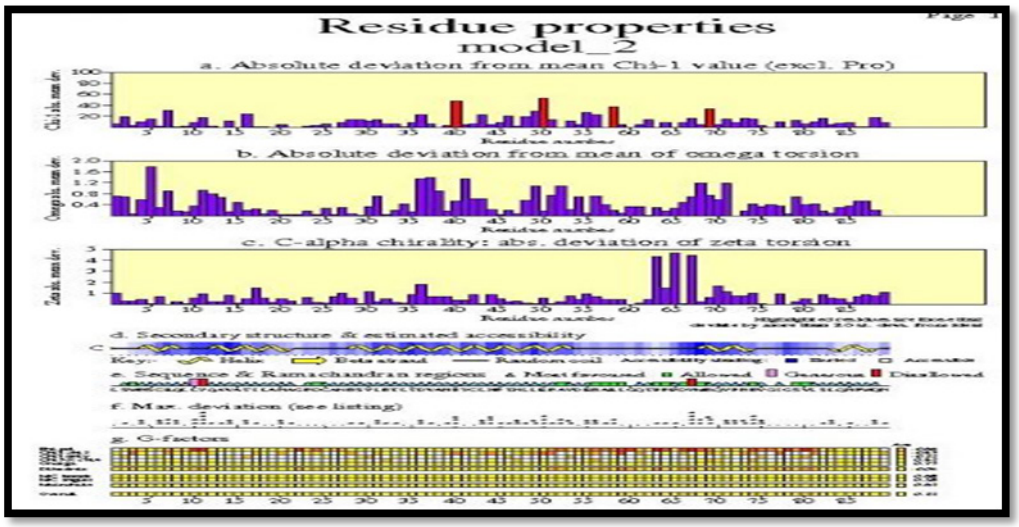
Table Continued....

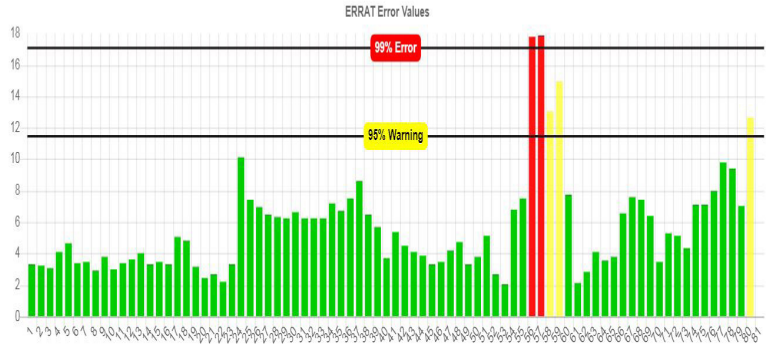
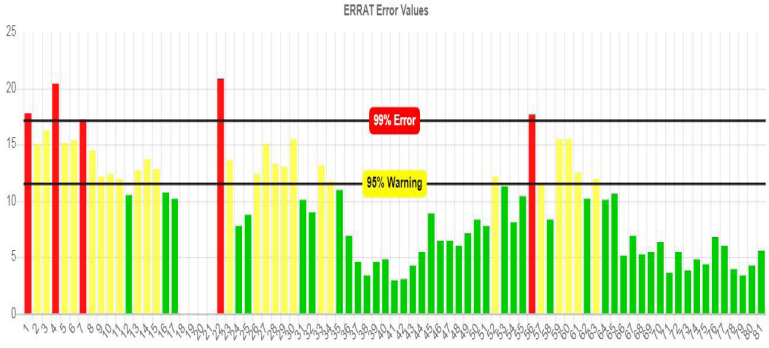
Residue properties



Model validation

Model validation completed with the help of SAVES server. It is type of online web server for model validation and for analyzing protein structure for validity and assessing how correct they are it's based on six programs Results: the Model 1 is pass by the SAVES server as per selection of model numbers we analyze the quality factors of model number one & eight for potential selection and analysis (Table 5).

Table 5 This table explains about the quality factor analysis on behalf of CADD paramets for the potential analysis

Validation of quality factor of modeled structures between model 1& 8
Model 1
Quality Factor: A: 93.75 | PDF | PostScript | Log

Model 8
Quality Factor: A: 61.039 | PDF | PostScript | Log


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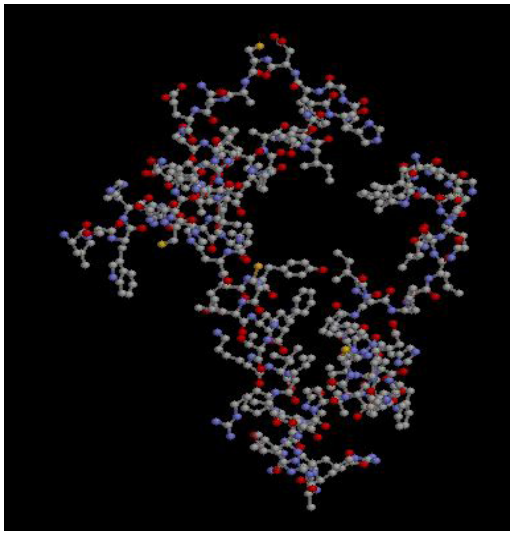
Visualization

Selected model analysis based on 2D and 3D structure visualization and the model visualization completed with the help of different type of software's for example: Chimera, Rasmol, and discovery studio computational predicted models via bioinformatics approaches and the method of homology modelling is based on the observations because that's protein tertiary structure is better conserved than amino acid sequence (Table 6).

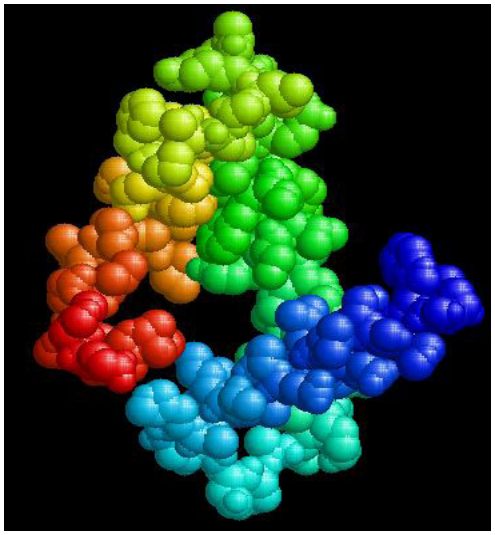
Table 6 This table explains about the different variants of selected models with labeled information

Different structure of modeled protein 1

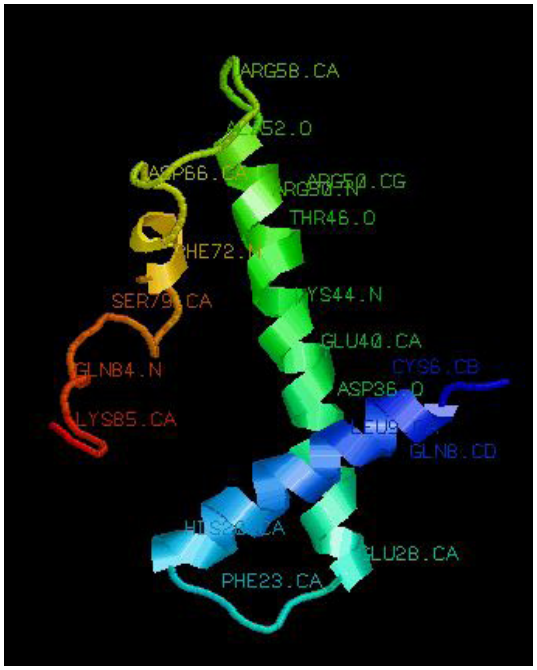
Ball & Stick structure of model 1



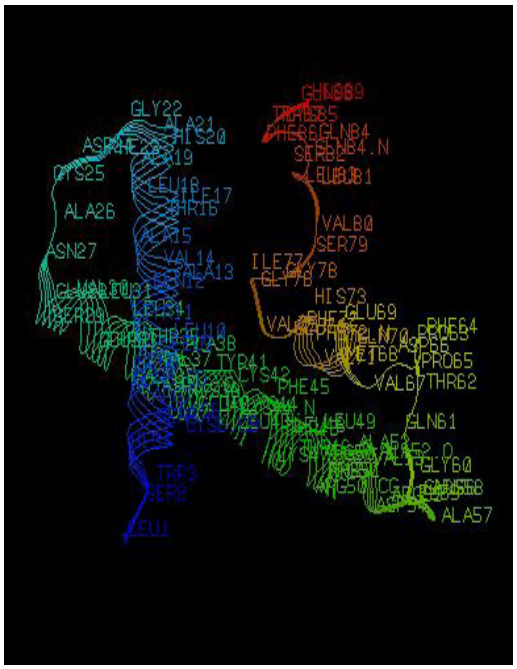
Space fill structure of model 1



Ribbon structure of model 1



Full labeled structure of model 1



Suitable ligand selection for receptor ligand binding

In this project the ligand selection for potential receptor based on ligand binding site and also available list favorable drugs for Adenocarcinoma Then select the potential ligand as drug candidate and change some confirmation on drug structure computationally then prepare final ligand for docking results analysis (Table 7).

Docking

Prediction of the optimal physical configuration and energy between two molecules and the phenomenon which enables the interaction between receptor molecules and the ligand molecule, and mainly (Tables 8-10).

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Table 7 This table explains about the different variants of selected ligand molecules with some modification on behalf of CADD with labeled information

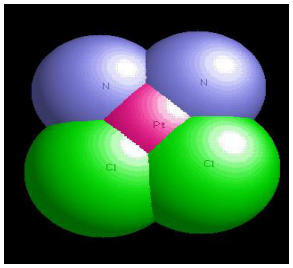
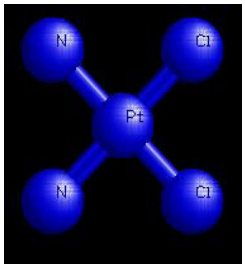
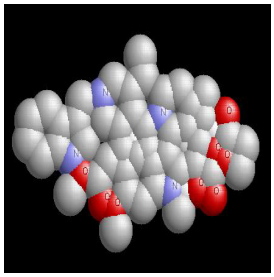
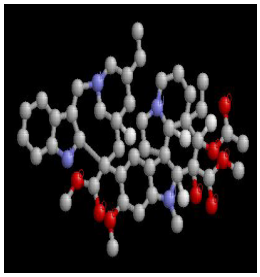
Modified ligand molecules (Structure of cisplatin & vinorelbine)	
Modified cisplatin **Space fill**	**Ball sticks**
	
Modified vinorelbine **Space fill**	**Ball sticks**
	

Table 8 This table structures explain the interaction of protein and modified ligand molecules

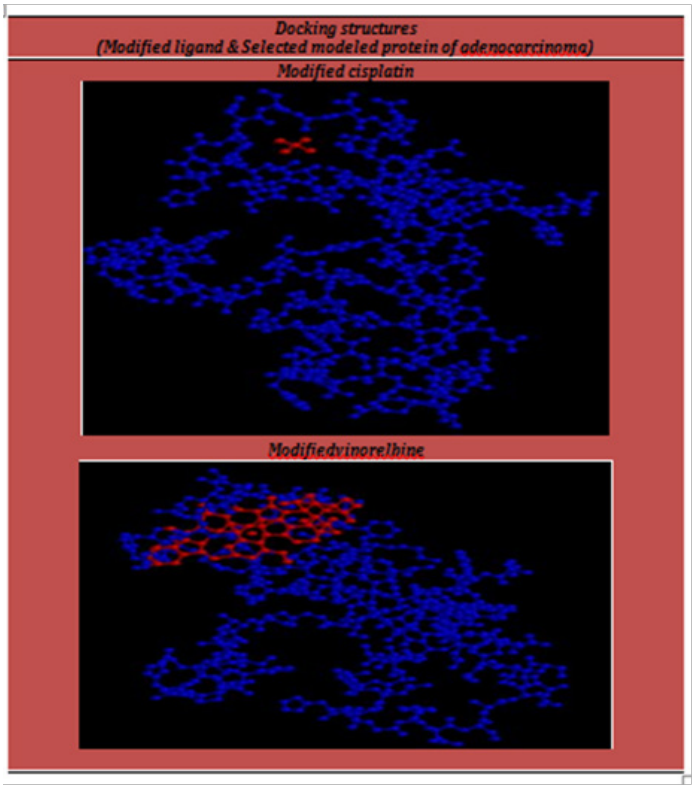


Table 9 This table explains the results of docking with Adenocarcinoma with modified vinorelbine. Total 20 models predicted with statical parameters but we selected model numbers 1 out of 20 because good bing score and area coverage of the molecule

Docking Model Number	Binding Score	Area	ACE	Transformation
Docking Model 1	6484	969.40	-488.42	-0.34 -0.89 -2.33 -0.66 1.16 14.47
Docking Model 2	6092	858.50	-516.24	0.87 0.15 -0.84 26.94 -8.85 -2.40
Docking Model 3	6038	770.60	-538.41	1.91 1.03 -1.12 10.82 -8.62 17.59
Docking Model 4	5956	745.90	-386.03	-0.91 -0.03 2.24 28.20 -9.65 -2.88
Docking Model 5	5948	791.90	-409.23	-0.49 0.88 2.02 -2.40 1.67 12.96
Docking Model 6	5902	845.40	-375.84	0.64 0.74 0.54 -2.93 0.89 13.01
Docking Model 7	5860	739.70	-477.23	-1.75 -0.95 2.28 10.98 -7.33 15.59
Docking Model 8	5702	810.00	-349.13	0.31 -0.77 -1.49 -2.45 1.06 11.90
Docking Model 9	5648	888.80	-533.52	0.45 0.96 0.86 0.75 1.34 15.40
Docking Model 10	5644	769.10	-363.72	-0.71 -0.63 2.50 24.25 -7.03 -4.95
Docking Model 11	5618	908.10	-590.07	1.14 -0.53 -0.39 -3.03 0.06 13.77
Docking Model 12	5616	738.90	-359.77	-1.00 0.10 2.65 1.32 0.60 12.19
Docking Model 13	5596	712.70	-348.23	0.49 0.71 -0.43 24.10 -5.34 -4.50
Docking Model 14	5594	725.20	-529.50	-1.42 -0.59 2.31 12.78 -10.56 18.25
Docking Model 15	5556	697.30	-399.67	-2.18 -0.59 -3.08 22.48 -5.53 9.24
Docking Model 16	5536	709.40	-420.11	1.67 -0.57 -0.92 9.93 -7.17 19.02
Docking Model 17	5530	738.20	-428.25	-0.75 -0.61 2.52 27.07 -8.49 -2.49
Docking Model 18	5526	758.30	-451.96	-1.02 -0.61 2.80 27.81 -12.64 -4.91
Docking Model 19	5500	742.50	-431.86	1.65 0.13 -0.88 8.80 -6.00 14.69
Docking Model 20	5478	740.40	-430.40	-0.92 0.54 2.35 -1.36 3.82 15.58

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Table 10 This table explains the results of docking with Adenocarcinoma with modified cisplatin Total 20 models predicted with statical parameters but we selected model numbers 1 out of 20 because good bing score and area coverage of the molecule

Docking Model Number	Binding Score	Area	ACE	Transformation
Docking Model 1	1638	178.20	-44.46	0.27 0.71 0.16 26.54 -10.96 -0.94
Docking Model 2	1504	157.40	-30.81	-3.02 -0.51 -2.06 -4.00 -6.29 20.85
Docking Model 3	1438	160.90	-13.19	-2.64 0.83 1.25 -6.84 -0.05 11.30
Docking Model 4	1436	163.50	-36.76	1.04 0.58 0.36 23.04 -17.00 0.24
Docking Model 5	1420	159.70	-29.52	-2.94 -1.02 -1.67 0.09 -1.10 13.21
Docking Model 6	1402	149.30	-34.38	-0.86 -0.01 -2.21 -9.17 1.49 14.51
Docking Model 7	1396	144.80	-19.11	-2.75 -0.45 -2.61 15.76 -5.16 -9.38
Docking Model 8	1374	151.90	-40.61	-0.16 0.14 1.92 15.39 -7.33 4.17
Docking Model 9	1362	145.00	-36.10	-0.90 -0.54 -1.02 5.62 -3.16 22.31
Docking Model 10	1360	156.70	-30.83	1.33 0.77 2.24 10.56 -10.98 14.40
Docking Model 11	1354	142.30	-36.61	-0.60 0.33 2.13 18.39 -12.55 4.51
Docking Model 12	1354	143.70	-28.74	-1.21 -1.11 0.95 14.12 -16.01 19.93
Docking Model 13	1350	148.30	-20.09	-0.45 -0.12 2.52 -2.01 -3.81 23.86
Docking Model 14	1330	136.30	-20.51	2.00 1.13 -0.52 7.50 -15.02 5.07
Docking Model 15	1324	145.00	-30.90	-1.54 -0.51 2.34 -2.05 -13.74 13.49
Docking Model 16	1324	147.10	-27.18	1.23 1.02 -2.68 24.98 -5.42 9.50
Docking Model 17	1322	142.20	-4.96	-2.49 -1.45 0.53 8.26 -6.39 -4.67
Docking Model 18	1318	137.30	-24.31	-1.36 1.12 1.87 8.50 -5.70 19.27
Docking Model 19	1316	136.00	-18.42	1.16 -0.25 2.57 1.00 -16.18 12.70
Docking Model 20	1308	142.40	-25.04	2.75 0.36 0.62 4.80 2.11 17.80

Conclusion

Finally in this study we modified cisplatin & vinorelbine chemical structures via online available tools on behalf of CADD parameters and 3Dstructure of Adenocarcinoma protein (homo sapience) which is predicted through the Insilico approaches and homology modeling and the docking of Modified cisplatin & vinorelbine with other selected various ligand and determined the interaction between protein and ligand that's bind on active site of the Modified cisplatin & vinorelbine, although docking process. It is very complicated because its depends on various parameters the main resultant obtained by different type of docking tools and docking completed with the help of HEX,PATHADOCK for identify the suitable Modified cisplatin & vinorelbine and other different ligands which are docked with the Adenocarcinoma protein for inhibit the growth of unnatural cell development . Only 2 numbers of ligand given the minimum energy out of other selected 10 ligands. Modified cisplatin & vinorelbine is playing an important role as inhibitor for treatment of Adenocarcinoma with minimum binding energy and its work as a potential Inhibitor for unnatural cell development only 2 number ligand has given the minimum energy out of other selected 10 ligands. Modified cisplatin & vinorelbine is playing an important role as inhibitor for treatment of adenocarcinoma with minimum binding energy and its work as a potential Inhibitor for unnatural cell development in lungs that causes adenocarcinoma as per the Table number 9 & 10 parameters. Perhaps the ultimate solution is to develop a potential drug candidate against this devastating unnatural cell development in lungs that causes adenocarcinoma.[20]

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Conflicts of interest

Author declare that there is no conflict of interest.

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