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Special Issue: Computational drug designing and molecular docking analyses

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Molecular docking and virtual screening to discover novel CYP4B1 inhibitor

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Abstract

Studies on Cytochrome p450 family B polypeptide 1(CYP4B1) so far unveiled a multiplex sketch of neurological proclaimed to be energetically related to cancer. The expression and localization of CYP4B1 in human are majority of neoplastic tissues, bladder and lungs specific tissue. The production of unassociated disease in human and rats were caused due to excretion of CYP4B1. The CYP4B1 isoforms personify an essential aspect in mutagenic stimulation in the bladder. CYP4B1 has interacting functional partner CYP20A1. The structure of CYP4B1 was not yet reported therefore, it was predicted through different structure prediction approaches. CYP4B1 analyzed and determined the protein-protein interaction analyses within the CYP20A1 and discovered possible interacting residues. The prediction of the prevailing binding mode of a protein with the ligand of selected 3D structure was assumed by docking. The molecular docking observed and revealed efficient results. The virtual screening was performed by utilizing FDA library of ZINC database against CYP4B1. The novel compound exhibits on the bases of affective binding affinity.

Introduction

Cytochrome p450 family 4 subfamily B member 1 (CYP4B1) causes the most common cancer in urinary tract and bladder cancer. The symptoms of the bladder cancer includes lower back pain, frequent urination and abdominal pain [1]. The patients with enlarged bladder had over expression of *CYP4B1* in bladder [2]. CYP4B1 is associated with the mutagenic stimulation of pro-carcinogens in the bladder cancer affects 68,000 adults in North America once a year [3, 4]. The tobacco inhaling also damages the bladder and causes bladder cancer in humans [5, 6]. The bladder cancer can be cured with medicinal and surgical treatments depend at the cancer stage. The treatment helps the immune system to fight against cancer in immunotherapy [7] however chemotherapy may deliver to the bladder for localized treatment. About 10-15% of bladder cancer have mutations targeted through drug [8] The bladder cancer causes due to the standard fatality and virulence of the urinary tract. The patients having advance treatment for the bladder cancer without muscle-incursive bladder cancer needs intravesical cytotoxic and other drug treatments though prevention of the disease [9]. The biochemical pathways have series of enzyme reactions for biochemical reactions, regulation of gene expression, assimilation and transmission of signals. Various online databases are available to elucidate the pathways of a specific protein within their species. This encodes a member of the conjugated protein p450 taxonomic category of the enzymes. p450, a monooxygenase that activates reactions utilized in drug assimilation and developing compounds of steroids, and different lipids [10]. The subcellular localization of CYP4B1 macromolecule in humans is at endoplasmic reticulum and many other compartments [11]. The substrates and predominant tissues of p4504B1 (*CYP4B1*) enzymes are adjacent to human respiratory organs, bladder, fat tissue. The *CYP4B1* assimilates the allocation of xenobiotics, all-inclusive 2-amino fluorine, 2-naphthylamine, 4-ipomeanol and benzidine [12]. Thus, *CYP4B1* entanglement within neoplasm has been based on its impression quality and assimilation of chemically active-carcinogens within the urinary bladder and respiratory organs [13]. The *CYP4B1* plays a vital role in the detoxification and activation of biological tissues [14]. The regulation of *CYP4B1* isoforms showed transitional cell carcinomas of the surpassing tract and vesical, symbolizing a supportive act of *CYP4B1* in patients with development of cancer in epithelial cells [1]. The covalent binding of heme to *CYP4B1* through Glu310 and also the accumulation of other members of the cyp4 family of enzymes, are covalently attached to their prosthetic heme group through an ester linkage [15]. Cytochrome p4504b1 plays a crucial role in bio-transformation of xenobiotics (xenobiotics can be kept as carcinogens, drugs, and hydrocarbons). *CYP4B1* relatively extrahepatic exposition has been narrated to bind with clear-cut tissues containing toxicity. Yet, the expression of *CYP4B1* in diverse cancers and therefore, their latent performance in tumor reduction were comprehensive and broad [16]. The entanglement of *CYP4B1* in cancer is considerable by the catalytic activation of pro-carcinogens and neovascularization. The biological group of *CYP4B1* is orderly assorted into subfamilies to hold up their organic compound homologies. The native peptide bonds on *CYP4B1* isoforms and participates in proto-heme (pigment) reliability to utilize chemical changes [17] and data will be essential to assume distribution fluctuation within the enterprise of *CYP4B1* summarize modification of variants. From the last decade, bioinformatics helped to solve numerous biological problems to understand cancer [18, 19] and neurological disorders [20-25] with significant contribution [26-28] in the field of medicine. Numerous biological problems have been solved by applying different approaches of bioinformatics collaborating with structural bioinformatics contribution [29]. The purpose of current effort was to predict, evaluate and validate of the 3D structure of CYP4B1 by virtual screening and protein-protein interactional studies.

Materials and Methods

The *CYP4B1* translates into 9 different forms encoded two different isoforms having accession number P13584-1 and P13584-2 in Uniport Knowledge Base [30]. The ENSEMBLE [31] (https://asia.ensembl.org) was utilized for sequence analyses of *CYP4B1* [32]. The

evolutionary relationship between the sequences was performed through Multiple Sequence Alignment (MSA). The ultimate goal of biological sequence alignment was to determine the similarity between the family of CYP4B1 and their isoforms, the function predictions and the phylogeny analyses.

T-Coffee [33] was used for MSA [34]. The MEME Suite [35] was utilized to cross validate the MSA [36]. ScanProsite [37] (https://prosite.expasy.org) was employed for the domain prediction of CYP4B1 macromolecule [38]. The amino acid sequences of isoforms of CYP4B1 retrieved from Uniport KB [30] (https://www.uniprot.org). BLASTP [39] was used for the identification of applicable and acceptable templates against Protein Data Bank (PDB) [40]. MODELLER 9.20 was engaged for the prediction of 3D structures of CYP4B1 by satisfying spatial restraints and comparative protein structure modeling predicts the 3D structure of selected protein. The protein structure prediction was also performed by threading approach tools including SWISS-MODEL [41], I-TASSER [42], HHpred [43], Robetta [44], phyre2 [45], PSIPRED [46] and SPARKS-X [47]. Homology modeling performed by query coverage and identity percentage and best one structure biased on their MolPDF values was selected. The selected 3D structure of CYP4B1 was visualized by UCSF Chimera 1.13 [48] and energy minimization of the predicted structure of protein was performed by Chem3D Ultra [49] and UCSF Chimera 1.13.1. The structures were evaluated by evaluation tools including MolProbity [50], favored region, allowed region, outlier region were also calculated by RAMPAGE [51]. WhatCHECK [52], Anolea [53], ERRAT [54] and Verify 3D [55] tools were used for an overall evaluation of protein structure identification, determination and validation of structure models quality.

The amino acid position of heme was observed through extensive literature review and it was observed that CYPs bind with heme for efficient working. The Glu-310 was observed and selected for the heme binding for CYP4B1. The blind and targeted dockings were performed by AutoDock Vina for the binding of heme against Glu-310. The molecular docking studies were carried out by using PyRx [56], and AutoDock Vina [57, 58]. The library was screened by employing the docking tools and their result were further evaluated by AutoDock tools and UCSF Chimera 1.13.1.

STITCH (Search Tool for Interacting Chemicals) [59] and STRING (Search Tool for the Retrieval of Interacting Genes and Proteins) [60] employed to predict the useful and functional interacting partner of *CYP4B1*. PatchDock [61, 62], FireDock [63] and GrammX [63, 64] were employed to analyze, verify for the validation of generated protein-protein interactional studies. Hydrophobicity and electrostatic interactions were plotted by using LigPlot. The fundamental objective of those methods is to predict the nature and strength of binding of selected molecule [65].

Results and Discussion

CYP4B1 have involvement in several tumors and cancer can be hit by targeting CYP4B1. It was observed from extensive literature review that the regulation of CYP4B1, the association of CYP4B1 with cancers, contradicting findings about human CYP4B1 activities as well as employing CYP4B1 in suicide gene approach for cancer treatment. The sphere of structural bioinformatics and neurobiology square measure the scientific discipline and therefore, the potential in cancer treatments is crystal clear. To date, there is no wide spectrum of tissue distribution of CYP4B1 with lungs because the prevailing sites. The involvement of CYP4B1 in cancer was considered through activation of pro-carcinogens and neovascularization. However, human CYP4B1 was found to be inactive due to a substitution of proline with serine [66]. The biological databases revealed countless impressive sequence information of CYP4B1. The macromolecule sequence data sets for many ranges of vertebrate and invertebrates' genomes are available for analyzing the macromolecule sequence.

The scrutinized templates were utilized to generate 3D structures of CYP4B1 and isoforms. The overall query coverage and similarity of the selected templates were observed and CYP4B1 isoforms showed >69% of similarity considered for reliable structures prediction by homology modeling approach (**Table 1**). Threading and *ab initio* approaches were also utilized for structure prediction of CYP4B1 to cross validate the

Table 1: Templates for CYP4B1 sorted by their query coverage, identity and E-values.

Accession numbers	Total score	Query coverage (%)	E-value	Identity (%)
5T6Q	870	91	0.0	86.6
6C93	868	91	0.0	83.3
5VEU	148	80	1e-38	25
4KF0	128	78	1e-31	25
3PSX	127	70	2e31	26

predicted structures. The 3D structures of CYP4B1 was not reported PDB through X-ray crystallography and NMR. The comparative modeling, threading and *ab initio* techniques were utilized for 3D structure prediction of CYP4B1. The sequences of CYP4B1 was subjected to BLASTp against PDB for suitable templates search. It was observed that the top-ranked aligned templates were belong from CYP family. The selected templates were used to predict the 3D structures of CYP4B1. Comparative modeling, *ab initio* and threading approaches were utilized by satisfying the spatial constraints to predict numerous models for CYP4B1 through MODELLER 9.20, Phrex2, SWISS MODEL, RaptorX, M4t and I-TASSER. All the predicted models were evaluated on favored region, allowed region, outliers region, quality factor and binding regions. The generated comparative graphs (**Fig. 1**) of all the predicted structures were evaluated and best structure among all was selected for further experiments.

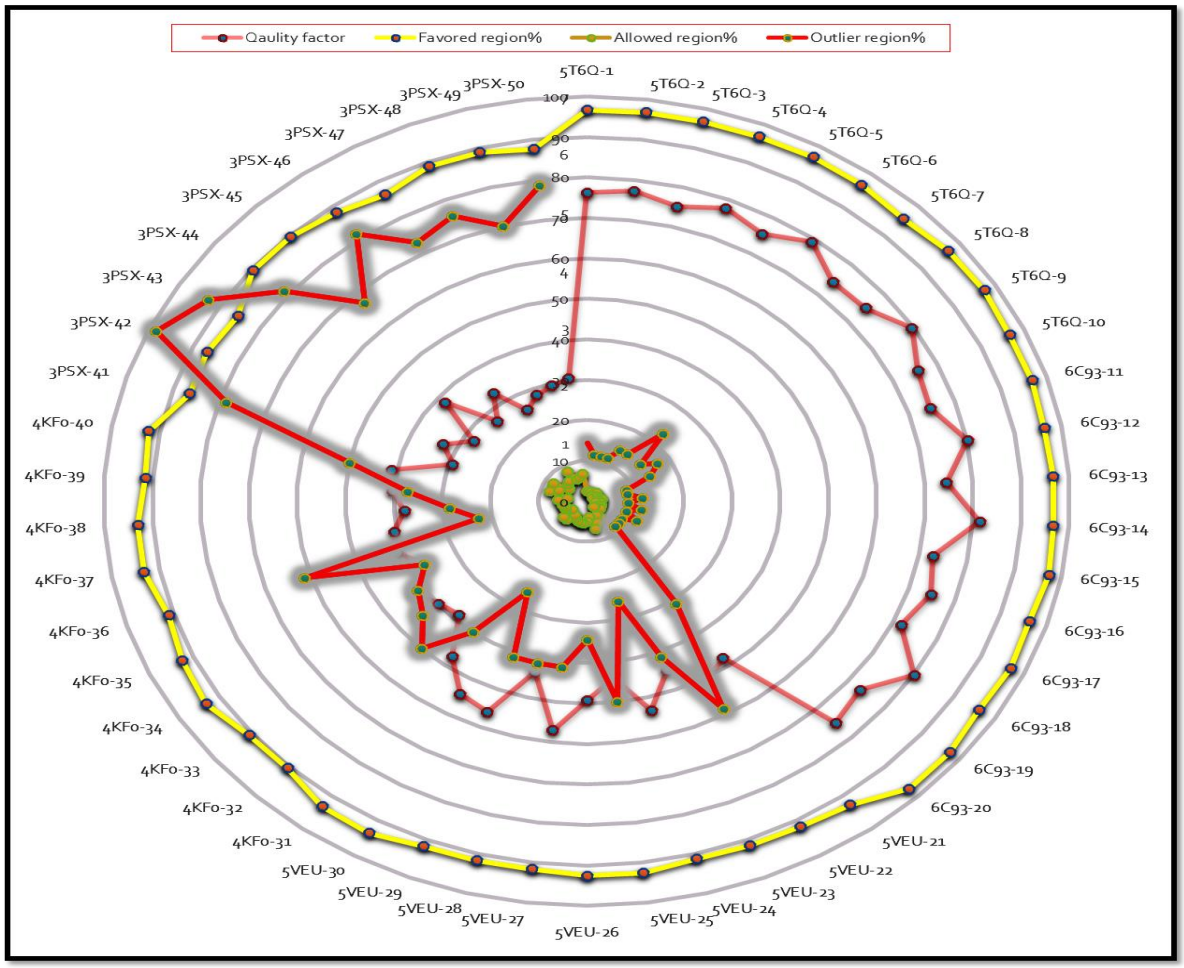

Fig. 1: A comparative structure evaluation graph having favored, allowed and outlier regions along with the overall quality factor values.

The viriation was observed in the the overall quality factor of all the predicted structure and the structure having over all quality factor of 76.161% for CYP4B1 was selected. The predicted structure (**Fig. 2**) have the potential to be utilized for further analyses. The energy minimization was performed for the predicted structure of CYP4B1 through a UCSF Chimera1.13.1 and Chem3D ultra was employed to minimize the ligands.

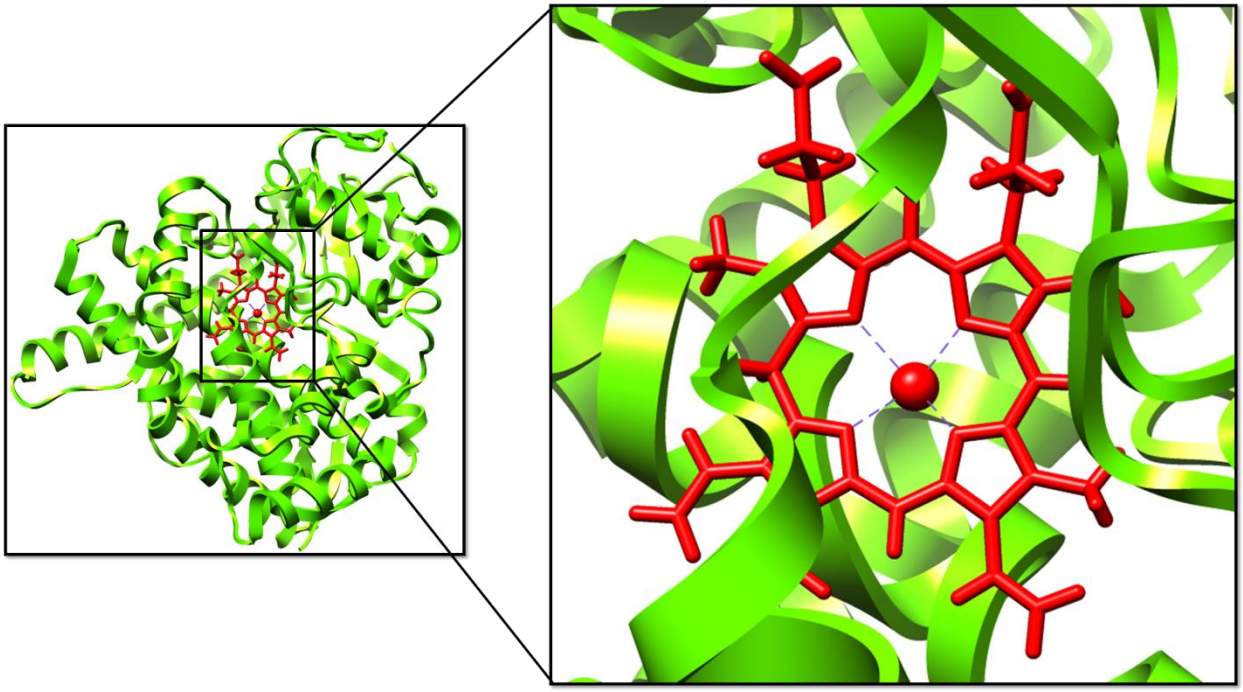

Fig. 2: The binding residue Glu-310 identified through literature and green color represents CYP4B1, whereas red color represents the heme and Fe.

The CYP4B1 structure was predicted and observed the heme binding site from literature. Interestingly, it was observed that Fe and heme showed binding at similar position in all the CYP family. The Fe and heme molecule was docked against CYP4B1 at Glu-310 by utilizing AutoDock Vina. The virtual screening of the selected FDA library of ZINC showed significance binding analyses of heme with CYP family. The molecular docking studies of selected library showed variations in binding energies, and the complex having least binding energy was selected. It was observed that FDA library of ZINC database showed effective binding against CYP4B1 and heme. The top ranked docked complex of CYP4B1 was critically analyzed. The molecular docking analyses revealed that the top ranked ligand showed least binding energy values and highest binding affinity with heme against CYP4B1. The binding residues TYR 218, ALA 98, PRO 368, ASN 214, VAL 101, HIS 106, PRO 213, LEU 360, LEU 367, PHE 113, VAL 212, GLY 478, PHE 477, VAL 210, VAL 479 and PHE 238 of CYP4B1 showed highest binding affinity against heme and CYP4B1 (**Fig. 3**).

CYP20A1, the interacting partner of CYP4B1 was utilized for protein-protein docking analyses. The docked complex of protein-protein docking analyses predicted the interacting residues (**Fig. 4, 5**). The docking analyses were analyzed on the basis of approximate interface area of complex and Atomic Contact Energy (ACE) by utilizing PatchDock. The docked complexes were analyzed having least ACE values and further refined by employing FireDock. The least binding values suggested that CYP4B1 and CYP20A1 have effective binding affinity (**Table 2**).

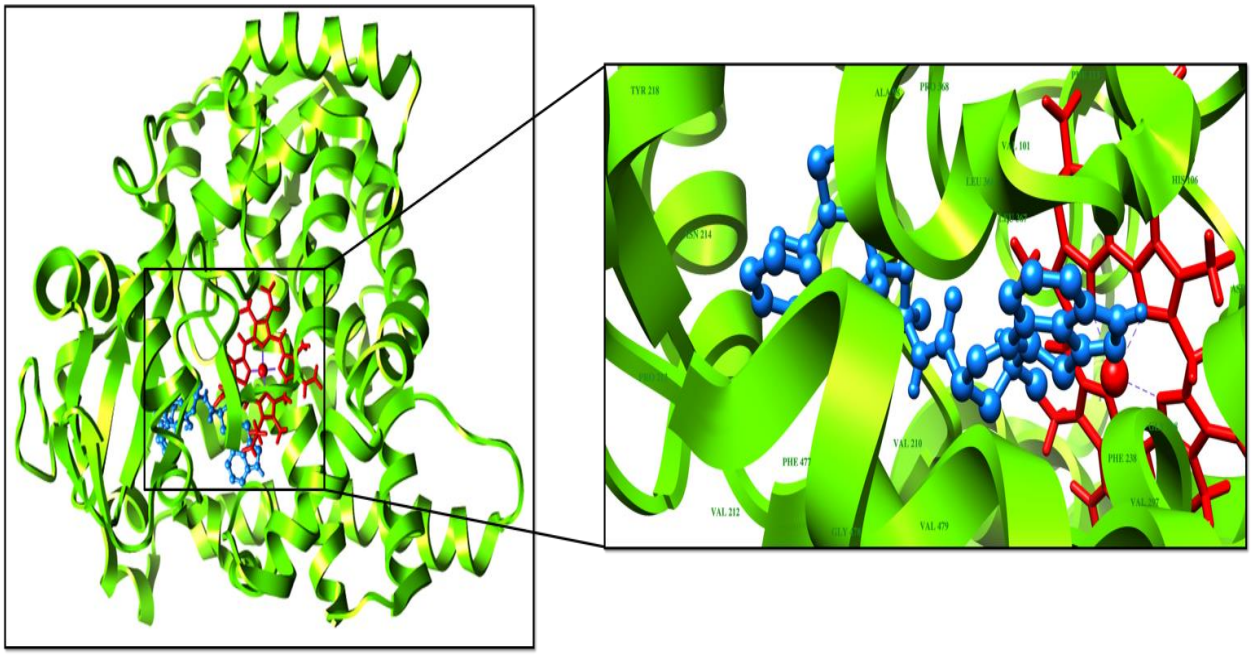

Fig. 3: 3D representation of interactional studies of CYP4B1. The green color represents the receptor protein, red represents the heme and blue color represents the ligand

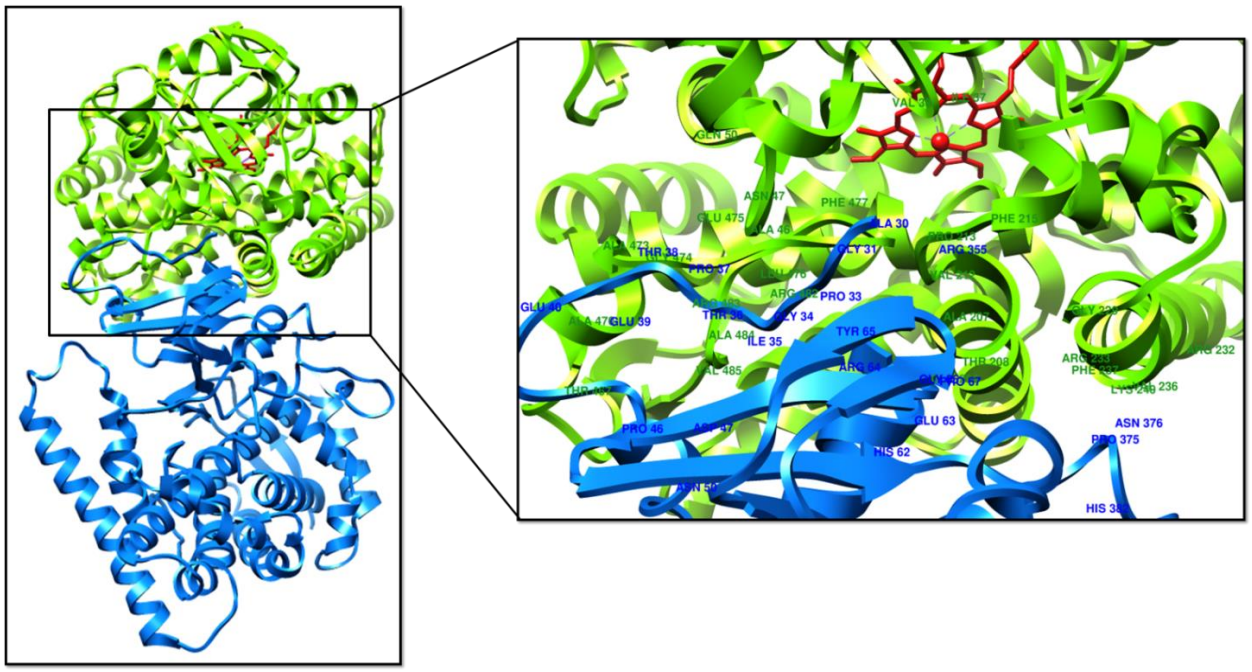

Fig. 4: Protein-protein interactional studies of CYP4B1 and CYP20A1.

of CYP4B1 containing the Heme oxygenase. The docking studies have been conducted with the purpose of ligand based, to predict the binding mode of a ligand with selected 3D protein structure.

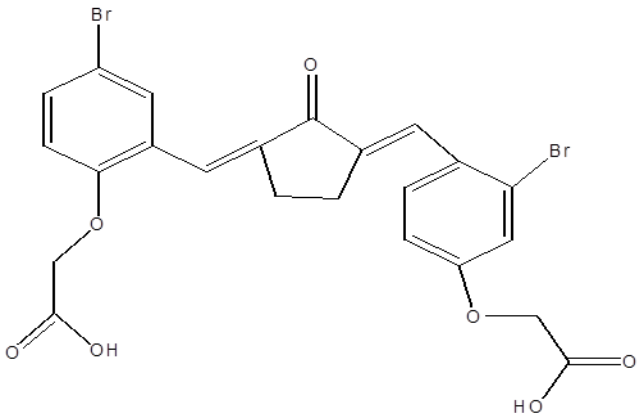

Fig. 5: 2D structure of ligand.

Table 2: Protein-protein interaction

Targeting Protein	Targeting Protein Residues	Interacting Protein	Interacting Protein Residues
CYP4B1	VAL 3, ILE 37, GLN 50, PHE 477, ASN 47, ALA-46, PHE 215, PRO 213, ALA 473, GLY 474, ARG 232, LYS 240, VAL 236, PHE 237, ARG 233, GLY 229, PRO 213, ARG 232, PHE 215, PRO 213, VAL 212, ALA 207, THR 208, PHE 477, ARG 483, LEU 470, ALA 46, ASN 47, GLU 475, GLY 474, ALA 473, ALA 470, THR 467, VAL 38, VAL 219, ARG 482, VAL 485, ALA 484	CYP20A1	THR 38, PRO 37, GLU 40, GLU 39, THR 36, ALA 30, GLY 31, PRO 33, ARG 355, GLY 34, ILE 35, TYR 65, ARG 64, GLY 67, ASN 376, PRO 375, GLU 63, HIS 62, HIS 382, ASN 50, ASP 47, PRO 46, PRO 40,

Conclusion

In conclusion, the *in-silico* analyses of CYP4B1 have higher probability and efficacy on the basis of binding energy and other used parameters. The uniform results clearly described the 3D structure.

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Conflict of interest

The authors declare no conflict of interest.

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