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ANTICANCER ACTIVITY AND DRUG LIKELINESS OF QUINOLINE THROUGH INSILICO DOCKING AGAINST CERVICAL AND LIVER CANCER RECEPTORS

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Keywords:
Quinoline, Biophytum Sensitivum, Liver cancer, Cervical Cancer, Insilico Docking.

Abstract

The oncogenic protein receptors were key molecular targets for cancers. Especially in tumor cells, they were frequently transformed or mutated at abnormal states. The normal cells encounter a programmed cell death (apoptosis). It is an imperative and striking focus for anticancer medication advancement and disclosure. Biophytum sensitivum is a medicinal plant rich in quinoline and amentoflavone. The aqueous extract of plant was still administered for various ailments in naturopathy medicines. Quinoline is a versatile heterocyclic compound used to anti-inflammatory and anti-malarial properties. The quinoline was evaluated for the drug likeliness score and insilico anticancer activity against liver and cervical cancer receptors. In this present study the 5 cervical (4K3J, 4COX, 4J96, 1PRH, 1YY9) and 4 liver cancer receptors (3S35, 3S37, 3LVQ, 4X47) were docked with quinoline through in silico docking. 4K3J and 1yy9 of cervical receptors indicated that the quinoline ligand inhibited significant inhibition than other receptors of the cervical cancer. Similarly liver receptors 3S35 and 4X47 were significantly inhibited by quinoline inhibitor. The drug likeliness score of quinoline indicates the best score attained as -0.53.

Introduction

The cancer progression was initiated by a process called angiogenesis. This phenomenon is an important state of normal physiological processes such as embryogenesis and wound healing. It also contributes to pathological disorders and in particular to tumor growth [1, 2]. Cancer progression an abnormal cell growth which links with high inflammation. The inflammation is chief response on the natural immunity to defend the organism against microbial pathogens. The nature of the microbial pathogens such as bacteria, virus occurs biochemically in the form of lipopolysacchrides which are detected by the cytokine expressions such as interleukin 1 beta (IL1β), tumor necrosis factor alpha (TNFα), interleukin 6 (Il6), Cyclooxygenase (COX), together with chemokines and cell adhesion proteins [3, 4], in turn, leading to the recruitment and the activation of immune cells.

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Cyclooxygenases (or prostaglandin H synthases),were generally referred to as COXs, are a family of myeloperoxidases originated at the luminal side of the endoplasmic reticulum and nuclear membrane [5],which catalyze the rate-limiting step of prostaglandin biosynthesis from arachidonic acid [6, 7]. These enzymes act by two coupled reactions. The first one is the conversion of arachidonic acid released from the plasma membrane by phospholipase A2 to prostaglandin G2 by the cyclooxygenase activity. The second reaction is mediated by the peroxidase activity and leads to the conversion of prostaglandin G2 to prostaglandin H2. Then, different synthases convert prostaglandin H2 to prostaglandin D2, F2α, E2, I2, and thromboxane A2. The COX-2, is the inducible form normally induced and implicated in inflammation, and intends to analyze the link between COX-2 and cancer, in terms of effects on cell proliferation and cell death. The correlation between the inflammation and cancer on literature reverts to more than century ago no such mechanism was linked between the two state of infection [8].

The mechanism of the inflammation during cancer was studied only recent years. The incidences of the several cancers were soundly associated with colon, breast and prostate cancer [9, 10]. This is evidenced by the tumor environment was characterized by the infiltration of various types of immune cells such as dendritic cells, lymphocytes, and macrophages which is responsible for the release of cytokines. The extraction and characterization of pharmacologically active biocompounds from the medicinal plants was gaining continue day by day, and the techniques on drug discovery were now be to standardize herbal medicines and to elucidate analytical marker compounds. Methods help to acquire compounds for drug discovery include isolation from plants and other natural sources, chemical synthesis, combinatorial chemistry and molecular modeling [11, 12].

Drug discovery from medicinal plants has contributed to cancer treatment, and most new clinical applications during the last half century relate to cancer. Approximately 15 million new cancer cases will be diagnosed around the globe, and 12 million patients will die in cancer. Cancer is caused by both internal factors such as inherited mutations, hormones, and immune conditions, environmental and acquired factors like tobacco, diet, radiation, and infectious organisms [13]. The attractiveness of natural compounds as drugs partly stems from their potential ability to influence multiple components of the carcinogenesis pathway.Therefore the present study focuses the key molecular targets which involved in the cancer progression and differentiation. The Key target with the PDB ID was identified in the cervical cancer were PDB ID: 4K3J, 4COX, 4J96, 1PRH, 1YY9 and liver cancer receptors were PDB ID: 3S35, 3S37, 3LVQ, 3S36 were involved in the cancer progression and inflammation. Hence the ligand quinoline was elucidated from medicinal plant *Biophytum sensitivum* and it was evaluated for understanding the molecular mechanism of anticancer activity through *Insilico* docking. The *Insilico* docking was performed by using Discovery studio tools on the ligand qunoline derivative and molecular targets of liver and cervical cancer receptors

Materials and methods

Preparation of Cancer receptors

The preparation of the cancer receptor was initially starts with mining of the target receptors in protein database Research Collaboration for Structural Biology (RCSB) (http://www.rcsb.org/pdb/). The structural data of the receptors were determined using x-ray crystallography and NMR methods which are deposited in the PDB. The 3D structure of the cervical cancer receptors (PDB ID: 4K3J, 4COX, 4J96, 1PRH, 1YY9) and liver cancer receptors were mined from the (PDB ID: 3S35, 3S37, 3LVQ, 3S36) from the Protein Data Bank (PDB). The water molecules were removed from the both liver and cervical cancer receptors before docking. Energy minimization was done by applying for CHARMM (Chemistry at Harvard Macromolecular Mechanics) force fields. This program performs energy minimization, normal modes and crystal optimizations. Further this program also incorporates free energy methods for chemical and conformational free energy calculations.

Preparation of Ligand structures

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The identified Chemical compounds namely Quinoline,1,2-dihydro-2,4-6- Tetramethyl was derived from Biophytum sensitivum whole plants and these compound structure were retrieved from Pubchem structural database. Both of these compounds were under investigation of Ligprep. The ligprep was used to prepare ligands. The ligand molecules were generated and the three dimensional optimizations were done and then saved as MOL file (a file format for holding information about the atoms, bonds, connectivity and coordinates of a molecule).

Molecular Properties and Drug Likeliness Score

The molecular properties of Quinoline,1,2-dihydro-2,4-6-Tetramethyl was first predicted for the number of hydrogen atoms, molecular weight, number of violated and non violated atoms, log polarity, log solubility, polar surface area, molecular volume and stereo centers. These properties were very essential to predict the compound is drug or toxic. The combinatorial high throughput screening works on the basis of algorithm which builds for evaluating the compounds based on the above parameters to predict the drug properties. The tools worked on the basis of artificial neural networks. Plenty of the tools were available to predict druglikeliness score viz., Molsoft, Molinspiration, etc. The druglikeliness score was analyzed by draw the structure in Java molecular editor. The ligand Quinoline,1,2-dihydro-2,4-6- Tetramethyl was drawn on the Jmol editor and select the option submit. The tool predicts the molecular properties and the results were opened on the same window.

Docking Analysis

The docking analysis was performed by Discover Studio Version 4.0 (Accelry's Software Inc. USA) for the receptors of cervical and liver cancer protein interaction with GC-MS of Biophytum sensitivum whole plant extract compounds. The fitting points were added to hydrogen bonding groups on the protein. The interaction between the binding pockets of target liver and cervical receptor protein and investigation compound was to find out the accurate binding model of the active site of protein. The mechanism of ligand with target receptors was performed based on binding site position. The receptor protein ligand docking energy values performance based on the compound identified in the spectrum of gas chromatography mass spectrum. Among the compounds quinoline was found with good drug likeliness score and molecular properties. The Scoring functions which are execute in docking program to make various assumptions and parameters to fit best complexes, which includes terms of hydrogen bonds for Discovery Studio to rank the docked bases and to assess the binding site and the number of rotatable bonds present.

Prediction of the active sites in the Receptor molecules

The prediction of active site in the liver and cervical cancer receptors were highly essential to understand the mechanism of the ligand quinoline binding at active amino acid residues to inhibit the activity of receptor molecules. The active site was predicted by using 'detect cavity' function of Q-site Finder (http://www.modelling.leeds.ac.uk/qsitefinder/). The prediction mechanism is an energy based method for the prediction of protein-ligand binding sites.

Results

The Noninfectious, life threatening and mortality causing one of the terrific disease is cancer. Pharmaceutical industry still thrives to give a permanent solution to find a new novel drug for cancer. The Insilico docking provides the inhibition of molecular targets and its mechanism on site specific action. For this purpose the prime step to stop cancer was to find suitable molecular target. The receptor proteins involved in cervical cancer receptors (PDB ID: 4K3J, 4COX, 4J96, 1PRH, 1YY9) and liver cancer receptors were mined from the (PDB ID: 3S35, 3S37, 4XAV, 3S36) from the Protein Data Bank (PDB) and presented in the Figures 2 and 3. The medicinal compounds like quinoline have anti-inflammatory, antioxidant and anticancer activity. Therefore the compound was elucidated and the structure was drawn in the molecular editor software Jmol. The smiles were generated and it was evaluated for the molecular properties through the high through put screening combinatorial chemistry database like pubchem and other drug databases. The molecular structure was drawn in the tool Molsoft and molinspiration tools. The drug likeliness score was evaluated and presented in the Figure 1. The molecular properties of the quinoline were found to be good score and drug properties. The Molecular properties of the quinoline was found to be molecular formula: C15H15No3, Molecular weight: 257.11, Number of HBA:3, Number of HBD :1, Mol

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LogP:1.93, Mol Logs:-3.09moles/L, MolPSA:43.86A2, MolVol: 262.08A3, Number of stereo centers :0. The drug score of the quinoline was found to be 0.53.

Binding site prediction of cervical and liver cancer receptors

The cervical and liver cancer receptors were evaluated for predicting the active site residues and presented in the Figure 4. The active site residues found in the cervical cancer receptors were PDB.ID. 4K3J active site residues ASN 45, THR 11,LYS 509,LEU 43, PRO 44,GLN 42, PDB.ID.4J96 active site residues LYS 658, MET 659,LEU 665, ARG 664, GLY 663, ASP 530, PDB.ID.1PRH active site residues TYR 404,PHE 407, PHE 200,LEU 390, TYR 385,TRP 381, PRO 389, TRP 404, VAL 451, HIS 446,ILE 444 , PDB.ID.4COX active site residues GLU67,GLY 66, SER 38, THR 70, CYS 60,PRO 40, ASN 65 and PDB.ID.1YY9 active site residues GLN28, ASN32, ASN33, ARG29.

Similarly the liver cancer receptors PDB.ID.3LVQ active site residues ALP 22, ALA23, VAL 38, LEU 27, GLU124, ALA156, THR 44, GLY66, ARG 469, SER 152, 154, PDB.ID.3S35 active site residues LEU 228,SER 231, ASN 318, SER 318, VAL 227, ASP225, VAL 305, PDB.ID.4X4V active site residues ARG 322,ILE 332, ASP 330, ASP348, LEU 349 and 3S37 active site residues GLN 126,ASP125, GLN 124,ALA156,CYC 155, GLY25,TYR 40,GLY 6,ARG 469, THR 41, LEU 126 were found as the potential catalytic sites to bind with the ligand molecule.

Docking study of Cervical and Liver cancer receptors with Quinoline inhibitor

Docking of cervical and liver cancer receptors were performed with quinoline inhibitor and it was presented in the Figure 4 and Table 1. Among the cervical receptors docked with the quinoline the 4k3j and 1yy9 have docked the best docking frequency 80 and 90 % attained than other receptors. Similarly the docking score 4k3j-0.2416 & 1yy9-0.5836 and other energy minimized parameters were pronouncedly reduced after docking with quinoline. The Liver cancer receptors were inhibited by quinoline 3s35 and 4x47 were shown (Table 1) to be highest docking frequency, score and energy minimization. The docking frequency of liver cancer 4x47 attained 93% and 3s35 have 95% of than other receptors docked. Similarly the docking score was achieved as 0.324 and 0.416.The energy minimization also pronouncedly reduced when calculated after post docking analysis presented in the Table 1. Similarly the docking binding sites of the cervical cancer catalytic residues were found in 4k3j ASN 45, THR 11,LYS 509,LEU 43, PRO 44,GLN 42, and in 1YY9 active site residues docked with quinoline were GLN28, ASN 32, ASN33, and ARG 29.

Subsequently the liver cancer receptors catalytic sites inhibited by the quinoline were 3S35 active site residues LEU 228,SER 231,ASN 318,SER 318,VAL 227, ASP 225,VAL 305, PDB.ID.4XAV active site residues ARG 322,ILE 332, ASP 330, ASP 348, LEU 349 and the 4x47 liver cancer receptor were inhibited by the quinoline at the amino acid residues at the catalytic sites ARG 322, ILE 332, ASP 330, ASP348, LEU 349. Among the two different cancer cervical and the liver cancer receptors, the inhibition were highly occurred by quinoline in the liver cancer receptors.

Discussion

In the present study the impact of the commercially available inflammatory inhibitors were studied by the literature and the Insilico experimental study was conducted to reveal the impact of synthetic and natural compounds from the medicinal plants were evaluated against the cervical and liver cancer receptors. The receptors of cervical cancer receptors (PDB ID: 4K3J, 4COX, 4J96, 1PRH, 1YY9) and liver cancer receptors were mined from the (PDB ID: 3S35, 3S37, 4XAV, 3S36) from the Protein Data Bank (PDB).The lead compound quinoline were isolated and elucidated from the ethanolic extract of Biophytum sensitivum. The compound quinoline was docked against the above mentioned cervical and liver cancer receptors. The Classical non specific drug inhibitors like aspirin, ibuprofen, naproxen, but not nimesulide, are non-selective inhibitors of both the COX isozymes revealed that the prolonged use can cause gastric bleeding and renal failure [14-16]. Similarly but the usage COX-1 inhibitory agents is significantly greater than COX- 2. Some COX-2 inhibitors have been evaluated in clinical trials, but some of them showed increased cardiovascular toxicity; celecoxib seems to be relatively safe COX-2 inhibitor [17-19]. It has meanwhile been hypothesized that there might be other isoforms of the COX

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enzyme yet to be discovered [15].

Nexrutine is an herbal alternative to COX inhibitor drugs for pain and soreness, and offers a number of advantages over both broad COX-1/2 inhibitors like aspirin and selective COX-2 inhibitors like Celebrex. Nexrutine inhibits the inflammatory COX-2 connected with pain without inhibiting the protective COX-1; thereby having a lower risk of producing gastrointestinal and bleeding side effects compared aspirin and Celebrex [20-23]. Synthetic compounds like mono-, di- and triaryl substituted tetrahydropyrans were also reported as COX-2 and tumor growth inhibitors. These compounds exhibit IC50 for COX-2 in the range 0.57-4.0 nM, and their selectivity for COX-2 over COX-1 is better than that of celecoxib and rofecoxib [24-27]. Similarly the quinoline inhibitor from the Biophytum sensitivum docked all the cervical and liver cancer receptors. Finally among the receptors the 4k3j and yy9 of cervical receptors indicated that the quinoline ligand inhibited significant inhibition than other receptors of the cervical cancers. The liver receptors revealed that the 3s35 and the 4x47 were notable and higher anticancer activity significantly inhibited by the quinoline inhibitor. The catalytic sites residue were found in the both receptors were 3S35 active site residues LEU 228,SER 231,ASN 318,SER 318,VAL 227, ASP225,VAL 305, PDB.ID.4XAV active site residues ARG 322,ILE 332, ASP 330, ASP348, LEU 349 and the 4x47 liver cancer receptor were inhibited by the quinoline at the amino acid residues at the catalytic sites ARG 322,ILE 332, ASP 330, ASP348, LEU 349. The highest docking frequency and score were achieved in the Liver cancer. Hence the Insilico study recommends that the liver cancer receptors were pronouncedly inhibited and the mechanism were elucidated.

Conclusion

The Present study presumes that the Quinoline compound elucidated from the Medicinal Plant Biophytum sensitivum interact with cancer receptors and demonstrated as a potent inhibitor for the liver and cervical cancer receptors. Henceforth the quinoline lead was proposed and prescribed as a promising drug for the liver and cervical malignancy.

Acknowledgement

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Figure 1. Prediction of Molecular Properties and Drug likeliness of quinoline.

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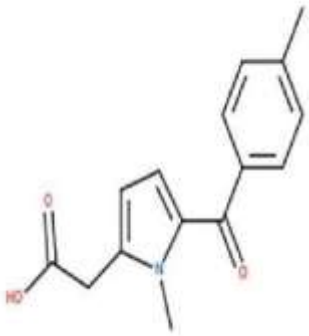
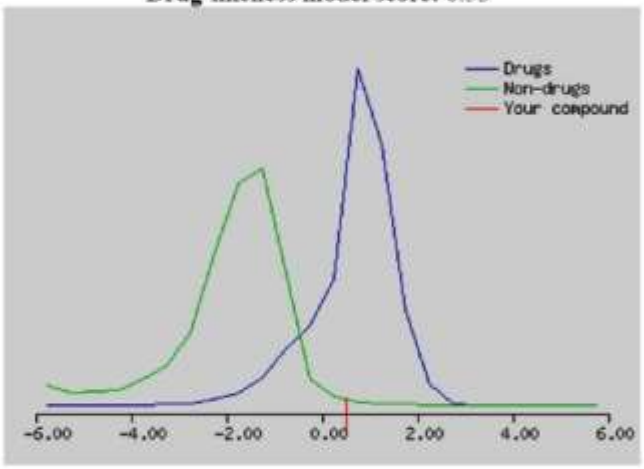
Molecular Properties and Drug-likeness.



Molecular formula: C15 H15 N O3
Molecular weight: 257.11
Number of HBA: 3
Number of HBD: 1
MolLogP : 1.93
MolLogS : -3.09 (in Log(moles/L)) 210.05 (in mg/L)
MolPSA : 43.86 A^2
MolVol : 262.08 A^3
Number of stereo centers: 0

Drug-likeness model score: 0.53



New molecule Modify molecule Search molecule

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Figure 2. Three dimensional structure of Cervical cancer receptors a. 4K3J, b. 4COX, C. 4J96, d.

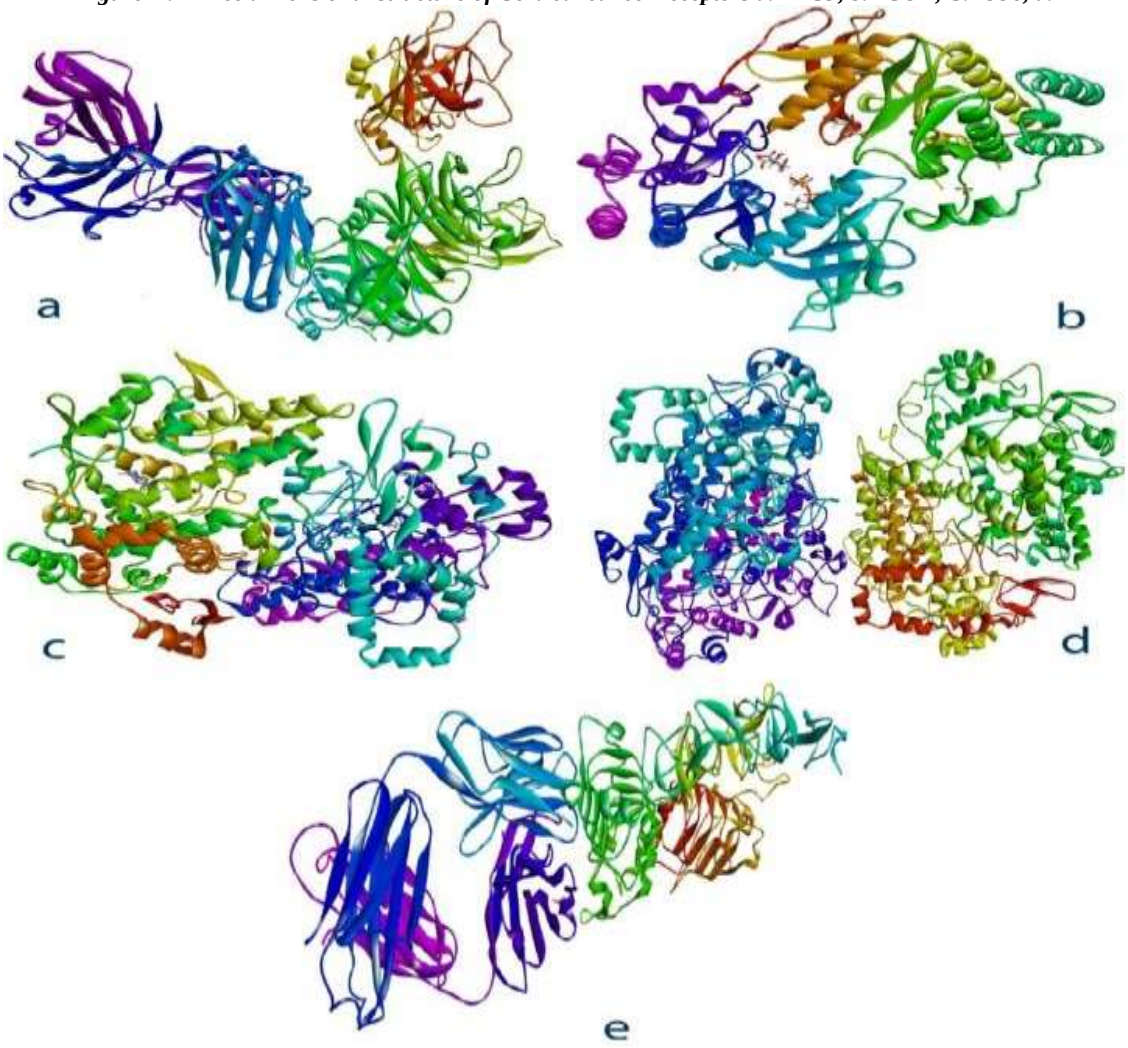

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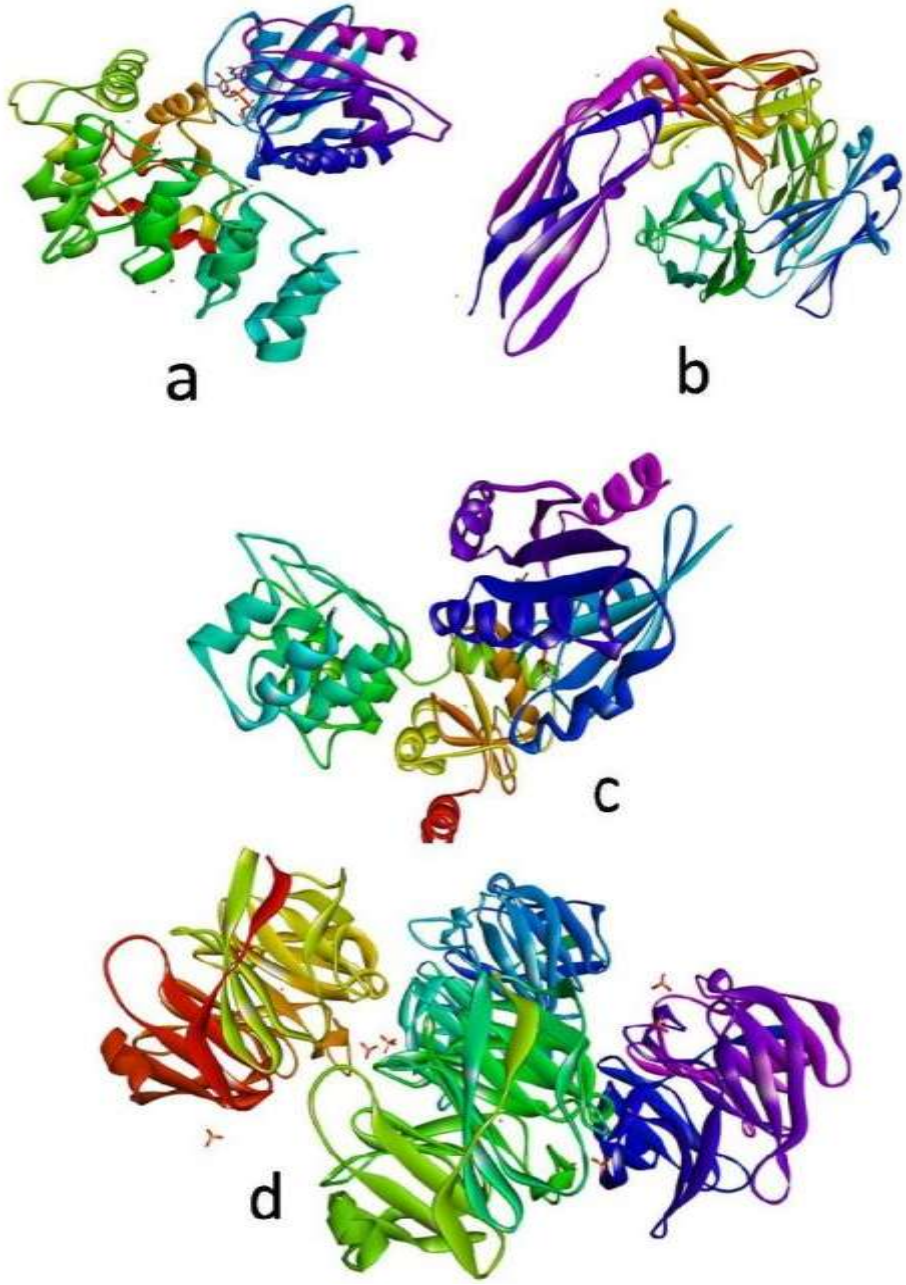
Figure 3. Three dimensional structure of Liver cancer receptors a.3S35, b. 3S37, c. 4xav, d.4X47.



1PRH, e. 1YY9

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Figure 4: Molecular interaction of Quinoline with cervical and liver cancer receptors a.4K3J, b.4COX, C.4J96, d.1PRH, e.1YY9, f.3S35, g.3LVQ, h.3S37 and i.4X4V.

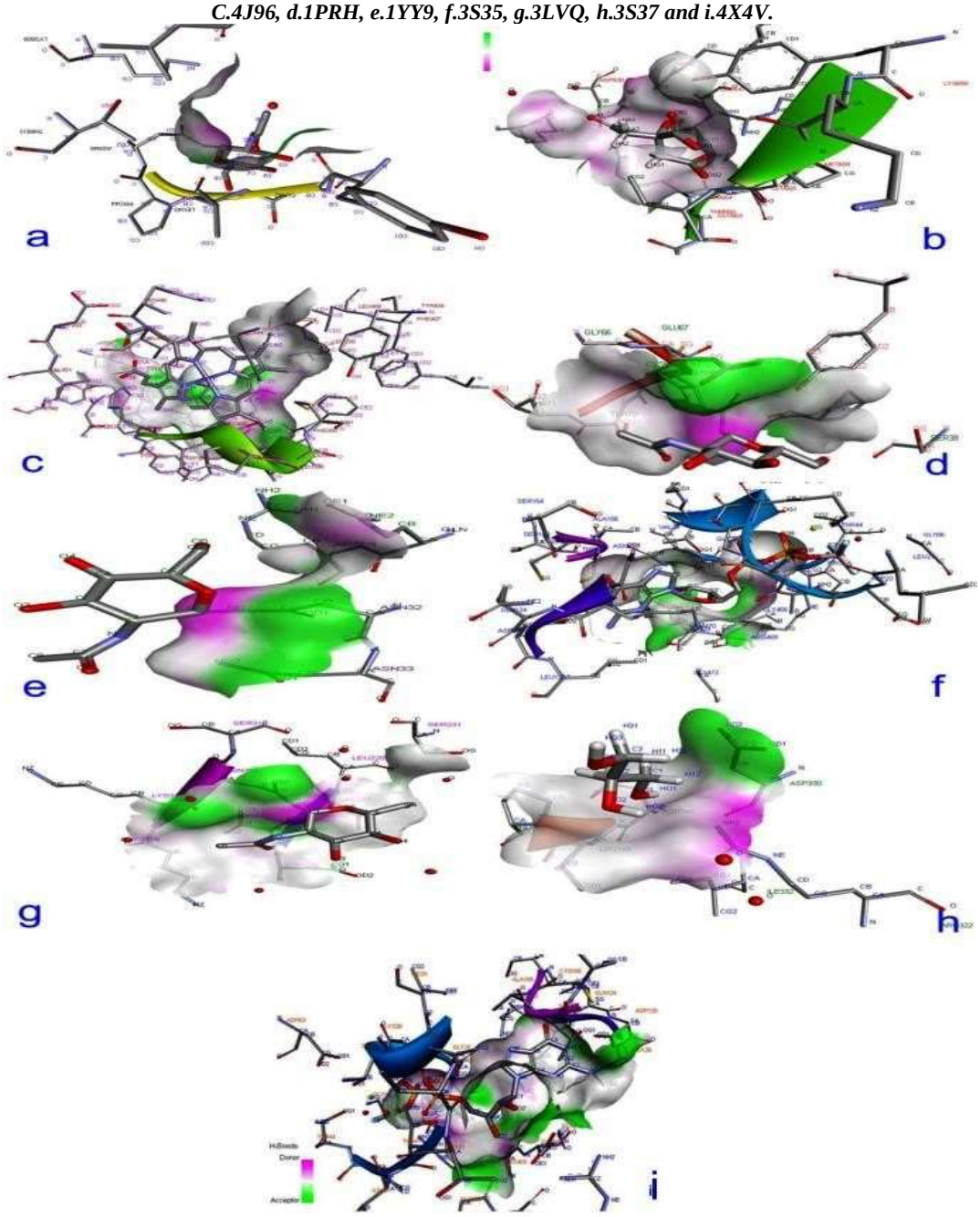

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Table 1. Docking parameters of Quinoline ligand with Cervical and liver cancer Receptors

Cancer Receptors	Free Binding Energy	Electrostatic Energy	Total Intermolecular Energy	Drug Score	Interact Surface	Frequency
Cervical						
4k3J	-5.20Kcal/mol	56.54uM	-8.32kcal/mol	0.5836	801.536	80%
4Cox	11.89Kcal/mol	1.32uM	2.32kcal/mol	12.15	104.284	30%
4j96	41.21Kcal/mol	7.24uM	14.31Kcal/mol	19.04	52.14	10%
1prh	32.21Kcal/mol	3.01uM	09.17Kcal/mol	16.04	36.24	13%
1yy9	-4.10Kcal/mol	60.32uM	-12.50Kcal/mol	0.2416	710.231	90%
Liver						
3s35	-2.10Kcal/mol	68.21uM	-5.65Kcal/mol	0.324	904.32	95%
3s37	21.54Kcal/mol	1.04uM	18.14Kcal/mol	14.04	62.14	25%
3lvq	34.41Kcal/mol	8.21uM	15.20Kcal/mol	12.04	46.24	15%
4x4v	-3.20Kcal/mol	54.12uM	-4.17Kcal/mol	0.416	752.12	93%