International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 11, Issue 3, 2019

Original Article

MOLECULAR DOCKING STUDY OF SIX PYRIMIDINE DERIVATIVES AS EGFR (EPIDERMAL GROWTH FACTOR RECEPTOR) AND CA IX (CARBONIC ANHYDRASE IX) INHIBITOR

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Received: 05 Dec 2018 Revised and Accepted: 26 Jan 2019

ABSTRACT

Objective: The present study was carried out to discover whether these pyrimidine derivatives have the potential to be used as epidermal growth factor receptor (EGFR) and carbonic anhydrase (CA) IX inhibitors through structure-based *in silico* study.

Methods: Docking was performed on 6 pyrimidine analogs; cetuximab and curcumin were taken as reference drug. The structure of the target protein retrieved from the RCSB Protein databank and the protein-ligand docking was performed using Pyrx AutoDock wizard with MGL tools 1.5.6 by using Lamarckian algorithm.

Results: All the compounds have shown lower binding energy and inhibition constant (Ki) value than reference drug cetuximab and curcumin. Out of the 6 inhibitors analyzed vkh has shown minimum binding energy against the target protein EGFR and CA IX respectively. Smaller Ki value shows stronger interaction. The scoring value of the interaction of vkh i. e-10.74 and-9.93 Kcal/mol and Ki 13.17ηM and 53.04ηM against the target protein EGFR and CA IX respectively while the reference drug cetuximab has shown binding energy-6.09 Kcal/mol with Ki value 34.44 µM and curcumin has shown binding energy-6.02 kcal/mol with Ki value 38.60 µM.

Conclusion: It can be concluded that the molecule vkh could have potential to be used as an EGFR inhibitor and CA IX inhibitor.

Keywords: Docking, Pyrimidine, Pyrx, Molecule

DOI: http://dx.doi.org/10.22159/ijpps.2019v11i3.31183

INTRODUCTION

Pyrimidines are the most vital heterocyclic aromatic organic compound containing two nitrogen atoms at positions 1 and 3 of the six-membered ring which shows the wide range of biological activities. These are the essential constituent of all cells and thus of all living matter. DNA and RNA is the main component of the chromosome carrying genetic information contain pyrimidine base in cytosine, uracil, and thymine. These occur in nature in two forms glycosylated pyrimidines and unglycosylated pyrimidines. Unglycosylated pyrimidines such as amino acids (ecotine), Vitamines (B_1), antibiotics (Becimethrin, Bleomycin) and quinazoline alkaloids while glycosylated as DNA and RNA [1]. Pyrimidine derivatives have been reported as anti-neoplastic, anti-malarial, diuretic, cardiovascular agents [2]. Condensed pyrimidine derivatives have been reported as antimicrobial [3, 4], analgesic, anti-convulsants, anti-inflammatory [5], antibacterial, antitubercular [6], antifungal [7], and anti-tumor [8] agents. Anti-breast cancer activity of some novel pyrimidine derivatives has been also reported [9]. Various activities displayed by these nitrogen-containing heterocyclic rings such as pyrimidine made it, promising structural moiety for future drug design.

Cancer is the most dreadful disease affecting the human population these days. It is characterized by abnormal growth of the cells. Different mechanisms account for the cytotoxic effect of pyrimidines, where they had been reported to act as glycogen synthase kinase (GSK) inhibitors [10], cyclin-dependent kinase (CDK) inhibitors [11], dual src/Ab1 kinase inhibitors, epidermal growth factor receptor (EGFR) inhibitors [12] and carbonic anhydrase (CA) [13]. In the present study, docking is performed against two macromolecules i.e. EGFR and CA IX. FDA approved EGFR as the successful target in colorectal cancer and various other types of cancers (as shown in table 1). The CA IX is reported to be associated with tumorigenesis being highly overexpressed in hypoxic tumors and restrictedly expressed in normal tissues. CA IX monoclonal antibody is already in Phase *III* clinical trials (as shown in table 1) and several small molecule inhibitors are in advanced preclinical evaluation with its overexpression in many cancer tissues and not in their normal counterparts [14]. This study includes the molecular docking study of the pyrimidine derivatives with EGFR and CA IX. All of the compounds were auto docked for the inhibition of the EGFR and CA IX. Cetuximab was taken as the reference drug in case of EGFR and curcumin for CA IX. This paper aims to elucidate the anti-cancer molecular mechanism of pyrimidines and provide the reference for its clinical application and further drug development.

Table 1: TTD ID of targeted receptor

TTD ID	Target name	Target type	Disease	Drugs
TTDS00355	Epidermal growth factor receptor	Successful target	Colorectal cancer, Cancers	Cetuximab
TTDR00211	Carbonic anhydrase IX	Clinical trial target	Cancer, Discovery agent	Curcumin

MATERIALS AND METHODS

Procurement of sample

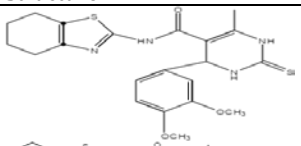
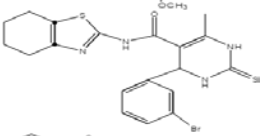
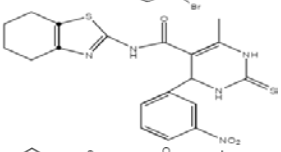
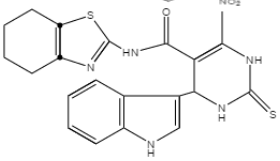
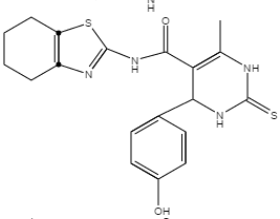
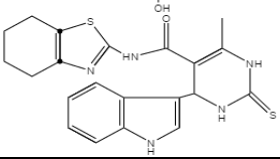
The samples were procured from Saurashtra University and code name was given to each of the molecule vkb, vkc, vkd, vkf, vkg, and vkh respectively. The "IUPAC" name of samples was obtained by using ChemDraw online while the molecular properties were generated by using ACD chemsketch (freeware) 2015 2.5(as shown in table 2 and 3).

Preparation of protein

Three-dimensional structure of the protein should be retrieved from the RCSB Protein data bank (PDB); afterward the retrieved structure

should be pre-processed for removal of heteroatoms then energy minimization was performed by using Argus lab and visualization was done by using UCSF Chimera 1.11.2. Ramachandran plot was generated by using Discovery studio 3.5.

Table 2: Chemical structure, code name and IUPAC name of compounds

Structure	Code	IUPAC Name
	vkb	"4-(3,4-dimethoxyphenyl)-6-methyl-N-(4,5,6,7-tetrahydro-3al5,7al5-benzo[d]thiazol-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide",
	vkc	"4-(3-bromophenyl)-6-methyl-N-(4,5,6,7-tetrahydro-3al5,7al5-benzo[d]thiazol-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide"
	vkd	"6-methyl-4-(3-nitrophenyl)-N-(4,5,6,7-tetrahydro-3al5,7al5-benzo[d]thiazol-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
	vkf	"4-(1H-indol-3-yl)-6-methyl-N-(4,5,6,7-tetrahydro-3al5,7al5-benzo[d]thiazol-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide",
	vkg	"4-(4-hydroxyphenyl)-6-methyl-N-(4,5,6,7-tetrahydro-3al5,7al5-benzo[d]thiazol-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
	vkh	"4-(anthracen-9-yl)-6-methyl-N-(4,5,6,7-tetrahydro-3al5,7al5-benzo[d]thiazol-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

Preparation of ligand

Ligands can be retrieved from several databases such as ZINC, PubChem or can be sketched by applying the Chemsketch tool. Ligand 2D structures were drawn using ACD chemsketch (freeware) 2015 2.5. Chem 3D viewer was used to convert the 2D structure into 3D. The drug molecules of cetuximab and curcumin were collected in 3D SDF format from the PubChem database. The compounds were added hydrogens and energy minimized with UFF force field using conjugate gradient algorithm by open babel in pyrx. All structures were saved as the pdb file format for input to pyrx 0.8. All the ligand structures were then saved in Pdbqt file format, for input into AutoDock version. Later, all lead molecules were converted into Auto Dock Pdbqt format.

While picking out the ligand, the LIPINSKY'S RULE OF 5 should be utilized. Lipinski rule of 5 assists in discerning amongst non-drug like and drug-like candidates. It promises the high chance of success or failure due to drug-likeness for molecules abiding by with 2 or more than of the complying rules. For the choice of a ligand allowing to the LIPINSKY'S RULE: (1) Less than five hydrogen bond donors (2) Less than ten hydrogen bond acceptors (3) Molecular mass of less than 500 Da (4) High lipophilicity (not over 5) and (5) Molar refractivity should be between 40-130. The rule is important in the drug discovery process to ensure the selectivity of the compound or determine if a chemical compound has physical or chemical properties that would make it likely orally active.

Docking

Ligand was docked against the protein and the interactions were analyzed by using by pyrx 0.8. For the docking of ligands into protein active site and to estimate the binding affinities of docked compounds, an advanced molecular docking program AutoDock Vina (4) was used in this study. All computational studies were carried out using pyrx AutoDock wizard with MGL tools 1.5.6 installed in a Pentium ®Dual–Core CPU T4200 machine running on a 2.0 GHz Intel core processor with 2GB RAM by using the lamarckian algorithm. The scoring function gives the score on the basis of best-docked ligand complex is picked out.

RESULTS

EGFR and CA IX is a clinically validated target for the treatment of various types of cancer and tumors has received considerable interest from the scientist in the design and development of newer anticancer drugs. The EGFR family plays an essential role in normal organ development by mediating morphogenesis and differentiation through effects on cell proliferation, differentiation, apoptosis, invasion, and angiogenesis [15, 16]. Whereas the CA from a family of enzymes that catalyze the interconversion between carbon dioxide and water and the dissociated ions of carbonic acid (i.e. bicarbonate and protons) and leads to regulation of tumor microenvironment. This interconversion is a reversible reaction and the enzyme catalyzes both reactions, forward and reverse. The active site of most carbonic anhydrases contains a zinc ion; they are therefore classified as metalloenzymes [17]. This study is primarily concerned with the *in silico* molecular docking of six pyrimidine derivatives with EFGR and CA IX proposing their role as an inhibitor in cancer studies. These compounds are tested *in silico* for drug-likeness and anticancer activity by docking with the protein via pyrx docking software.

Table 3: Molecular properties of the compounds

Molecular properties	vkb	vkc	vkd	vkf	vkg	vkh
Molecular formula	$C_{21}H_{24}N_4S_2O_2$	$C_{19}H_{19}Br_4OS_2$	$C_{19}H_{19}N_5O_3S_2$	$C_{21}H_{21}N_5OS_2$	$C_{19}H_{20}N_4S_2O_2$	$C_{27}H_{24}N_4OS_2$
Composition	C(56.73%) H(5.44%) N(12.6%) O(10.80%) S(14.44%)	C(49.24%), H(4.13%), N(12.1%), O(3.45%), S(13.84%) Br(17.24%)	C(53.13%) H(4.46%) N (16.3%) O(11.17%) S(14.93%)	C(59.55%) H(5.00%) N(16.5%) O(3.78%) S(15.14%)	C(56.98%) H(5.03%) N(13.9%) O(7.99%) S(16.01%)	C(66.91%) H(4.99%) N(11.5%) O(3.30%) S(13.23%)
Molar refractivity	119.95± 0.4 cm^3	114.94± 0.4 cm^3	113.26± 0.4 cm^3	118.70± 0.4 cm^3	108.75± 0.4 cm^3	142.34± 0.4 cm^3
Molar value	319.9±5.0c m^3	289.2±5.0c m^3	287.6±5.0c m^3	289.3±5.0 cm^3	273.3±5.0c m^3	342.1±5.0 cm^3
Parachor	927.9±6.0c m^3	861.7±6.0c m^3	867.7±6.0c m^3	876.9±6.0 cm^3	825.9±6.0c m^3	1020.5±6.0 cm^3
Index of refraction	1.673±0.03	1.725±0.03	1.717±0.03	1.757±0.03	1.726±0.03	1.771±0.03
Surface tension	70.7±5.0 $dyne/cm^3$	78.7±5.0 $dyne/cm^3$	82.8±5.0 $dyne/cm^3$	84.4±5.0 $dyne/cm^3$	83.3±5.0 $dyne/cm^3$	79.1±5.0 $dyne/cm^3$
Density	1.38±o.1 g/cm^3	1.60±o.1 g/cm^3	1.49±o.1 g/cm^3	1.48±o.1 g/cm^3	1.46±o.1 g/cm^3	1.41±o.1 g/cm^3
Polarisabi lity	47.55±0.5 $10^{24}cm^3$	45.56±0.5 10^2 cm^3	44.90±0.5 $10^{24}cm^3$	47.06±0.5 $10^{24}cm^3$	43.11±0.5 $10^{24}cm^3$	56.42±0.5 $10^{24}cm^3$
RDBE	12	12	13	14	12	18
Monoisotr opic mass	444.12898 1Da	462.01835 8Da	429.09292 9Da	423.11875 Da	400.10276 6Da	484.13915 1Da
Nominal mass	444Da	462Da	429Da	423Da	400Da	484Da
Avg. mass	444.5703Da	463.4144Da	429.5159Da	423.5543Da	400.5177Da	484.6357Da
m+	444.12843 2Da	462.01780 82Da	429.09238 1Da	423.11820 2Da	400.10221 7Da	484.13860 3Da
m-	444.12952 9Da	462.01890 5Da	429.09347 8Da	423.11929 9Da	400.10331 5Da	484.1397 Da
$(m+H)^+$	445.13625 7Da	463.25633 Da	430.10020 6Da	424.12602 7Da	401.11004 2Da	485.14642 8Da
$(m+H)^-$	445.13735 4Da	463.2673 Da	430.10130 3Da	424.12712 4Da	401.11114 Da	485.14752 5Da
$(m-H)^+$	443.12060 7Da	461.00998 3Da	428.08456 6Da	422.11037 7Da	399.09439 2Da	483.13077 8Da
$(m-H)^-$	443.12170 4Da	461.01108 Da	428.08566 3Da	422.11147 4Da	399.09548 9Da	483.13187 5Da

Table 4: Results of the lipinski rule calculator

Compound	Mass (Da)	H bond donor	H bond acceptors	LOG P	Molar refractivity
Vkb	444	1	6	4.7463	124.68478
Vkc	420	1	4	5.548411	117.3252
Vkd	421	1	6	4.56482	114.10259
Vkf	420	3	4	0.854811	115.55609
Vkg	394	2	5	2.0183	110.24445
Vkh	482	2	4	4.73961	138.71896

Table 5: Output of molecular docking score of ligand-EGFR with respect to minimum binding energy and inhibition constant

S. No.	Name	Run	Minimum binding energy (Kcal/mol)	Inhibition constant
1	vkb	6	-6.63	13.71 µM
2	vkc	9	-8.03	1.29µM
3	vkd	5	-7.77	2.03 µM
4	vkf	8	-8.7	419.55 ηM
5	vkg	5	-7.7	2.26 uM
6	vkh	5	-10.75	13.17ηM
7	Cetuximab	4	-6.09	34.44 µm

The Protein-Ligand interaction plays a significant role in structural based designing. All the compounds have shown≥5 hydrogen bond donors≯10hydrogen bond acceptors, molecular mass ≥500 Da, highly lipophilic in nature and molar refractivity between 40-130 (except for vkh has shown molar refractivity of 138.71) as shown in table 4. The rule describes molecular properties imperative for drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion.

Docking studies of pyrimidine derivatives with both the receptors revealed that all the compounds have lower binding energy and inhibition constant (Ki) value than reference drugs. 3-D structure of EGFR, Ramachandran plot of EGFR and various docked conformations

and active site interactions with EGFR have been shown in fig. 1 and 3-D structure of CA IX, Ramachandran plot of CA IX and various docked conformations and active site interactions with CA IX have been shown in fig. 2. Further details of important interactions in terms of energies between ligands and the proteins with EGFR and CA IX receptor with predicted Ki values are shown in the table is given in table 5 and 6.

Table 6: Output of molecular docking score of ligand-CA IX with respect to minimum binding energy and inhibition constant

S. no	Name	Run	Minimum binding energy (Kcal/mol)	Inhibition constant
1	vkb	7	-7.83	1.82 µM
2	vkc	9	-9.47	114.57 ηM
3	vkd	9	-7.17	5.55 µM
4	vkf	5	-8.4	690.47ηM
5	vkg	5	-9.39	131.71 ηM
6	vkh	9	-9.93	53.04 ηM
7	Curcumin	4	-6.02	38.60 µM

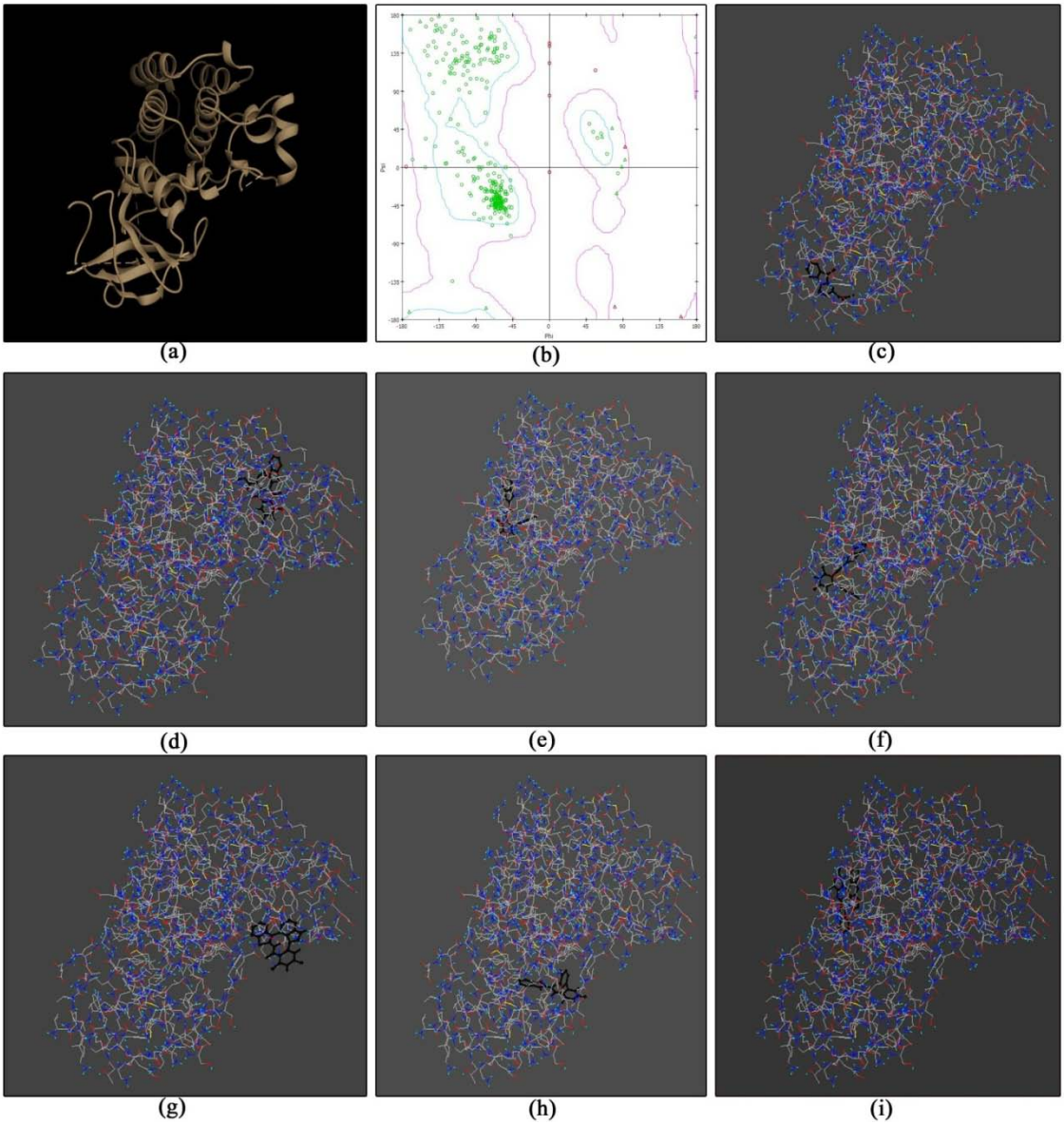


Fig. 1: (a) 3D structure of EGFR; (b) Ramachandran plot of EGFR; (c) Docking of EGFR Protein receptor with Cetuximab; (d) Docking of EGFR Protein receptor with vkb; (e) Docking of EGFR Protein receptor with vkc; (f) Docking of EGFR Protein receptor with vkd; (g) Docking of EGFR Protein receptor with vkf; (h) Docking of EGFR Protein receptor with vkg; (i) Docking of EGFR Protein receptor with vkh

DISCUSSION

The EGF is the prototype of a large family of peptide ligands that bind to cell membrane receptors and activate a myriad of intracellular signaling pathways to control tumor cell growth, proliferation, survival, metastasis, and angiogenesis [18]. Whereas CA IX enzymes catalyze a very simple physiological reaction, the interconversion between carbon dioxide and the bicarbonate ion, and are thus involved in crucial physiological processes connected with respiration and transport of CO_2/bicarbonate, pH and CO_2 homeostasis, electrolyte secretion in a variety of tissue/organs, biosynthetic reactions, bone resorption, calcification, tumorigenicity and many other physiologic or pathologic processes [19]. In this work, totally 6 compounds which are pyrimidine derivatives were examined for ligand-based docking. The ligands are screened for their ability to dock within the active site of the inhibitor protein. All the compounds have shown ≥5 hydrogen bond donors, ≥10hydrogen bond acceptors, molecular mass ≥500 Da, log P value ≥5 and molar refractivity between 40-130 (except for vkh has shown molar refractivity of 138.71) which means compounds have good oral bioavailability. The Ramachandran plot generated displays the dihedral angles φ and ψ for each residue in the protein that is displayed in the workspace. The plot area displays a plot of protein dihedrals for all residues in the protein. The area "green region" corresponds to "core" region representing the most favorable combinations. Ideally, 90% of the residues should be in this “core” region. After analyzing the different docking interactions of ligands, out of the 6 inhibitors analyzed vkh has shown the binding energy of-10.74 and-9.93 Kcal/mol and Ki 13.17ηM and 53.04ηM against the target protein EGFR and CA IX respectively. The best drug was selected, depending upon the binding energy and Ki. Smaller Ki value shows the stronger interaction [20, 21]. Out of the 6 derivatives compound, vkh shows the highest affinity towards the protein compared with the standard drug cetuximab and curcumin. Thus compound vkh may act as a better and efficient anticancer drug.

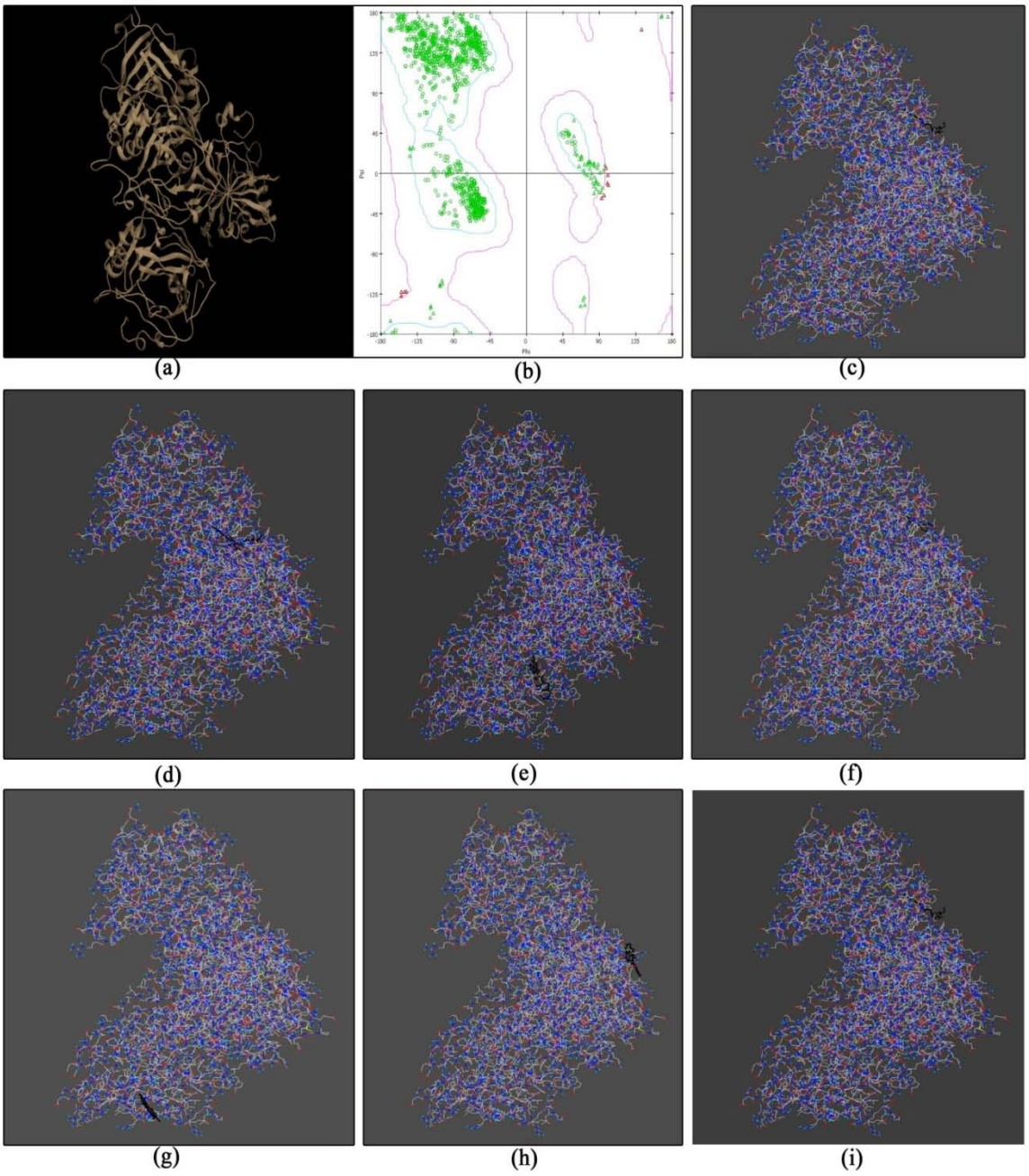


Fig. 2: (a) 3D structure of CA IX; (b) Ramachandran plot of CA IX; (c) Docking of CA IX Protein receptor with Cetuximab; (d) Docking of CA IX Protein receptor with vkb; (e) Docking of CA IX Protein receptor with vkc; (f) Docking of CA IX Protein receptor with vkd; (g) Docking of CA IX Protein receptor with vkf; (h) Docking of CA IX Protein receptor with vkg; (i) Docking of CA IX Protein receptor with vkh

CONCLUSION

EGFR kinase domain and CA IX have been emphasized in the majority of cancers including colorectal cancer, breast, lung, ovarian, anal cancers, and tumors etc. Owing to their dominant role in cancer, molecular docking of EGFR and CA IX against the pyrimidine molecule was carried out. Based upon the results obtained from the docking study in the present study all the compounds may be suggested as the potential therapeutic drug for the treatment of cancer. However, vkh has a strong interaction and binding with target protein as evident by docking score. Further *in vitro* and *in vivo* experimental work is required for validation of our *in silico* results and to generate more effective and potential drug through ligand-based drug designing approaches.

ACKNOWLEDGMENT

Last but not the least, the author expresses sincere thanks to the Institute of Post Graduate Teaching and Research in Ayurveda, Gujarat Ayurved University and Saurashtra University for their encouragement, co-operation, support, suggestions, and affection throughout my studies.

AUTHORS CONTRIBUTIONS

This work is carried out by Shikha Sharma under the valuable guidance of Dr. V. J. Shukla sir. He guided me and helped me throughout the study.

CONFLICT OF INTERESTS

All the authors declared that there is no conflict of interest

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