STM JOURNALS

International Journal of
Antibiotics

Volume 1, Issue 1, 2024
January–June
DOI (Journal): 10.37591/IJAB

https://journals.stmjournals.com/ijab

Research IJAB

Grid Based Docking Study of Some 2-(4-methylsulfonyl phenyl) Pyrimidine Derivatives (Designed After QSAR Studies) with Cyclooxygenase-2

Satish Sarankar[1], A. K. Pathak[2]

Abstract

Molecular docking helps in studying drug/ligand or receptor/ protein interactions by identifying the suitable active sites in protein, obtaining the best geometry of ligand-receptor complex and calculating the energy of interaction for different ligands to design more effective ligands. In Grid based docking, after unique conformers of the ligand are generated, the receptor cavity of interest is chosen and a grid is generated around the cavity. Cavity points are found and the centre of mass of the ligand is moved to each cavity point. All rotations of ligand are scanned at each cavity point where ligand is placed. Efficiency and precision of docking rely upon scoring function. Scoring functions are based on force fields that are used to simulate the functions of proteins. With known 3D structure of receptor molecule or protein, the binding affinity of the protein ligand complex was calculated and it is termed as Dock Score. In our research work, to know the biding affinity of some 2-(4-methylsulfonylphenyl) pyrimidine derivatives (designed after QSAR studies) with Cyclooxygenase-2, the compounds were docked with three different receptors namely Cyclooxygenase-2 (Prostaglandin synthase-2), Uninhibited Mouse Cyclooxygenase-2 (Prostaglandin Synthase-2) and Membrane Protein Prostaglandin H_2 Synthase-1) using VLifeMDS software. Among all compounds, three compounds having 2,2-dibromoethanamine, 2,2-diiodoethanamine and 2,2,2-triiodoethanamine substituted pyrimidine derivatives showed best docking score with all three COX-2 receptors. With Prostaglandin synthase-2 after successful completion of docking process, the minimum score obtained was -6.199069, -6.180829 and -6.049794 for three compounds respectively. The compounds were docked with a different receptor Uninhibited Mouse Cyclooxygenase-2 and the same three compounds showed minimum score of -6.293567, -6.202445, -6.100384 respectively. The docking score was found -6.345966, -6.245738, -6.150805 with Membrane Protein Prostaglandin H_2 Synthase-1 with the same substituted pyrimidine derivatives. The present research work opened a new path to fulfill the increasing demand of COX-2 inhibitors which can be used in the treatment and cure of various ailments those are mediated through COX-2 pathway.

Keywords: Docking, Pyrimidine derivatives, Cyclooxygenase-2, Docking score, VLifeMDS software

***Author for Correspondence**
Satish Sarankar
E-mail: satish.sarankar@gmail.com

[1]Research Fellow, Department of Pharmacy, Barkatullah University, Bhopal, Madhya Pradesh, India
[2]Head of the Department and Professor, Department of Pharmacy, Barkutullah University Bhopal, Madhya Pradesh, India

Received Date: January 19, 2024
Accepted Date: January 23, 2024
Published Date: January 31, 2024

Citation: Satish Sarankar, A. K. Pathak. Grid Based Docking Study of Some 2-(4-methylsulfonyl phenyl) Pyrimidine Derivatives (Designed After QSAR Studies) with Cyclooxygenase-2, International Journal of Antibiotics. 2024; 1(1): 23–41p.

INTRODUCTION

An important goal in computer-aided design is to find a correlation between the structural features of ligands and their biological activity, that is, their ability to bind to specific target proteins. In some cases, simple mathematical models may provide a means for identifying the property related to biological activity; in other cases a multitude of parameters are necessary to describe the complex behavior of a compound in a biological system [1-3]. In general, the necessary parameters can be derived by forming a relationship between those properties that describe the structural variation

within the group of molecules under investigation and those that describe their biological activities. This relationship is termed a quantitative structure–activity relationship (QSAR). Historically, the primary objective of QSAR was to understand which properties are important to control a specific biological activity of a series of compounds. However, the main objective of these techniques nowadays is the prediction of novel compounds on the basis of previously synthesized molecules [4-7].

Drug exerts its biological activity by binding to the pocket of receptor molecule (usually protein). The computational process of searching for a ligand that is able to fit both geometrically and energetically into the binding site of a protein is called molecular docking. A Grid based algorithm exhaustively explores binding mode of ligand over a grid on the protein cavity. The Grid based method is a type of rigid docking where both the ligand and receptor are treated as rigid. In this method, after unique conformers of the ligand are generated, the receptor cavity of interest is chosen by the user and a grid is generated around the cavity (default grid interval size 1 Å). Cavity points are found and the centre of mass of the ligand is moved to each cavity point. All rotations of ligand are scanned at each cavity point where ligand is placed (step size of rotation could be typically 100 -150). For each rotation a pose of the ligand is generated and the corresponding bumps are checked for each pose of ligand. The X-C score is calculated for each valid pose (determined by the cut off criteria fed by user in terms of max no of allowed bumps) and the pose of the ligand with the best score is given as output to user. Though this method is for one ligand for a given receptor, it can also be applied to a set of ligands/their conformers in a batch grid docking mode [8-13].

The discovery and characterization of the cyclooxygenase-2 (COX-2) enzyme early in the 1990s led to the hypothesis that selective inhibitors of this isoform would exhibit similar clinical efficacy but reduced ulcerogenicity than traditional nonsteroidal antiinflammatory drugs (NSAIDs), which were dual nonselective cyclooxygenase-1 (COX-1) and COX-2 inhibitors. Rofecoxib and Celecoxib were the first COX-2 selective inhibitors to reach the market followed by Valdecoxib and Etoricoxib. The worldwide withdrawal of Rofecoxib (Vioxx) because of evidence of increased cardiovascular risk has raised concern about the safety of COX-2 selective inhibitors. Research efforts to clarify if the observed cardiovascular events are due to the mechanism of action of the entire class of compounds or to the particular structure of Rofecoxib point out to the first reason as the most probable cause of aforementioned undesired adverse effects [14-16]. Nevertheless, the potential therapeutic applications of selective COX-2 inhibitors have been expanded beyond the areas of analgesia and inflammation, as shown by recent studies on COX-2 that have been focused on cancer and neurodegenerative disorders along with various other disease.

Tricyclic molecules possessing as a common feature 1,2-diaryl substitution on a central heterocyclic or carbocyclic ring system represent a major class of selective COX-2 inhibitors and extensive work has been carried out in this area. On the other hand, pyrimidine ring has scarcely been used as template for the synthesis of new selective COX-2 inhibitors. Nevertheless, a group of pyrimidine derivatives have been described recently as a new class of potent and selective COX-2 inhibitors [17-20].

By 2D QSAR and 3D-QSAR methods, it has been revealed that pyrimidine derivatives have been found to possess the COX inhibitory activity [21]. There is a need to analyze the binding affinities of pyrimidine derivatives with COX-2 so that new compounds can be synthesized having specific COX-2 inhibitory activity and improved biological response with no or less adverse effects.

In this research work, a new class of 2-(4-methylsulfonylphenyl)pyrimidine derivatives have been designed on the basis of results obtained by 3D QSAR studies, and their activity was predicted using Vlife MDS software. Newly designed molecules with good predictive activity were subjected for docking to find out the ligand-receptor interaction.

EXPERIMENTAL WORK

3D-QSAR study had been done on a series of Novel 2- (4-methylsulfonylphenyl)pyrimidine derivatives using VLife MDS Software[22]. to find out the essential substitution pattern to design newer compounds with potent COX-2 inhibitory activity. In that study, regression was performed by k-NN method on a series of 24 compounds reported by Aurelio Orjales et al. [23]. The kNN-MFA model showed q^2 (cross validated r^2) of 0.78 with three descriptors namely E_1207, E_874, and S_1036. The predicted r^2 of 0.55 and number nearest neighbor k of 2 (two) were observed with the 3D model. From the derived QSAR model, it was concluded that COX-2 inhibitory activity of 2-(4-methylsulfonyl phenyl)pyrimidine derivatives is strongly influenced by the steric and electrostatic interactions.[24] The show point grid of 3D model with positive and negative values suggested pattern of substitution to improve the biological activity of already existing compounds. This study has been found very helpful in development and optimization of this class of compounds as well as designing of new compounds with improved COX-2 inhibitory activity.

Designing

Designing of the compounds consisted modification on the lead structure with various possible substituting groups. The substituent groups have their effect on the specific COX-2 inhibitory activity. Different types of substitution were done on the lead moiety on the basis of the electrostatic and steric points suggested by the 3D result map and new compounds (ss-25 to ss-49) were designed to predict their biological activity. All the new designed compounds were subjected to the batch optimization process to minimize the energy. After optimization, conformers of all compounds were generated by Monte Carlo method and the conformer having least energy was selected for the alignment. Alignment of all the new designed compounds was done by following the rules of template based alignment [24-26]. Specific COX-2 inhibitory activity of all these compounds was predicted by using the result of best 3D model.

Considering the electrostatic and steric points shown in 3D QSAR map various modifications have been done on the substitution site of the lead structure. The lead structure selected for the designing of new compounds is given below (Figure 1) and substitution was done on R position in the lead structure. New compound name, substituting group and predicted activity of new compounds is shown in Table 1.

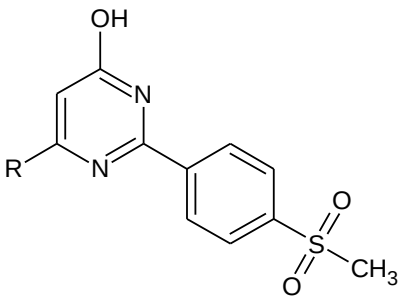


Figure 1. Lead structure used for designing of new molecules.

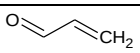
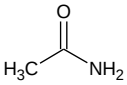
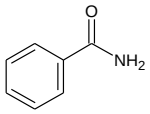
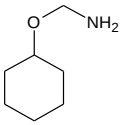
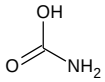
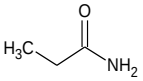
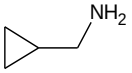
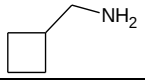
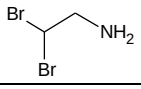
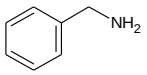
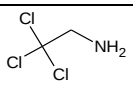
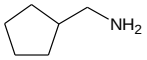
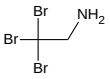
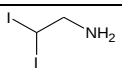
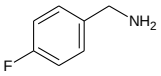
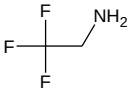
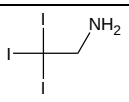
DOCKING

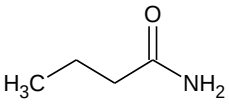
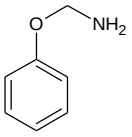
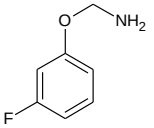
VLifeMDS uses following fitness function for searching docking space.

Rigid docking

E = InterEq (selected option electrostatic)
E = InterEvdW + InterEq (selected option steric + electrostatic)
E = EEPIC (selected option electrostatic)

Table 1. List of new designed compounds and their predicted activity.

S.N.	Compound Name	R	Predicted Activity
01	ss25		6.857124
02	ss26		6.857016
03	ss27	NO_2	7.465399
04	ss28	$CF_3CO(CH_3)N$	6.857059
05	ss29	$CH_2C(OH)(CH_3)_2$	6.856702
06	ss30		7.264675
07	ss31		7.264178
08	ss32		7.465498
09	ss33		7.264404
10	ss34		7.465487
11	ss35		6.857151
12	ss36	$SO_2CF_3CH_2NH_2$	7.264246
13	ss37		6.934809
14	ss38		6.857158
15	ss39		7.465537
16	ss40		6.857232
17	ss41		6.857168
18	ss42		6.857073
19	ss43		6.857154
20	ss44		7.263851
21	ss45		7.264703
22	ss46		6.857094

23	ss47		6.857146
24	ss48		6.936801
25	ss49		6.857076

Ligand Flexible Docking

E = InterEq + InterEvdW + IntraEq + IntravdW + IntraEtor

Where,

InterEvdW intermolecular vdW energy of complex
InterEq intermolecular electrostatic energy of complex
EEPIC electrostatic potential for intermolecular complex
IntraEvdW intramolecular vdW energy of ligand
IntraEq intramolecular electrostatic energy of ligand
IntraEtor intramolecular torsion energy of ligand
All the energy components are calculated using MMFF force field.

All newly designed compound namely ss25 to ss49 were docked with Cyclooxygenase-2 (Prostaglandin synthase-2, PDB ID- 1CX2), Uninhibited Mouse Cyclooxygenase-2 (Prostaglandin Synthase-2, PDB ID-5COX) and The Membrane Protein Prostaglandin H_2 Synthase-1, PDB ID-1PRH) using Grid based docking method. The receptor (enzyme) files were obtained online from Protein Data Bank [27]. Appropriate selections were done after selecting the receptor and ligand. Cavity Number 1 was chosen in the Grid over panel for the receptor where the docking was performed. The default grid size automatically chosen by VLifeMDS was 1Å. Rotation Angle for ligand rotation step size was set as 100, Dock Score was selected as fitness function, and No of bump allowed was set as 4. The docking score obtained for all designed compounds with three different receptors are given in Table 2.

RESULTS AND DISCUSSION

Molecular modeling is employed to measure the energy of conformations and interactions utilizing either quantum mechanics or empirical energy functions. Molecular docking shows the energy calculation in terms of the scoring function. Efficiency and precision of docking rely upon scoring function. Scoring functions are based on force fields that are used to simulate the functions of proteins. With known 3D structure of receptor molecule or protein, the binding affinity of the protein ligand complex is calculated and it is termed as Dock score.

Among all designed compounds (ss25 to ss49), three compounds ss-43, ss-46 and ss-38 showed minimum score of -6.199069, -6.180829, and 6.049794 respectively with 1CX2 and with the same compounds the minimum score obtained with 5COX were -6.293567, -6.202445, -6.100384 respectively. With 1PRH, the same three compounds showed minimum score of -6.345966, -6.245738, and -6.150805 respectively and these scores were considered as the best scores among the minimum scores of designed compounds. Receptor-ligand interactions by docking studies were found that there were hydogenbond interaction, hydrophobic interaction and Vdw_Interaction between the receptor and ligand moiety. The binding interaction between designed compounds and the receptors are shown in the tables and figures below (Fig.2-19) (Table. 3-10).

Table 2. Docking score of compounds with receptors.

Compound Name	Minimum Score		
	1CX2	***5COX***	***1PRH***
ss25	-5.256125	-5.154857	-5.356521
ss26	-4.982222	-4.454769	-4.682425
ss27	-5.056120	-5.284109	-5.136150
ss28	-5.203038	-5.411900	-5.233059
ss29	-4.858810	-4.995813	-4.656815
ss30	-5.058738	-4.958922	-5.256749
ss31	-5.524672	-5.773288	-5.444561
ss32	-5.306515	-5.315657	-5.406515
ss33	-5.903116	-5.903116	-5.613516
ss34	-5.530099	-5.763159	-5.430698
ss35	-5.311790	-5.545676	-5.931548
ss36	-5.509337	-5.985274	-5.719345
ss37	-5.254801	-5.649463	-5.554657
ss38	-6.049794	-6.100384	-6.150805
ss39	-5.519462	-5.894349	-5.519462
ss40	-5.738106	-5.342540	-5.237983
ss41	-5.772520	-5.328595	-5.350341
ss42	-5.970706	-5.852865	-5.887338
ss43	-6.199069	-6.293567	-6.345966
ss44	-5.608083	-5.589586	-5.238683
ss45	-5.781208	-5.432986	-5.552431
ss46	-6.180829	-6.202445	-6.245738
ss47	-5.342018	-5.432868	-5.034012
ss48	-5.556170	-5.568957	-5.879211
ss49	-5.426270	-5.342895	-5.689927

Table 3. Binding interactions between ss43 and 1CX2.

S.N.	Residue Atom	Interaction Type
1	TYR115D 14061O	Hydrogenbond_Interaction
2	VAL89D 13829C	Hydrophobic_Interaction
3	ILE92D 13861C	Hydrophobic_Interaction
4	LEU93D 13869C	Hydrophobic_Interaction
5	LEU82D 13778O	Vdw_Interaction
6	PRO84D 13798C	Vdw_Interaction
7	VAL89D 13833C	Vdw_Interaction
8	ILE92D 13864C	Vdw_Interaction
9	TYR115D 14061O	Vdw_Interaction
10	SER119D 14087O	Vdw_Interaction

Table 4. Binding interactions between ss46 and 1CX2.

S.N.	Residue Atom	Interaction Type
1	LYS83D 13790C	Hydrophobic_Interaction
2	VAL89D 13829C	Hydrophobic_Interaction
3	ILE92D 13858C	Hydrophobic_Interaction
4	LEU93D 13869C	Hydrophobic_Interaction
5	LYS83D 13784C	Vdw_Interaction
6	PRO84D 13798C	Vdw_Interaction
7	VAL89D 13829C	Vdw_Interaction
8	ILE92D 13861C	Vdw_Interaction
9	TYR115D 14061O	Vdw_Interaction
10	SER119D 14087O	Vdw_Interaction
11	TYR122D 14118O	Vdw_Interaction

Table 5. Binding interaction between ss38 and 1CX2.

S.N.	Residue Atom	Interaction Type
1	ASN43C 9005O	Hydrogen bond_Interaction
2	TYR122C 9653O	Hydrogen bond_Interaction
3	ARG61C 9143C	Hydrophobic_Interaction
4	ASN43C 9000C	Vdw_Interaction
5	ARG61C 9144C	Vdw_Interaction
6	THR62C 9150C	Vdw_Interaction
7	PHE64C 9168C	Vdw_Interaction
8	LYS83C 9326N	Vdw_Interaction
9	TYR122C 9653O	Vdw_Interaction
10	SER471C 12532O	Vdw_Interaction

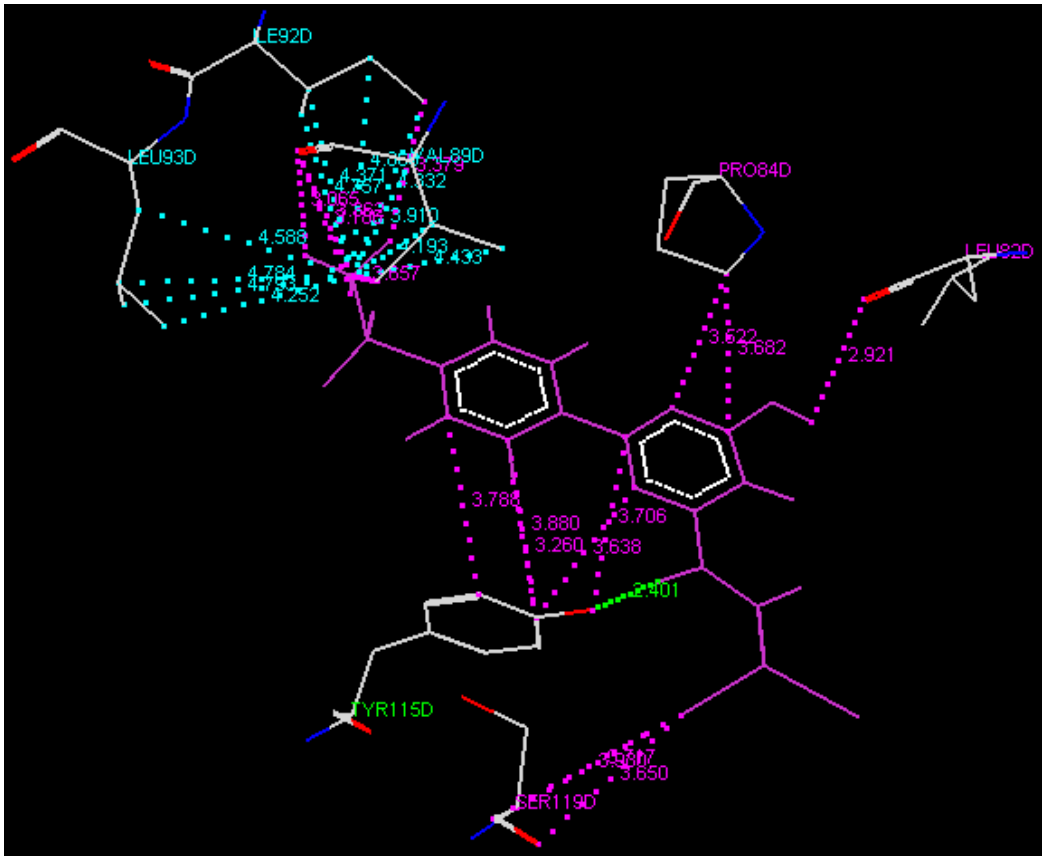


Figure 2. Complex of ss43 with 1CX2.

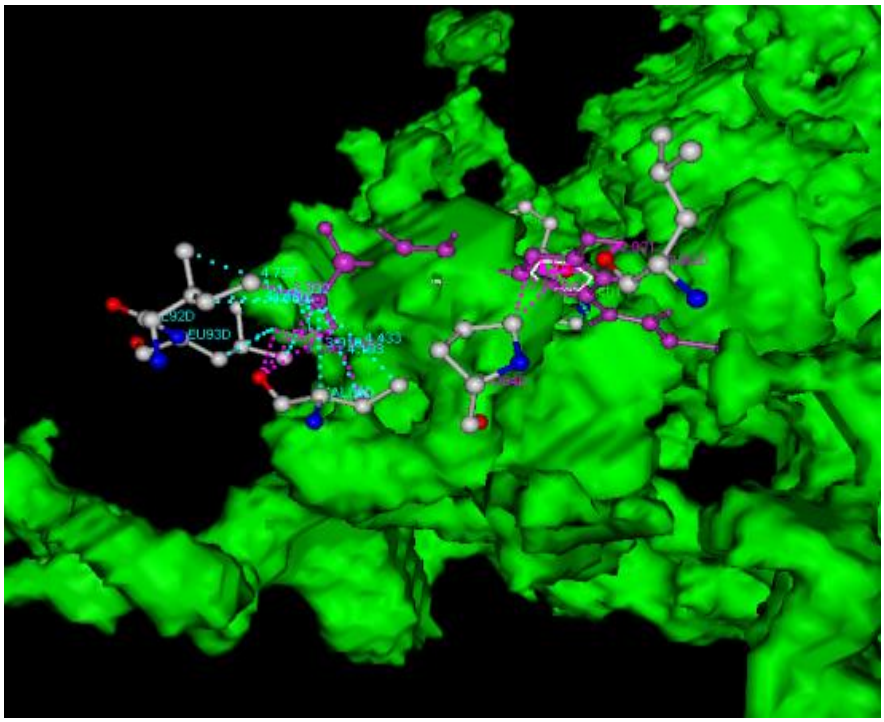


Figure 3. Compound ss43 docked in 1CX2 cavity.

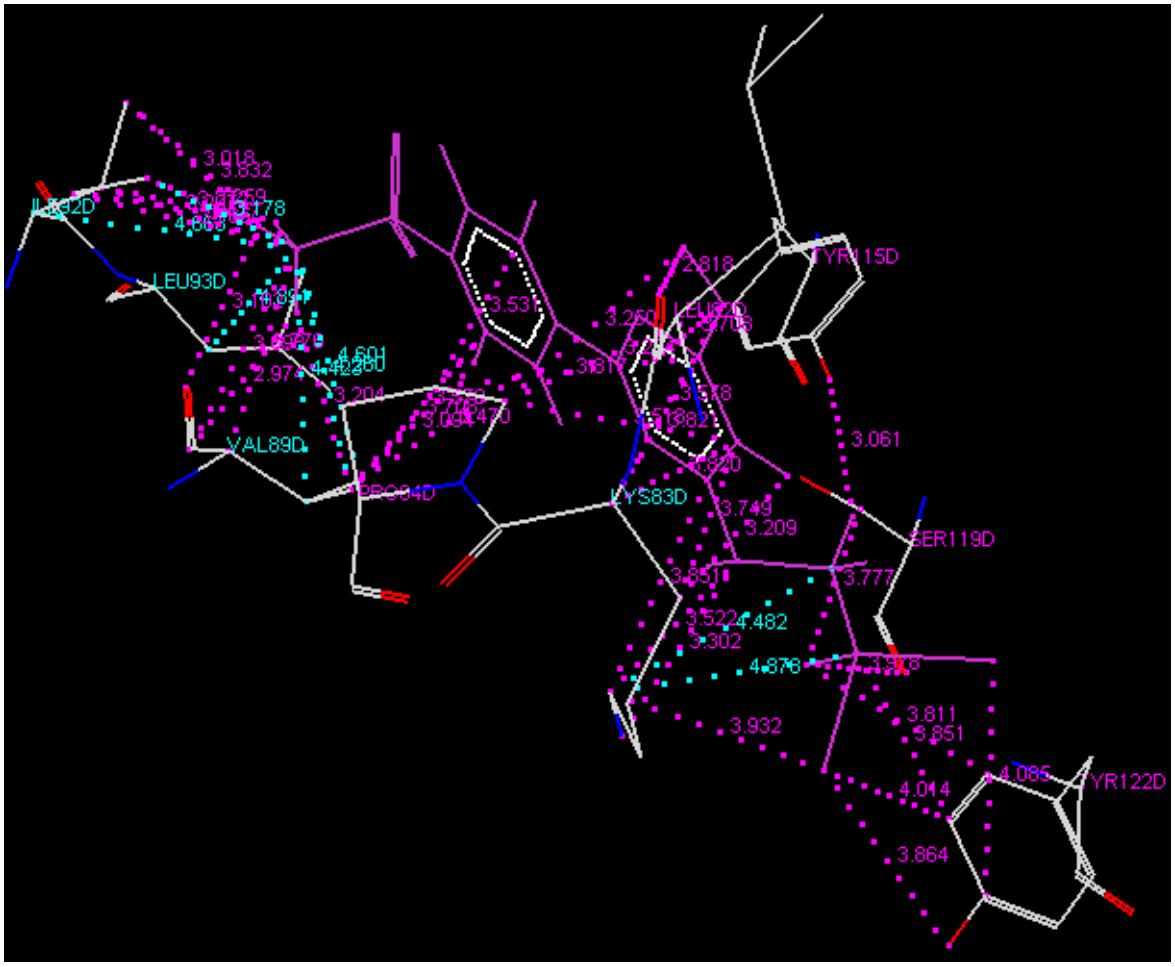


Figure 4. Complex of ss46 with 1CX2.

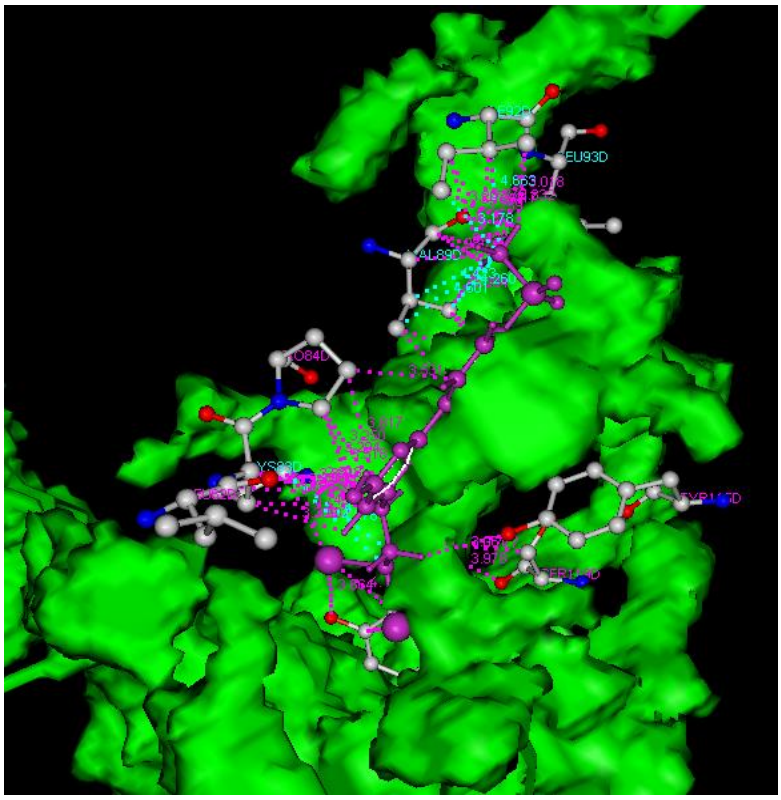


Figure 5. Compound ss46 docked in 1CX2 cavity.

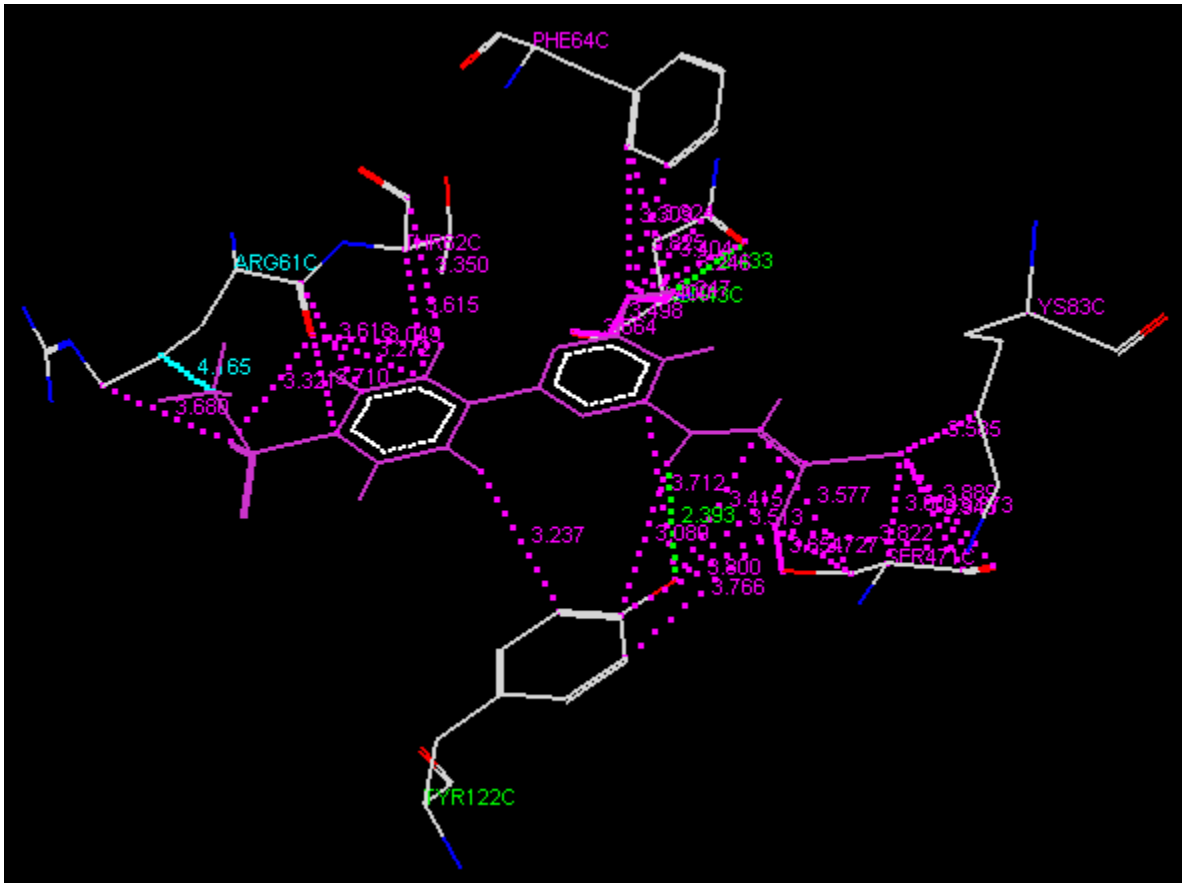


Figure 6. Complex of ss38 with 1CX2.

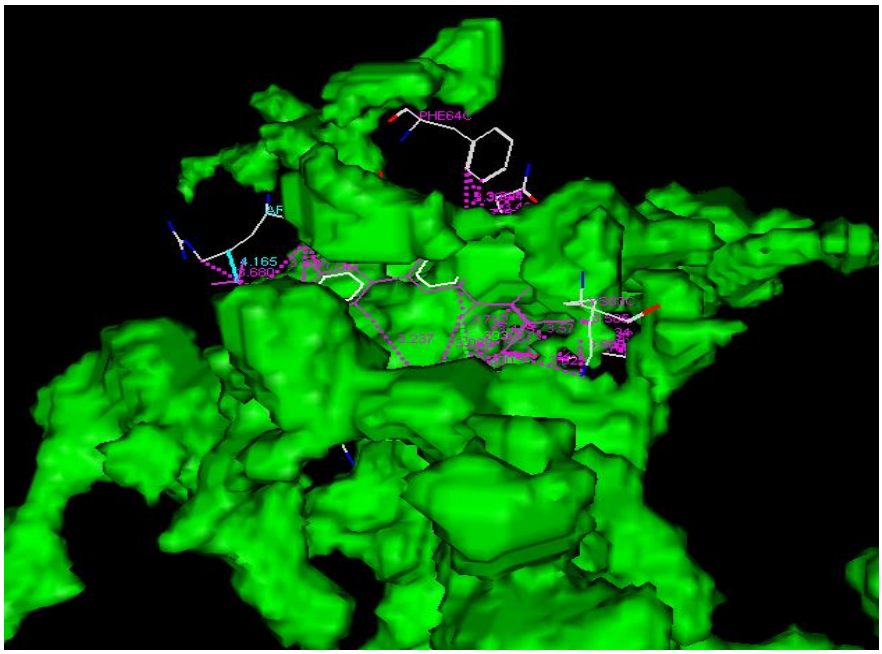


Figure 7. Compound ss38 docked in 1CX2 cavity.

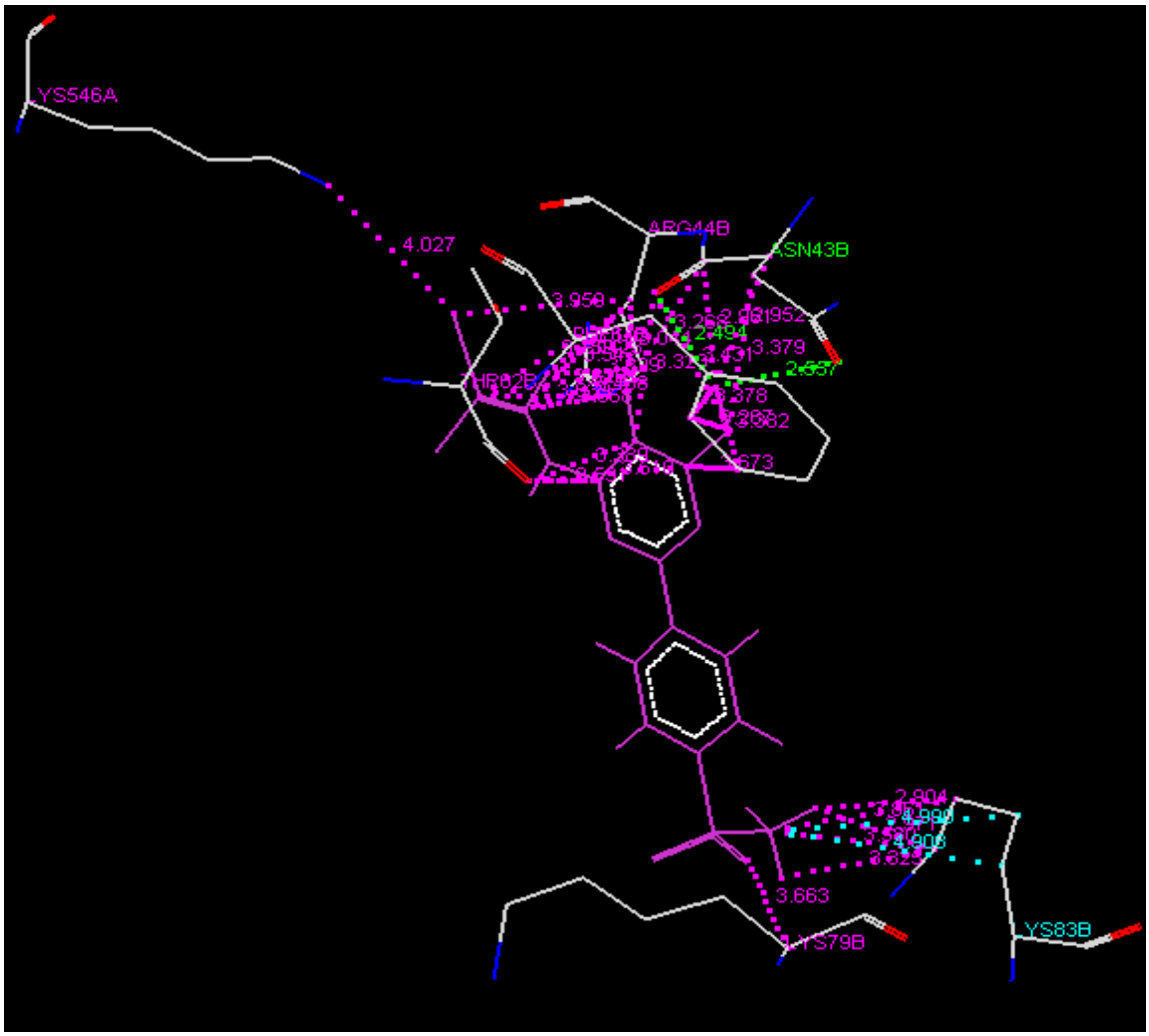


Figure 8. Complex for ss43 with 5COX.

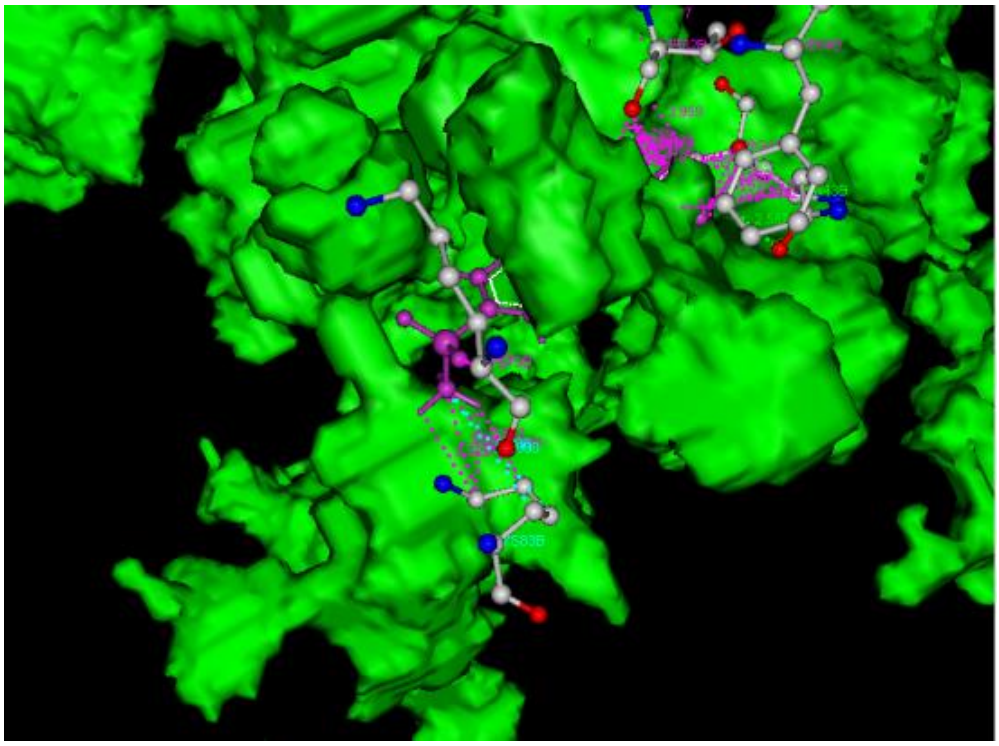


Figure 9. Compound ss43 docked in 5COX cavity.

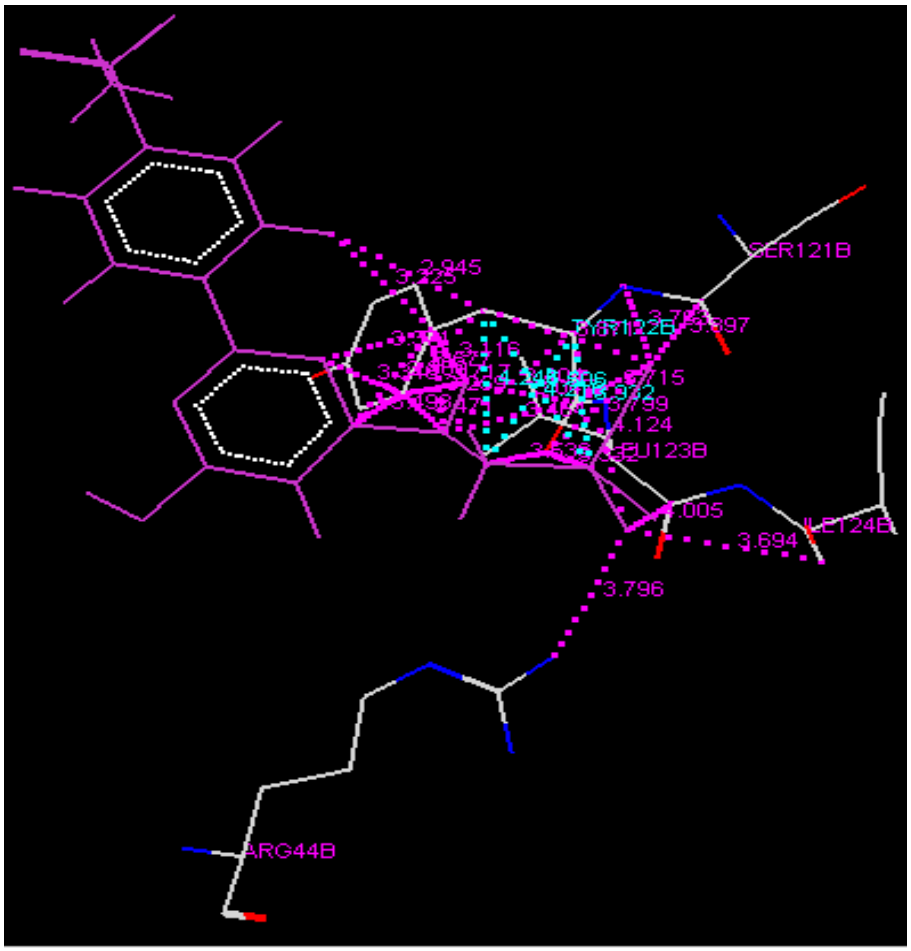


Figure 10. Complex of ss46 with 5COX.

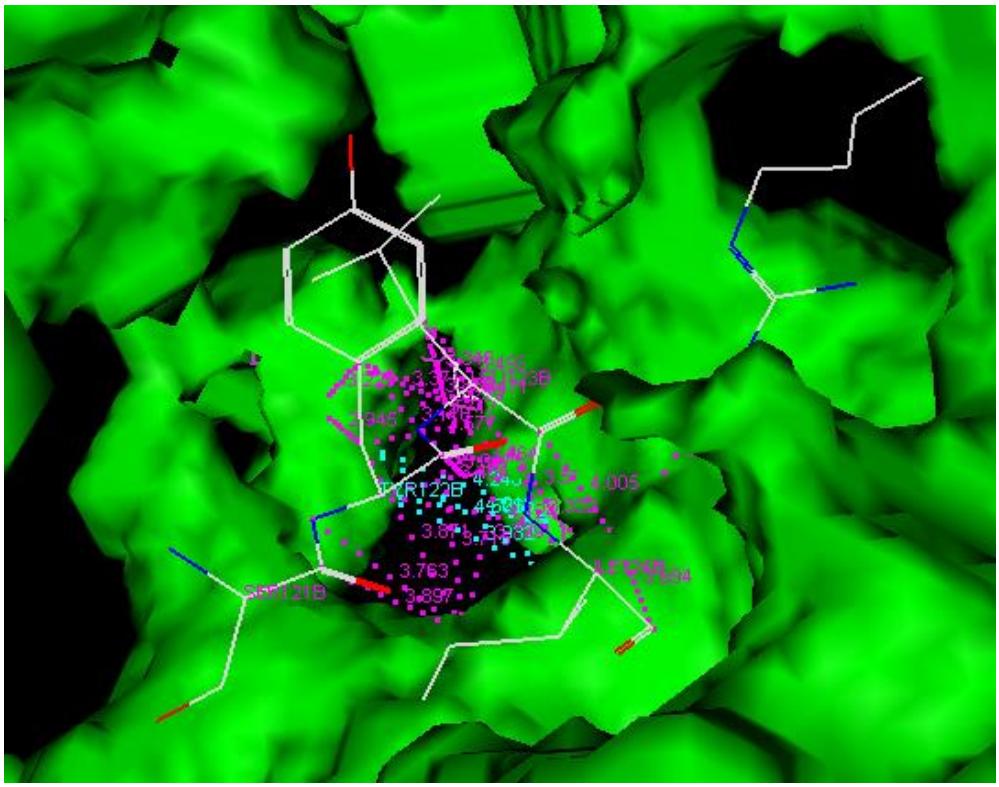


Figure 11. Compound ss46 docked in 5COX cavity.

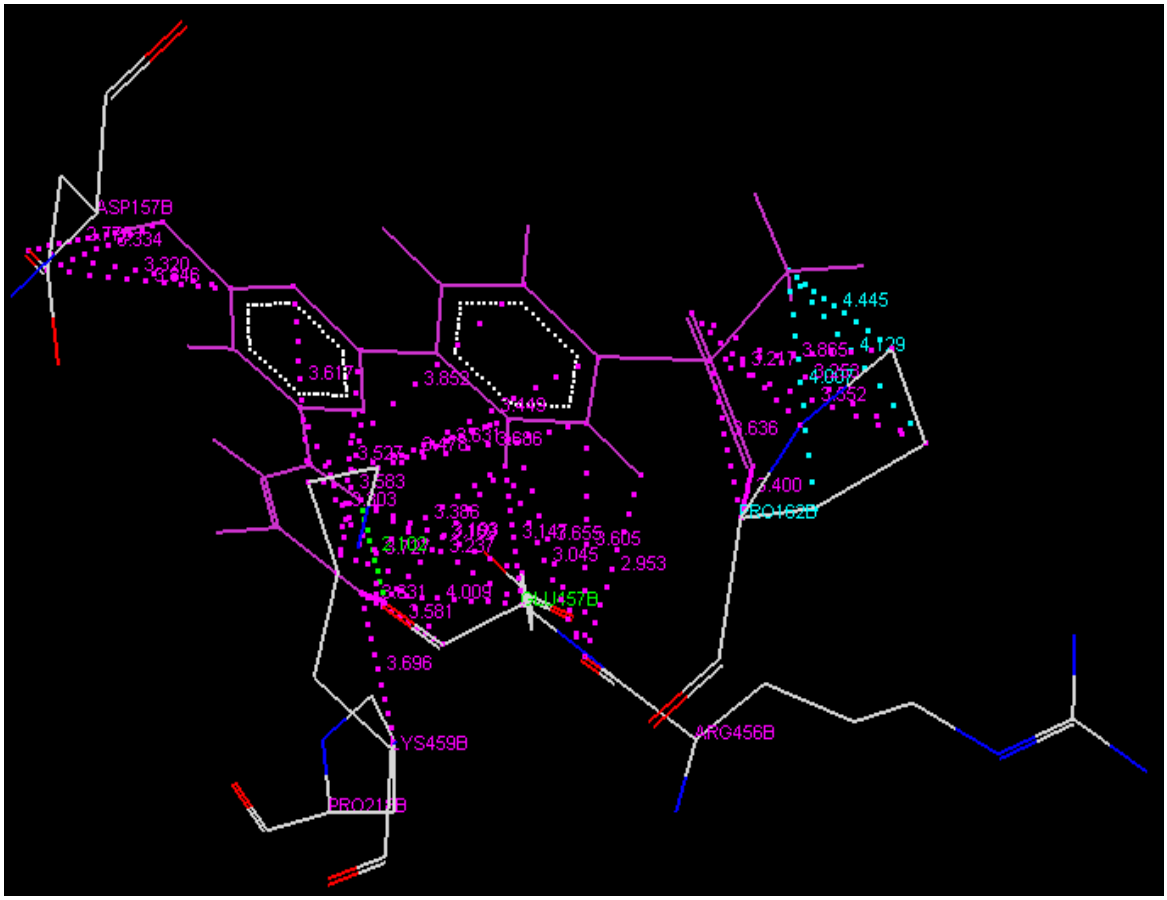


Figure 12. Complex of ss38 with 5COX.

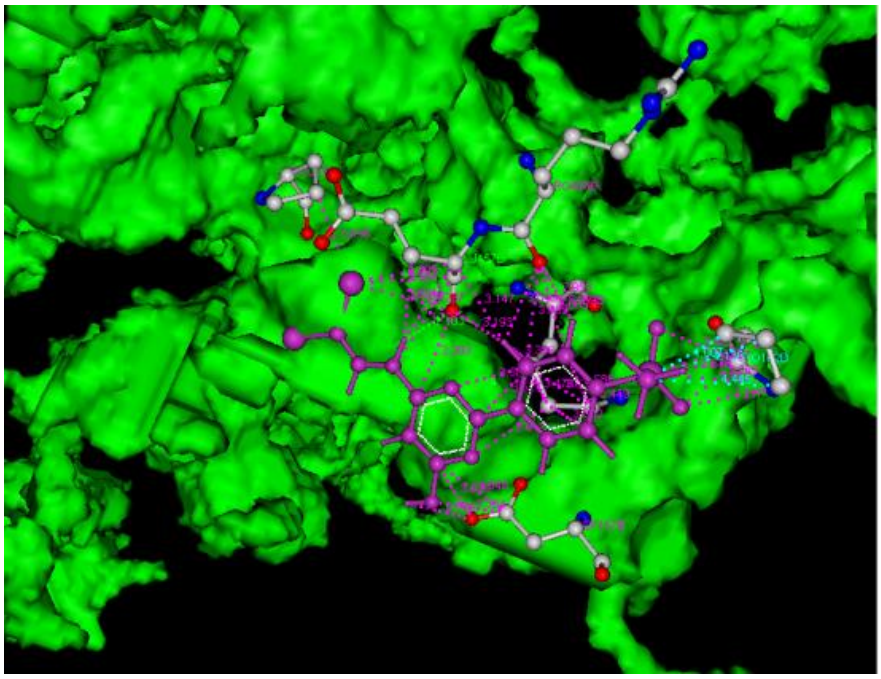


Figure 13. Compound ss38 docked in 5COX cavity.

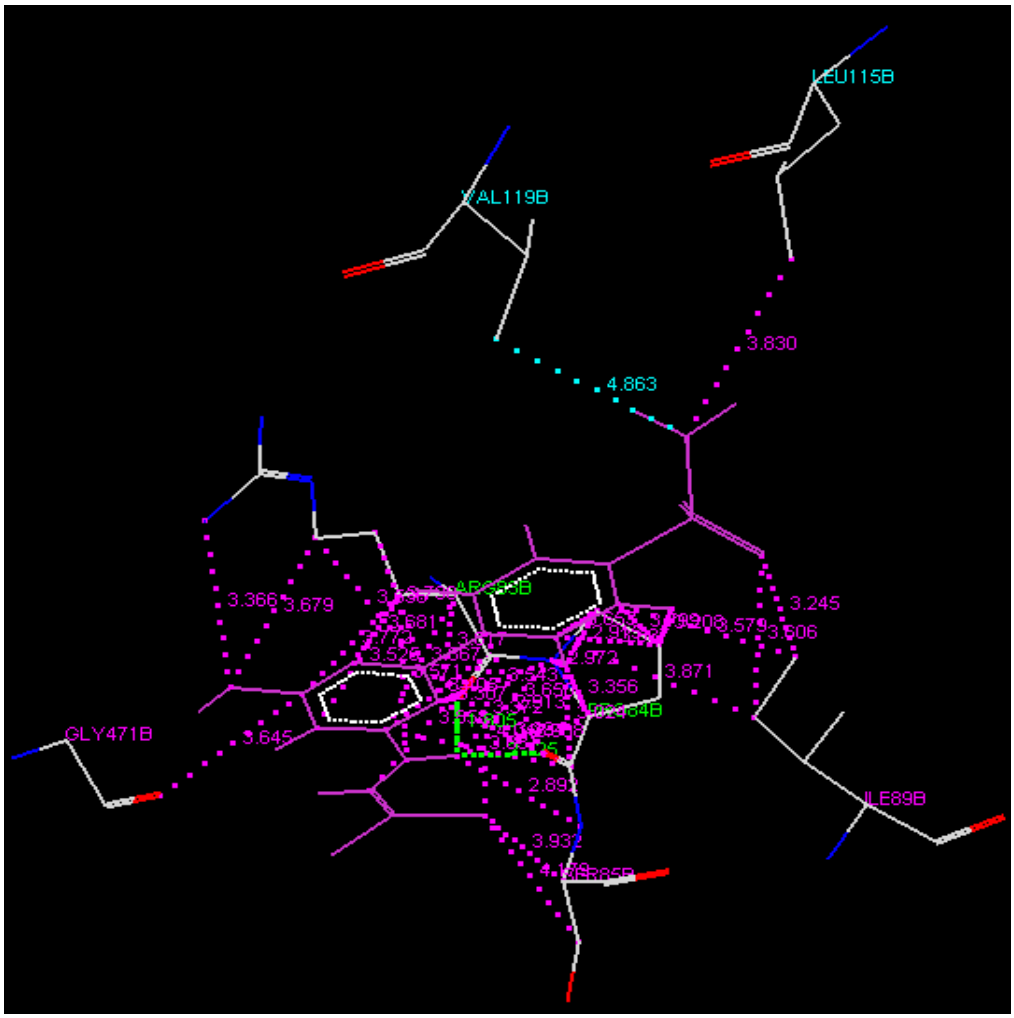


Figure 14. Complex of ss43 with 1PRH.

Table 6. Binding interaction between ss43 and 5COX.

S.N.	Residue Atom	Interaction Type
1	ASN43B 4537O	Hydrogenbond_Interaction
2	LYS83B 4860C	Hydrophobic_Interaction
3	LYS546A 4191N	Vdw_Interaction
4	ASN43B 4538C	Vdw_Interaction
5	THR62B 4687O	Vdw_Interaction
6	PHE64B 4701C	Vdw_Interaction
7	LYS79B 4821C	Vdw_Interaction

Table 7. Binding interaction between ss46 and 5COX.

S.N.	Residue Atom	Interaction Type
1	TYR122B 5178C	Hydrophobic_Interaction
2	ARG44B 4552N	Vdw_Interaction
3	SER121B 5173C	Vdw_Interaction
4	TYR122B 5183C	Vdw_Interaction
5	LEU123B 5191C	Vdw_Interaction
6	ILE124B 5199C	Vdw_Interaction

Table 8. Binding interaction between ss38 and 5COX.

S.N.	Residue Atom	Interaction Type
1	GLU457B 7933O	Hydrogenbond_Interaction
2	PRO162B 5508C	Hydrophobic_Interaction
3	ASP157B 5475O	Vdw_Interaction
4	PRO162B 5510C	Vdw_Interaction
5	PRO218B 5971C	Vdw_Interaction
6	ARG456B 7922O	Vdw_Interaction
7	GLU457B 7931C	Vdw_Interaction
8	LYS459B 7954C	Vdw_Interaction

Table 9. Binding interaction between ss43 and 1PRH.

S.N.	Residue Atom	Interaction Type
1	ARG83B 4912O	Hydrogenbond_Interaction
2	PRO84B 4923O	Hydrogenbond_Interaction
3	LEU115B 5195C	Hydrophobic_Interaction
4	VAL119B 5223C	Hydrophobic_Interaction
5	ARG83B 4918N	Vdw_Interaction
6	PRO84B 4926C	Vdw_Interaction
7	SER85B 4931C	Vdw_Interaction
8	ILE89B 4964C	Vdw_Interaction
9	LEU115B 5195C	Vdw_Interaction
10	GLY471B 8110O	Vdw_Interaction

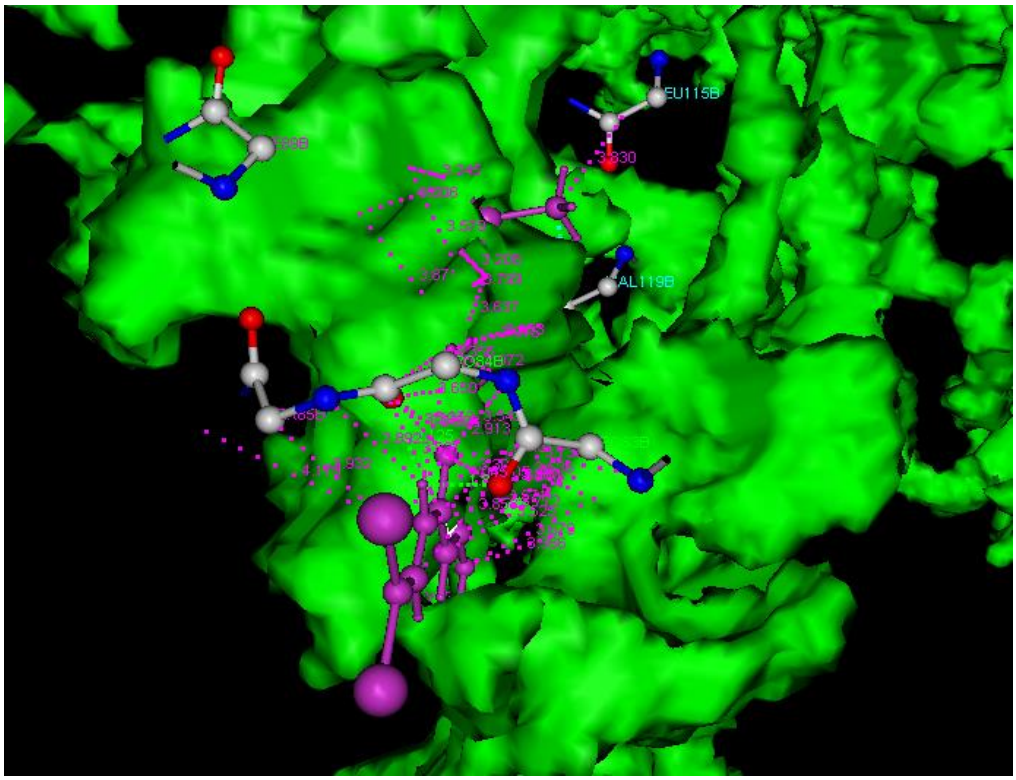


Figure 15. Compound ss43 docked in 1PRH cavity.

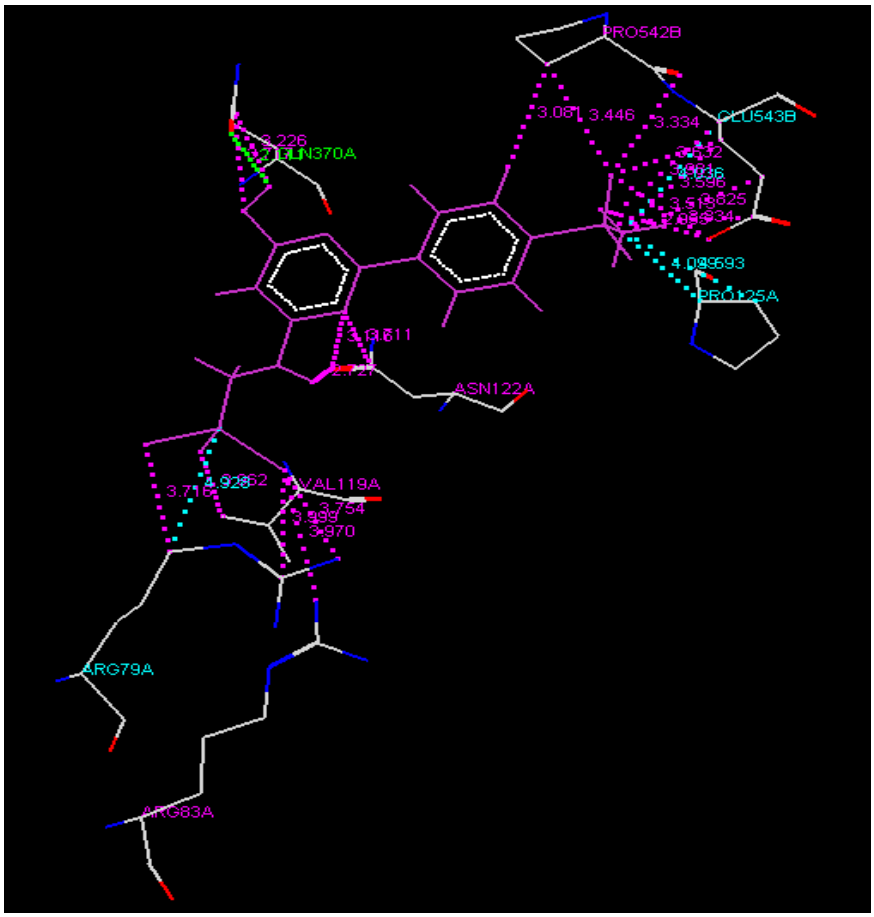


Figure 16. Complex of ss46 with 1PRH.

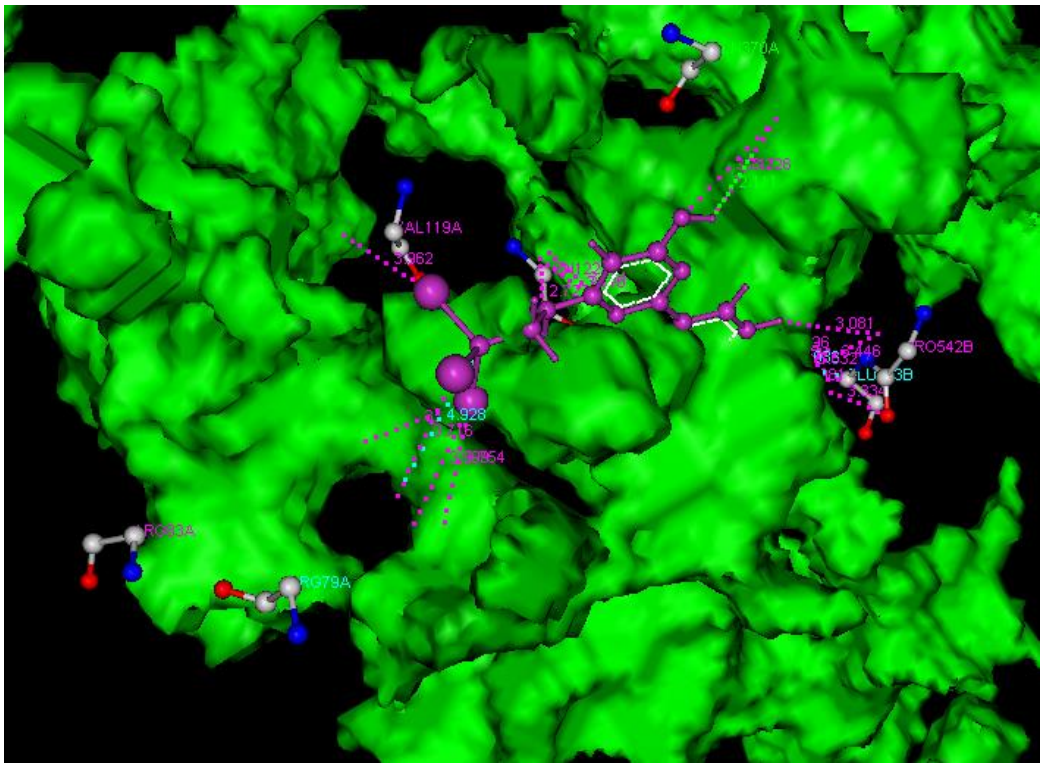


Figure 17. Compound ss46 docked in 1PRH cavity.

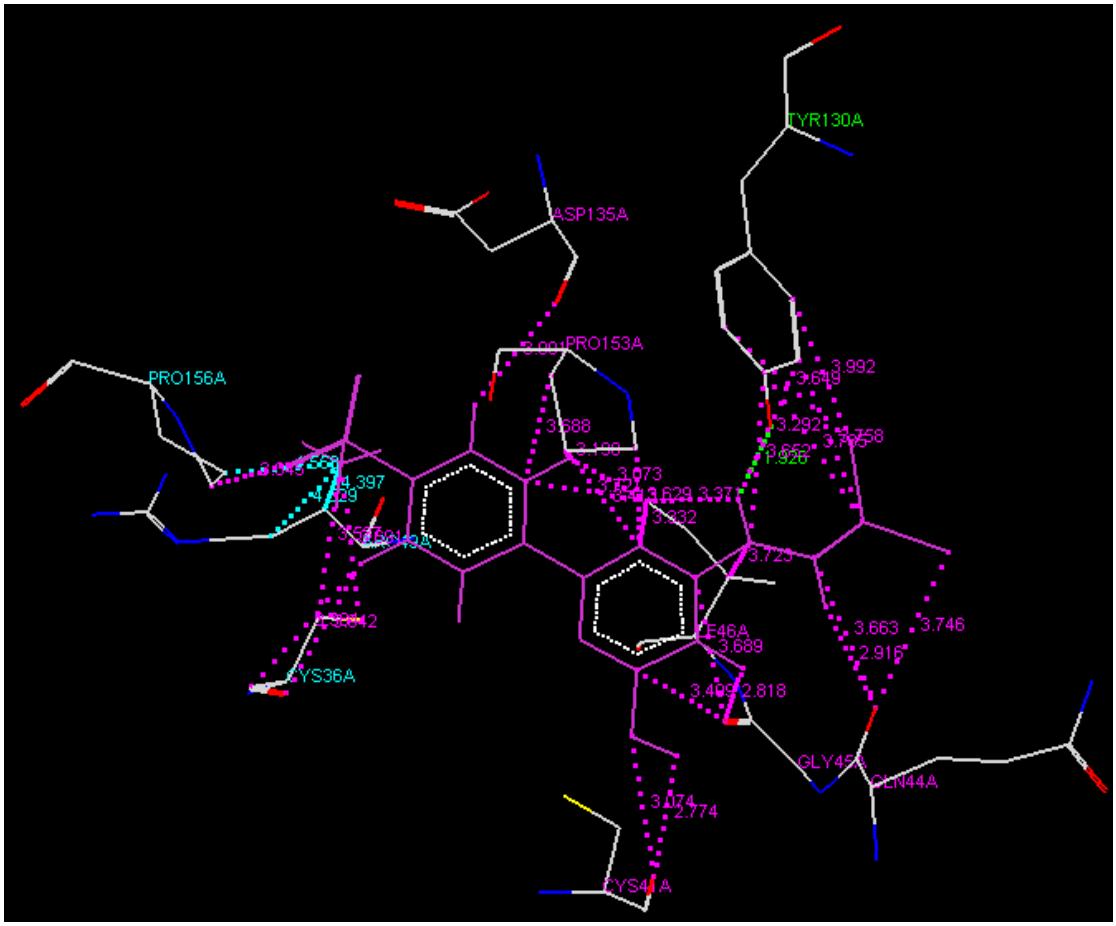


Figure 18. Complex of ss38 with 1PRH.

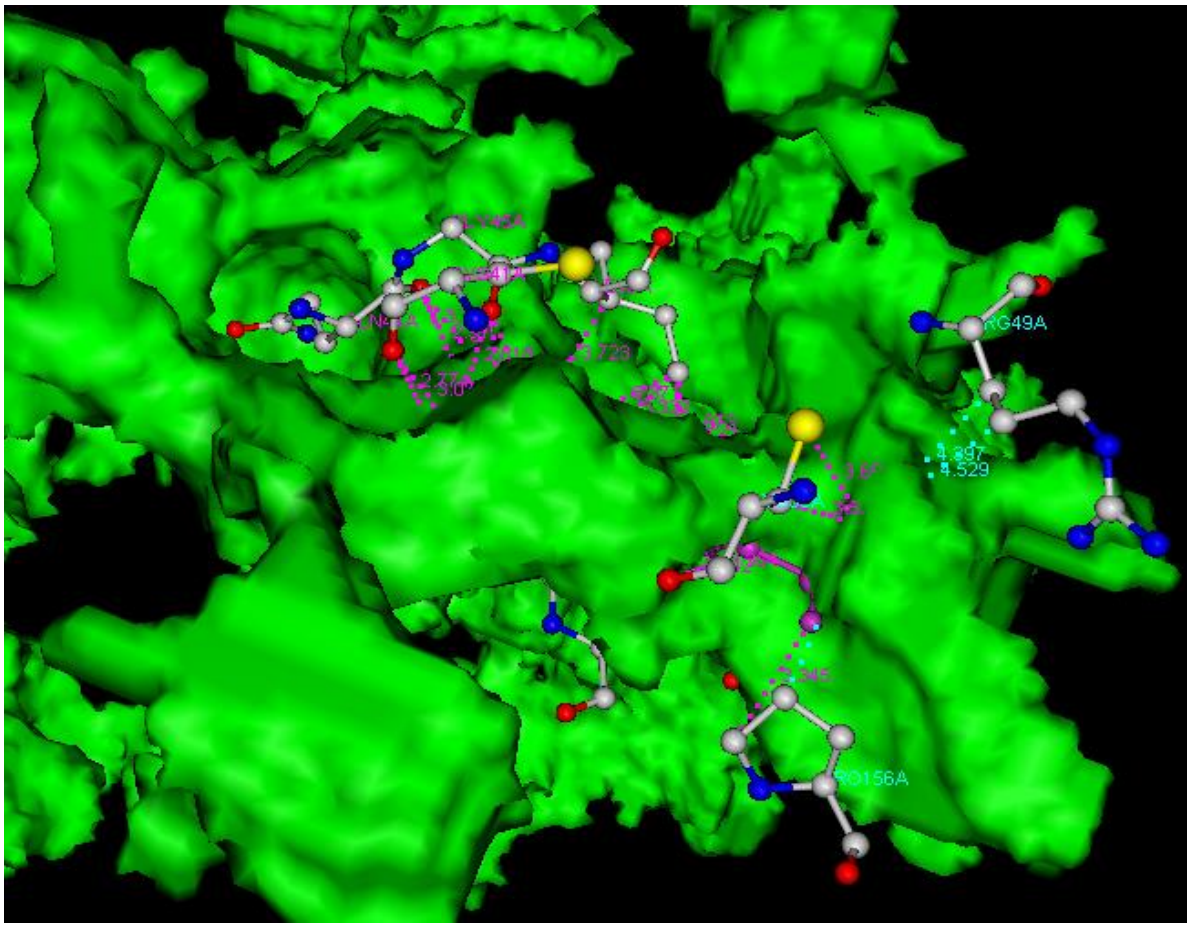


Figure 19. Compound ss38 docked in 1PRH cavity.

Table 10. Binding interaction between ss46 and 1PRH.

S.N.	Residue Atom	Interaction Type
1	GLN370A 2758O	Hydrogenbond_Interaction
2	ARG79A 379C	Hydrophobic_Interaction
3	PRO125A 764C	Hydrophobic_Interaction
4	GLU543B 8663C	Hydrophobic_Interaction
5	ARG79A 383N	Vdw_Interaction
6	ARG83A 416N	Vdw_Interaction
7	VAL119A 721C	Vdw_Interaction
8	ASN122A 745O	Vdw_Interaction
9	GLN370A 2757C	Vdw_Interaction
10	PRO542B 8655C	Vdw_Interaction
11	GLU543B 8665O	Vdw_Interaction

CONCLUSION

Considering the parameters resulted in 2D and 3D QSAR study, number of substitution were done on the lead moiety to get improved COX-2 inhibitory activity. Total of 25 new compounds were designed namely ss25-ss49 (Table-11). All the newly designed compounds showed good to moderate predicted activity. To confirm the predictions form models, docking studies were done by taking designed compounds as ligand and COX-2 as receptors (enzymes). The receptors were downloaded from Protein Data Bank and docked with designed compounds to check the binding affinity of ligands.

Three different types of receptors were chosen for docking studies to cross check the ability of designed compounds for ligand-receptor interaction. Among 25 designed compounds three compounds ss38, ss43 and ss46 showed best binding interactions.

Table 11. Binding interaction between ss38 and 1PRH.

S.N.	Residue Atom	Interaction Type
1	ASN34A 15N	Hydrogenbond_Interaction
2	CYS47A 116C	Hydrophobic_Interaction
3	ASP135A 844C	Hydrophobic_Interaction
4	PRO153A 1003C	Hydrophobic_Interaction
5	ASN34A 15N	Vdw_Interaction
6	CYS36A 24C	Vdw_Interaction
7	CYS47A 116C	Vdw_Interaction
8	ALA133A 828O	Vdw_Interaction
9	HIS134A 830N	Vdw_Interaction
10	ASP135A 841C	Vdw_Interaction
11	PRO153A 1004C	Vdw_Interaction
12	PRO156A 1020C	Vdw_Interaction
13	ARG157A 1036N	Vdw_Interaction
14	ASP158A 1042C	Vdw_Interaction
15	GLN461A 3514N	Vdw_Interaction

Acknowledgement

Author wishes to thank Department of Science and Technology, Delhi for providing INSPIRE fellowship to pursue PhD program. Author is also thankful to supervisor for his help and support, and Department of Pharmacy, Barkatullah University, Bhopal for providing various computational and molecular modeling facilities. Author is also thankful to Vlife Sciences for their valuable support.

REFERENCES

1. M. T. Cronin, J. C. Dearden, Quantitative structure-activity relationships for human health effects: Commonalities with other endpoints, Environ. Toxicol. Chem. 22 (2003) 1829-1843.
2. B. L. Podlogar, D. M. Ferguson, QSAR and CoMFA: A perspective on the practical application to drug discovery. Drug Des Discov 1 (2000) 4-12.
3. A. Z. Dudek, O. Arodz, J. Galvez, Computational methods in developing quantitative structure-activity relationships (QSAR): A Review. Combinatorial Chemistry & High Throughput Screening, 9(3) (2006) 213.
4. A. Vedani, M. Dobler, *et. al.*, Combining protein modeling and 6D-QSAR: Simulating the binding of structurally diverse ligands to the estrogen receptor, J. Med. Chem.,48 (2005) 3700-3703.
5. R. Todeschini, V. Consonni, Descriptors from molecular geometry. In: Gasteiger J (ed) Handbook of Chemoinformatics, Wiley-VCH, Weinheim (2003)
6. Q. S. Du, R. B. Huang, *et. al.*, Fragment-based quantitative structure-activity relationship (FB-QSAR) for fragment-based drug design, Journal of Computational Chemistry,30(2) (2009) 295-304.
7. K. Z. Myint, C. Ma, *et. al.*, Fragment-Similarity-Based QSAR (FS-QSAR) algorithm for ligand biological activity predictions, SAR and QSAR in Environmental Research 22 (3-4) (2010) 1-26.
8. A. S. Reddy, S. P. Pati *et. al.*, Virtual screening in drug discovery - A computational perspective, Current protein and peptide science, 8 (2007) 329-351.
9. R. A. Lewis, S. D. Pickett, D. E Clark, Computer-aided molecular diversity analysis and combinatorial library design. In: Reviews in Computational Chemistry, Edited by Kenny B. Lipkowitz DBB (2007) 1-51.

10. S. Bansal, B. Sinha *et. al.,* QSAR and docking-based computational chemistry approach to novel GABA-AT inhibitors: kNN-MFA-based 3DQSAR model for phenyl-substituted analogs of phenylethylidene hydrazine, Medicinal Chemistry Research, 20 (5)(2011) 549-553.
11. D. B. Kitchen, H. Decornez *et. al.,* Docking and scoring in virtual screening for drug discovery: methods and applications, Nature Reviews Drug Discovery, 3(11) (2004) 935.
12. A. Danjuma, Abdullahi, A. M. Abdualkader, Application of group-based QSAR and molecular docking in the design of insulin-like growth factor antagonists, Tropical Journal of Pharmaceutical Research,14 (6) (2015) 941-951.
13. A. N. Jain, Effects of protein conformation in docking : Improved pose prediction through protein pocket adaptation, J Comput Aided Mol Des, 23 (2009) 355–374.
14. J. Hippisley-Cox, C. Coupland *et. al.,* Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis, BMJ, 331 (2005) 1310-1316.
15. W. Richard, J. Barbara, Do cox-2 inhibitors worsen renal function? The Journal of Family Practice, 56 (11) (2007).
16. RS B. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352:1092-102.
17. Nofal ZM, Fahmy HH, Zarea ES, El-Eraky W. Synthesis of new pyrimidine derivatives with evaluation of their anti-inflammatory and analgesic activities. Acta Pol Pharm. 2011 Jul 1;68(4):507-17.
18. Tirlapur VK, Narasimha G, Raga B, Prasad YR. Synthesis, characterization and biological activities of some new pyrimidines and isoxazoles bearing benzofuran moiety. International Journal of ChemTech Research. 2010;2(3):1434-40.
19. Singour PK, Khare A, Dewangan H, Pawar RS. Synthesis and biological evaluation of novel pyrimidine derivatives as anti-inflammatory agents. J Pharm Res. 2012 Sep;5:4853-8.
20. Ghorab MM, Alsaid MS. Synthesis of some tricyclic indeno [1, 2-d] pyrimidine derivatives as a new class of anti-breast cancer agents. Biomedical Research. 2015 Jan 1;26(3):420-5.
21. Pathak AK, Sarankar SK, Mehta P. Two dimensional QSAR study of novel 2-(4-methyl sulfonylphenyl) pyrimidine derivatives as highly potent and specific COX-2 inhibitors. Journal of Pharmacy Research. 2011 Jun;4(6):1592-5.
22. Jain SK, Bharti SK, Jagan BG, Gupta AK. 3D-QSAR and Pharmacophoric study on 2, 6-Disubstituted Thiazolo [4, 5-b] Pyridines as H3 Receptor Antagonists. Research Journal of Pharmacy and Technology. 2023 Oct 1;16(10):4575-82.
23. Orjales A, Mosquera R, Lopez B, Olivera R, Labeaga L, Núñez MT. Novel 2-(4-methylsulfonylphenyl) pyrimidine derivatives as highly potent and specific COX-2 inhibitors. Bioorganic & medicinal chemistry. 2008 Mar 1;16(5):2183-99.
24. Tervo AJ, Nyrönen TH, Rönkkö T, Poso A. Comparing the quality and predictiveness between 3D QSAR models obtained from manual and automated alignment. Journal of chemical information and computer sciences. 2004 May 24;44(3):807-16.
25. Tervo AJ, Nyrönen TH, Rönkkö T, Poso A. Comparing the quality and predictiveness between 3D QSAR models obtained from manual and automated alignment. Journal of chemical information and computer sciences. 2004 May 24;44(3):807-16.
26. Asikainen A, Kolehmainen M, Ruuskanen J, Tuppurainen K. Structure-based classification of active and inactive estrogenic compounds by decision tree, LVQ and kNN methods. Chemosphere. 2006 Jan 1;62(4):658-73.
27. Burley SK, Berman HM, Bhikadiya C, Bi C, Chen L, Di Costanzo L, Christie C, Dalenberg K, Duarte JM, Dutta S, Feng Z. RCSB Protein Data Bank: biological macromolecular structures enabling research and education in fundamental biology, biomedicine, biotechnology and energy. Nucleic acids research. 2019 Jan 8;47(D1):D464-74.

