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Design, Docking, ADMET and PASS Prediction Studies of Novel Chromen-4-one Derivatives for Prospective Anti-Cancer Agent

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In-silico analysis is being used nowadays as an efficient method for drug design to address the pharmacokinetic profile of the drug under study and also to predict the optimized orientation of the ligand against a specific drug target by docking software. It is a cost-effective and time saving technique that requires limited manpower. In this present study a library of substituted benzimidazolyl chromen-4-one chalcones and substituted benzimidazolyl pyrimidinyl chromen-4-one derivatives were designed, molecular docking was accomplished using AutoDock Vina and *in-silico* ADMET were estimated using online tools. Out of 16 analogues having lower binding energy only 12 were selected on the basis of "Lipinski Rule of Five" as orally bioavailable lead compounds. PASS (Prediction of activity spectra of substances) was also performed on the selected compounds. The pharmacokinetic information and molecular docking patterns of compounds obtained in this study can give an important lead in development of novel COX-2 inhibitors with safer pharmacokinetic and pharmacodynamic characteristics.

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Keywords: Benzimidazole; chromone; COX-2 inhibition; molecular docking; ADMET; PASS prediction; antineoplastic activity.

1. INTRODUCTION

In every country of the world cancer is the foremost cause of death and an important obstacle to increasing life probability. 19.3 million new cancer cases have been projected and almost 10.0 million deaths have occurred in 2020 due to cancer worldwide [1]. A number of anticancer agents having different modes of action have been introduced by researchers but some of these may suffer from severe side effects and also affect the life of patients. A number of new approaches of cures such as targeted drug delivery and new drug families have been introduced to lessen these side effects [2]. The selective cyclooxygenase-2 inhibitors are better lead compounds which could be used not only to cure cancers as an adjunct therapy but also have fewer side effects and a high efficiency [3,4]. Cyclooxygenase (COX) enzyme well-known as "prostaglandin-endoperoxide" synthase which is involved in the synthesis of biological mediators prostanoids, including prostaglandin, thromboxane, and prostacyclin. It occurs into two isoforms COX-1 and COX-2. Over expression of COX-2 is involved in various varieties of cancers, including breast, prostate ovarian, melanoma, glioblastoma, colon, etc. resulting in cell mortality [5]. Cycloxygenase-2 is synthesized at very low levels under normal conditions but during the inflammation and pathogenic stimuli as well as in cancer progression high production of prostaglandins occur [6].

In-silico technique is reducing the number of molecules synthesized and helping researchers in the process of drug development. Tools and models available are used to estimate the ADMET properties, and structure-based molecular docking, helps in predicting the possible interactions with the target under study [7]. Major information whether the compound under study can work as a drug at an early stage of development is provided by *in-silico* physicochemical properties such as saturation, size, lipophilicity, solubility, polarity, and flexibility [8]. A number of heterocyclic compounds such as 4H–chromen–4–one and benzimidazole derivative exhibit interesting anti-inflammatory and anticancer activity [9]. Chromones are benzoannelated γ- pyrone ring occurring naturally in a number of compounds. Over the years chromones have been synthesized and isolated by several modified methods have been implemented for the synthesis and isolation of chromones and the compounds were then selected for different biological activities e.g. anti-inflammatory, antioxidant, antiviral, anti-tumor, antimicrobial, etc. [10]. The benzimidazole ring is present in different natural and pharmacologically active compound and is a pharmacophore of great importance in the present situation. It has been used as fortunate scaffolds for the synthesis of selective drugs of interest in medicinal field including antiulcer, antioxidant, anticancer, antimicrobial, antihistamine HIV-RT inhibitor, anthelmintic, etc. [11].

The purpose of the current study was to perform simulated screening of molecules through molecular docking strategy with COX-2 as the receptor and identify possible lead molecules which could serve as a template for designing new proposed molecules with improved binding affinities, and better molecular interactions with the receptor. Additionally *in-silico* ADME and drug likeness properties of the designed compounds were also evaluated for oral bioavailability and safety of the compound. PASS prediction was performed on selected compounds to assess the probability of anti-cancer activity.

2. MATERIALS AND METHODS

2.1 Protein Preparation

The COX-2 human receptor protein bound with ligand (PDB id-5kir) was downloaded from the protein data bank (https://www.rcsb.org/). Research collaboratory for structural bioinformatics (RCSB) is a single, universal assortment of information about the 3D structure of macromolecules (proteins and DNA) and their complexes [12]. The 5kir protein complex contains two same polypeptide chains of 551 amino acids. Chain B was removed with the help of pymol and chain A was used for the trial. The binding site of ligand with the human COX-2 protein was identified by using protein imagining software such as PyMol. PyMol software was also used to separate the bound ligand celecoxib and water from the complex. This was followed by energy minimization of protein. Through Energy minimization the poor contact in the protein structure can be removed and the conformational error in PDB structured protein

can also be eliminated. AutoDockVina was used for converting the pdb file to pdbqt file which also included additional 3-4 steps such as adding polar hydrogen atoms only and further adding partial atomic charge to the macromolecule [13,14].

2.2 Grid Preparation

In docking studies one of the major steps is setting of the grid by AutoDock Tools. Best grid structures and coordinates were selected that covered the whole binding pocket of the target protein. After the grid had been calculated the grid parameter file was saved in conf file which was used for docking [14]. The Grid coordinates for Human COX-2 enzyme 5Kir are tabulated in Table 1.

2.3 Ligand Preparation

An indirect approach used for smoothing of the development of active compounds by studying compounds that will interact with the biological receptor is Ligand based drug design15.Structures of selective COX-2 inhibitors (celecoxib and SC-558) were saved from the PubChem database (http://pubchem.ncbi.nlm.nih) in SDF file format ligands under study were designed from the SAR of chromones and benzimidazole nucleus and prediction of its interaction with COX-2 receptor. They were designed based on synthetic convenience, and possible blends of nucleus and substituent which could provide a good fit. A library of designed compounds was drawn in Chem Draw Pro 12.0, followed by energy minimization by chem3D Pro 12.0. The structures are stored in pdb file format which was then converted to pdbqt by Auto dock software and additional steps like adding all hydrogens, computing charge and setting torsion were performed.

2.4 Molecular Docking

In-silico docking process was carried out on the molecules with 5kir receptor using AutoDock Vina. Stochastic gradient optimization algorithm is used by Vina for predicting the binding affinities between ligands and receptors [13]. Additionally, Discovery Studio (DS) Visualizer 2021 was implemented to envision various intermolecular interactions such as Hydrogen bond, hydrophobic vander waals interaction and pi-pi interactions. Molecular docking involves the selection of three dimensional active binding site of the receptor molecule and calculation of the binding affinity and energy of the resulting orientation of the molecule within the binding site forming a complex [16]. The binding affinity values are determined by the highest binding affinity or lowest binding energy (more negative value) showing the most favorable conformation [17]. The position and orientations of the ligand after docking signify possible binding arrangements of the inhibitors. Out of the several compounds under investigation only those compounds were selected which were having binding energy more negative than -9.0 kcal / mol. The synthetic route and structure of the designed compounds has been illustrated in Fig. 1.

2.5 Estimation of Pharmacokinetics, Drug Likeness Properties, Bioactive Scores and Toxicity

Computational tools are used to identify the newer drug candidate and to decrease the number of experimental researches leading to a rise in the success rate. For this purpose, SwissADME (www.swiss adme.ch/) was used to estimate Lipinski's rule of five for drug-likeness. "The Simplified Molecular Input Line Entry System'' (SMILES) format of the molecules generated by ChemDraw Pro 12 was inserted on the SwissADME webserver to generate their ADME profile and drug-likeness parameters. Next, the bioactivity scores were calculated using molinspiration software [18] and toxicity of the deigned compounds was evaluated by Osiris online tool.

2.6 Prediction of Activity Spectra of Substances (PASS)

Prediction of activity spectra for substances (PASS) is an online server (http://www.way2drug.com/) that was used to predict probable pharmacological effects of compound based on its structural information. This tool is based on the comparative study of <300 pharmacological activities and mechanism of action of different compounds. It gives us the probability of activity (Pa) and inactivity (Pi) values of a particular compound under study [19]. The compounds selected after molecular docking and ADMET analysis were subjected to PASS studies.

Table 1. The Grid Coordinates for Human Cycloxygenase-2 enzyme (PDB id 5Kir)

Protein	Size_x	Size_y	Size_z	Center_x	Center_y	Center_z
5kir	72	50	56	31.397	7.830	35.276

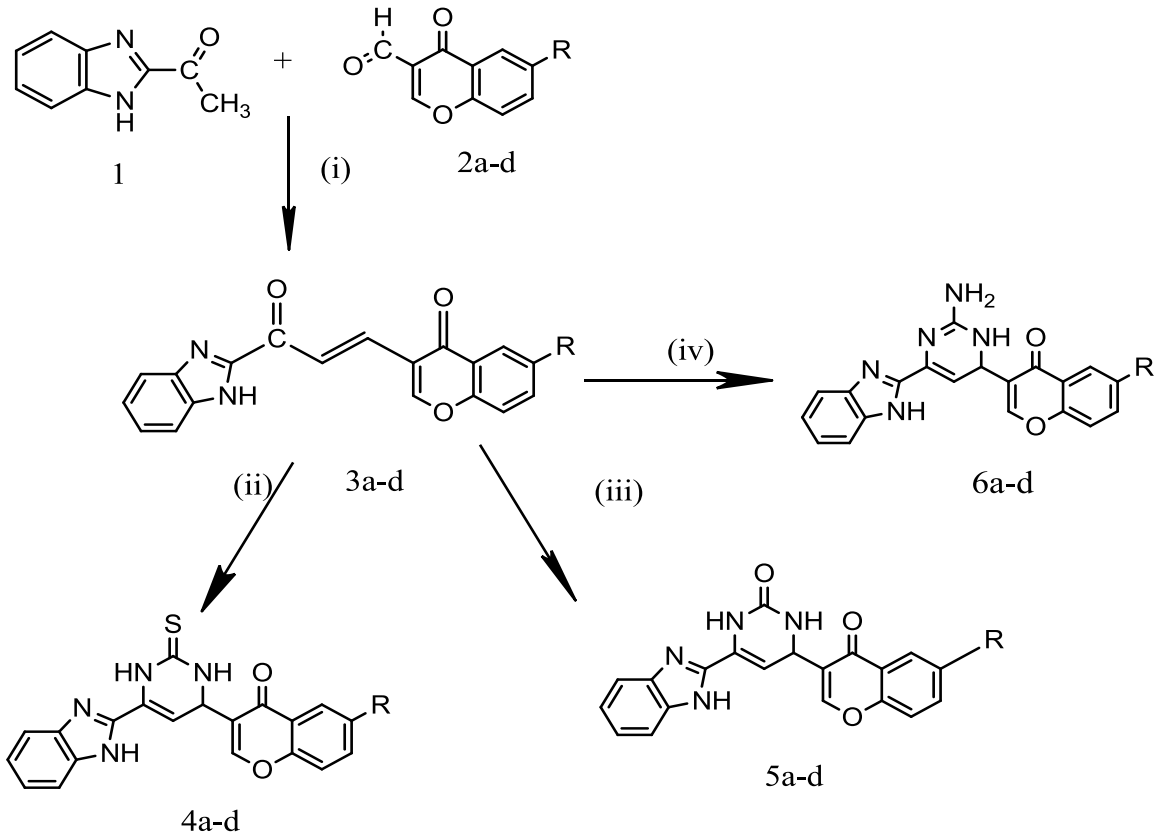

Fig. 1. Synthetic scheme and structures of designed compounds 2-6 a-d

1:2-Acetyl Benzimidazole, **2a-d:** substituted formyl chromone

(i) Clasein schmidt condensation **(ii)** reaction with thiourea **(iii)** reaction with urea **(iv)** reaction with guanidine hydrochloride

3a-d: (E)-3-(3-(1H-benzo[d]imidazol-2-yl)-3-oxoprop-1-en-1-yl)-6-substituted-4H-chromen-4-one derivatives

4a-d: 3-(6-(1H-benzo[d]imidazol-2-yl)-2-thioxo-1, 2, 3, 4-tetrahydropyrimidin-4-yl)-6-substituted-4H-chromen-4-one derivatives

5a-d: 6-(1H-benzo[d]imidazol-2-yl)-4-(6-substituted-4-oxo-4H-chromen-3-yl)-3,4-dihydropyrimidin-2(1H)-one derivatives

6a-d: 3-(2-amino-6-(1H-benzo[d]imidazol-2-yl)-3,4-dihydropyrimidin-4-yl)-6-substituted-4H-chromen-4-one derivatives

3. RESULTS

3.1 Molecular Docking: Binding Energies and Interactions with the Receptor

The results obtained after molecular docking of the various designed ligands as well as the standard compound with the human COX-2 receptor are presented in Table 2.

3.2 Assessment of Molecular descriptive properties

The Data obtained from SwissADME online tool is presented in Table 3, the drug-likeness

properties is being used as the main criteria for the choice of newer molecule at an initial stage of drug discovery [20]. The important parameters for the prediction of good oral bioavailability is good absorption, lower flexibility of the molecule (measured by the number of rotatable bonds) and lower total polar surface area or TPSA (sum of donors and acceptors) [21,22]. Permeability and bioavailability of a compound can be estimated by some simple molecular parameters such as "molecular weight, number of hydrogen bond acceptors and donors, partition coefficient in a molecule'' [23]. Christopher A (1997) gave a major rule that is followed for evaluation of drug likeness. It is called the Lipinski's rule of five or Ro5. This rule is used to decide whether a compound having a certain biological and pharmacological properties could be an orally active drug in the human body [24]. This rule considers a particular compound as a drug moiety if it fulfils the following parameters:

a. number of hydrogen bond donors ≤ 5,
b. number of hydrogen bond acceptors ≤ 10,
c. partition coefficient logP ≤ 5,
d. molecular weight ≤ 500 Daltons.

In case a molecule does not follow more than one of the rules it might not be orally bioavailable [25]. Percentage of absorption can be used to express magnitude of absorption. Absorption percent can be calculated using the expression: %AB =109- 0.345 TPSA. TPSA is determined by Ertl and coworkers' fragment-based method [26]. TPSA is obtained by the addition of polar atoms surface in a molecule and is inversely proportional to % Absorption.

3.3 Calculation of Bioactivity Score Using Molinspiration Toolkit

Bioactivity score the designed compounds against various receptor ligands, inhibitors and enzyme inhibitory activity were estimated using Molinspiration online toolkit (http://www.molinspiration.com) that is summarized in Table 4. If the molecule is having bioactivity score more than 0.00 is possible that it will possess considerable biological activities, values -0.50 to 0.00 are expected to have moderate activity and if score is less than -0.50, it is supposed to be inactive.

3.4 Prediction of drug score and Toxicity by OSIRIS Property Explorer

The data obtained is summarized in Table 5. The drug likeness for a compound should be 0 or positive. The drug score is the combination of drug likeness, lipophilicity, solubility, molecular weight and toxicity risks that evaluates the compound qualifies to be a drug or not.

3.5 Prediction of Activity Spectra of Substances

The selected compounds from the above studies were subjected to PASS prediction for antineoplastic activity and data is tabulated in Table 6.

4. DISCUSSION

The results of molecular docking analysis showed that many of designed molecules exhibited good binding energies in the range of **-9.2 to -10.5 Kcal/mol** compared to **selective COX-2 inhibitors SC-558 and celecoxib** with docking energy of **-9.2 and 9.0 Kcal/mol respectively** as tabulated in Table-2. The compounds marked with asterisk (*) had similar interactions shown by SC-558. The H-bonding distance for most of the compounds was found out to be less than 3 Å and the bond length was lesser than that of SC-558 for example if we compare compound 3c with SC-558 (**Phe210** 2.77 vs 2.98, **His386** 2.54 vs 2.63**, Asn382** 2.26 vs 2.63). This explains the reason why the compounds are having more negative binding energy and are binding tightly to the receptor**.** The **chalcones 3a-d** are having greater binding affinity due to more number of hydrogen bonds compared to the other series.The number of vanderwaal interactions with the surrounding amino acids were also found to be more in the designed compounds. Fig. 2 and Fig. 3 shows the 3D and 2D binding interactions of compounds 3a, 3c, 6a and selective COX-2 inhibitor SC-558. The figures show that compound 3a, 3c and 6a have hydrophobic interactions with 8, 8 and 6 amino acids respectively compared to SC-558 which has interaction with 5 amino acids. Overall the number and length of hydrogen bonds as well as hydrophobic interactions explain the reason for more negative binding energy of the selected compounds.

Table 2. Summary of Results of Molecular docking showing binding Energy (Kcal/mol) and interactions of the designed compound with the target COX-2 receptor (PDB id-5Kir)

Compound Code	Binding Energy measured in kcal/mol	Number of Hydrogen bonds formed	Name and ID of Amino acids involved in Hydrogen Bond interaction	Length of Hydrogen bond measured in Angstroms	Hydrophobic interactions	Pi-Pi interaction
*3a	-9.9	3	Phe210 His386 Asn382	2.85 2.24 2.49	Tyr385,Trp387,Leu390, Gln289,Thr212,His214, Thr206, Gln203	His388, Ala202
*3b	-10.5	3	Phe210 His386 Asn382	2.92 2.30 2.38	Tyr385,Trp387,Gln289,His 214, Thr212, Lys 211, His207, Gln203, Ala199	His388, Ala202
*3c	-10.4	3	Phe210 His386 Asn382	2.77 2.54 2.26	Tyr385, Trp387, Leu391, Gln289, Gln203, Lys211, Thr206, Ala199	His388, Ala202
*3d	-10.6	3	Phe210 His386 Asn382	2.71 2.60 2.23	Tyr385,Trp387,Leu391,Leu390,His388,Gln289,Gln203,Thr 212, Lys211,Ala199	Ala202
*4a	-9.3	1	Gln289	2.46	His388,His386,Tyr385, Asn382, Glu290, Phe210, Thr212, His207	-
*4b	-9.6	1	Gln289	2.42	His388,His386,Tyr385, Asn382, Glu290, Phe210, Thr212, His207	-
*4c	-9.5	1	Gln289	2.44	His388,His386,Tyr385, Asn382, Glu290, Phe210, Thr212, His207	-
*4d	-10.5	2	Gln289 Asn222	2.35 2.72	His388,His386,Tyr385, Asn382, Glu290, Phe210, Thr212, His207	-
*5a	-9.5	3	Gln289 Asn382 Phe210	2.55 2.59 2.06	Gln454,His386,Glu290,Thr212, Tyr148	His214
5b	-10.8	1	Cys36	2.92	Tyr130, Val155, Lys134, Leu152, Gly45, Arg44	Gly135
*5c	-9.5	1	Gln289	2.44	His388,His386,Tyr385, Trp387, Leu390, Gln203,Asn222, His214, Thr212, His207	-
*5d	-10.0	2	Gln289 Asn222	2.39 2.72	His388,His386,Tyr385, Trp387, Leu390, Gln203,Asn222, His214, Thr212, His207	-

Compound Code	Binding Energy measured in kcal/mol	Number of Hydrogen bonds formed	Name and ID of Amino acids involved in Hydrogen Bond interaction	Length of Hydrogen bond measured in Angstroms	Hydrophobic interactions	Pi-Pi interaction
*6a	-9.8	3	Asn382, His386, Thr206	2.36, 2.22, 2.99	Trp387,Tyr385,Phe210, Thr212, His214, Gln203	-
6b	-9.2	4	Asn350 Glu346, Leu359	2.11 1.97,2.67 1.86	Ser581, Lys358, Lys342, Arg109	-
6c	-11.3	1	Cys44	2.45	Tyr130, Val155, Lys134, Leu152, Gly45, Arg44	-
6d	-9.8	1	Glu524	2.92	Arg120, Tyr115, Val116, Lys83, Leu123	-
SC-558	-9.2	6	His386, Asn382 Glu 290, Gln289, Asn222, Phe 210	2.63, 2.55, 2.40, 2.22, 2.01, 2.98	His388, Tyr409,His214, Thr212, Lys211	His207
Celecoxib	-9.0	2	Tyr348 Tyr385	2.99 2.47	Ser530,Phe518, Arg120, His90	Tyr355

**Compounds binding at the active site and showing interactions similar to SC-558*

Phe-Phenylalanine,Tyr-Tyrosine,Thr-Threonine,His-Histidine,Gln-Glutamine,Asn-Asparagine, Trp-Tryptophan, Leu- Leucine, Lys-Lysine, Ala-Alanine, Val-Valine, Ser-Serine, Arg- Arginine, Cys-Cysteine, Glu-Glutamic acid

Table 3. Molecular descriptive properties of designed compounds by SwissADME

Compound Code	MW	iLog P	WLog P	TPSA	HBA	HBD	N rotb	nLV	GI	% AB
3a	316.31	2.46	3.46	75.96	4	1	3	0	High	82.79
3b	330.34	2.87	3.76	75.96	4	1	3	0	High	82.79
3c	350.76	1.88	4.11	75.96	4	1	3	0	High	82.79
3d	361.31	1.65	3.36	121.78	6	1	4	0	High	66.99
4a	374.42	2.39	2.14	115.04	3	3	2	0	High	69.31
4b	388.44	2.61	2.45	115.04	3	3	2	0	High	69.31
4c	408.36	2.63	2.80	115.04	3	3	2	0	High	69.31
4d	419.42	2.15	2.30	129.11	6	2	3	0	Low	64.46
5a	358.35	2.02	1.98	100.02	4	3	2	0	High	74.49
5b	372.38	2.29	2.29	100.02	4	3	2	0	High	74.49
5c	392.80	2.25	2.63	100.02	4	3	2	0	High	74.49
5d	403.35	1.45	1.89	145.84	6	3	3	0	Low	58.69
6a	357.37	2.36	1.58	109.30	4	3	2	0	High	71.29
6b	371.39	2.25	1.89	109.30	4	3	2	0	High	71.29
6c	391.81	2.59	2.24	109.30	4	3	2	0	High	71.29
6d	402.36	1.94	1.49	155.13	6	3	3	0	Low	55.48

MW = Molecular weight; g/mol; lipophilicity (expressed as LogP) iLogP = implicit logPmethod; WlogP = method developed by Wildman and Crippen; TPSA = Topological polar surface area; HBA = Hydrogen bond acceptor; HBD = Hydrogen bond donor; nrotb = no. of rotatable bonds; nLV = no. of Lipinski violation: GI= Gastrointestinal absorption; %AB= percent absorption

Table 4. Bioactivity score of designed compounds by molinspiration software

Compound Code	GPCR ligand	Ion Channel modulator	Kinase inhibitor	Nuclear Receptor ligand	Protease inhibitor	Enzyme inhibitor
3a	0.02	-0.34	-0.15	-0.14	-0.32	0.12
3b	-0.03	-0.42	-0.02	-0.17	-0.35	0.06
3c	0.01	-0.34	-0.17	-0.16	-0.33	0.08
3d	-0.12	-0.35	-0.25	-0.23	-0.41	0.00
4a	-0.50	-0.54	-0.63	-0.77	-0.82	-0.40
4b	-0.52	-0.60	-0.65	-0.77	-0.85	-0.44
4c	-0.49	-0.53	-0.62	-0.77	-0.82	-0.41
4d	-0.57	-0.53	-0.66	-0.78	-0.86	-0.45
5a	-0.23	-0.46	-0.37	-0.49	-0.54	-0.27
5b	-0.26	-0.52	-0.40	-0.50	-0.57	-0.31
5c	-0.23	-0.45	-0.37	-0.49	-0.55	-0.29
5d	-0.33	-0.46	-0.44	-0.53	-0.61	-0.33
6a	-0.07	-0.23	-0.28	-0.61	-0.36	-0.15
6b	-0.10	-0.30	-0.32	-0.61	-0.40	-0.20
6c	-0.07	-0.23	-0.29	-0.61	-0.38	-0.18
6d	-0.19	-0.25	-0.35	-0.64	-0.45	-0.23

Table 5. Toxicity prediction of designed compounds by osiris property explorer

Compound Code	Drug Likeness	Drug Score	Mutagenic	Tumorigenic	Irritant	Reproductive effect
3a	**3.62**	**0.79**	No	No	No	No
3b	2.39	0.72	No	No	No	No
3c	**3.91**	**0.68**	No	No	No	No
3d	-3.01	0.39	No	No	No	No
4a	2.28	0.73	No	No	No	No
4b	1.56	0.63	No	No	No	No

Compound Code	Drug Likeness	Drug Score	Mutagenic	Tumorigenic	Irritant	Reproductive effect
4c	3.10	0.61	No	No	No	No
4d	-3.82	0.35	No	No	No	No
5a	**3.62**	**0.76**	No	No	No	No
5b	2.39	0.69	No	No	No	No
5c	**3.90**	**0.66**	No	No	No	No
5d	-3.00	0.37	No	No	No	No
6a	**3.09**	**0.75**	No	No	No	No
6b	1.85	0.67	No	No	No	No
6c	3.38	0.65	No	No	No	No
6d	-3.54	0.36	No	No	No	No

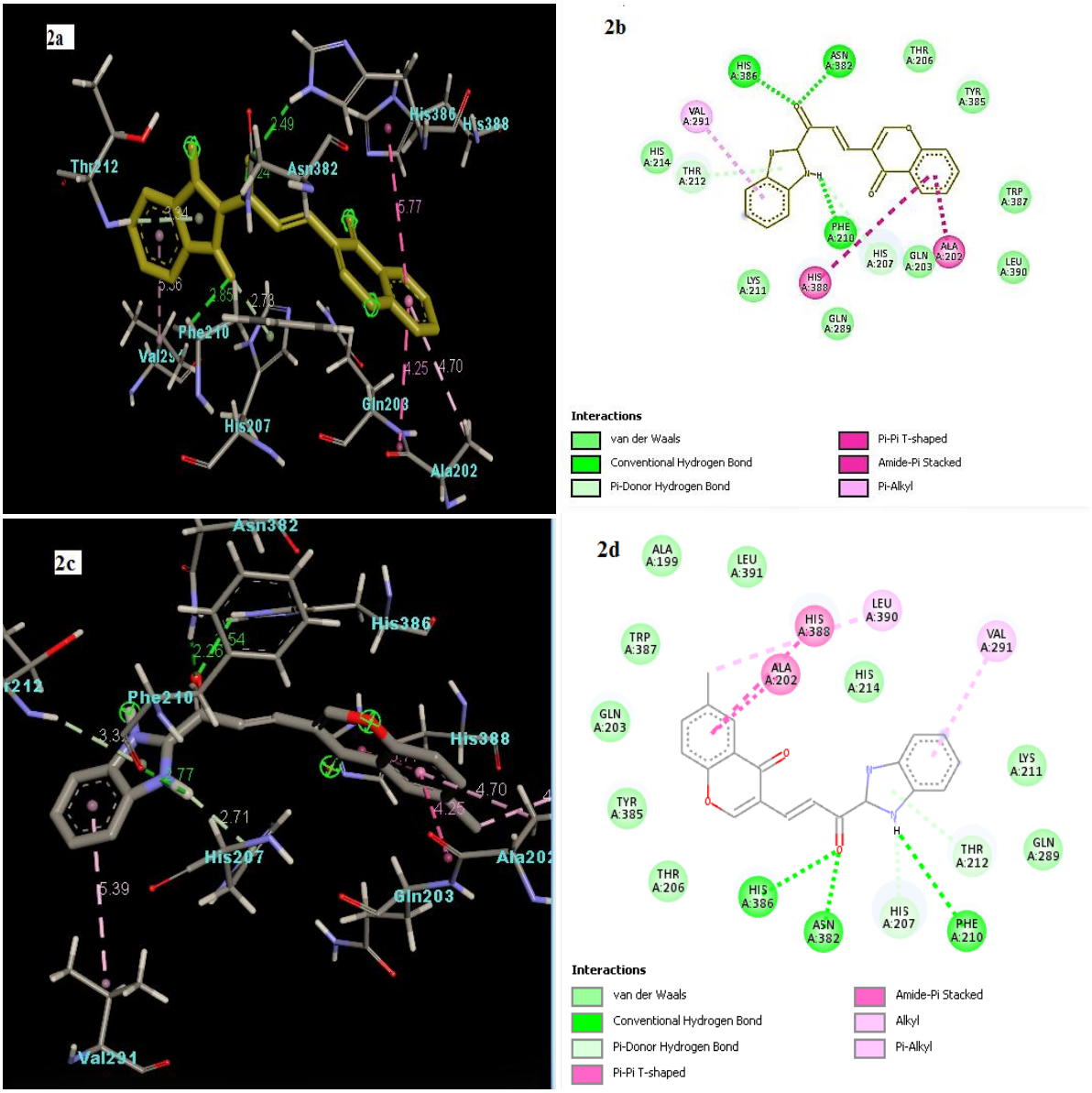

Fig. 2a and 2b. 3D and 2D binding interactions of compound 3a with 5Kir COX-2 protein (Binding energy -9.9 kcal/mol)
Fig. 2c and 2d. 3D and 2D binding interactions of compound 3c with 5Kir COX-2 protein (Binding energy -10.4 kcal/mol)

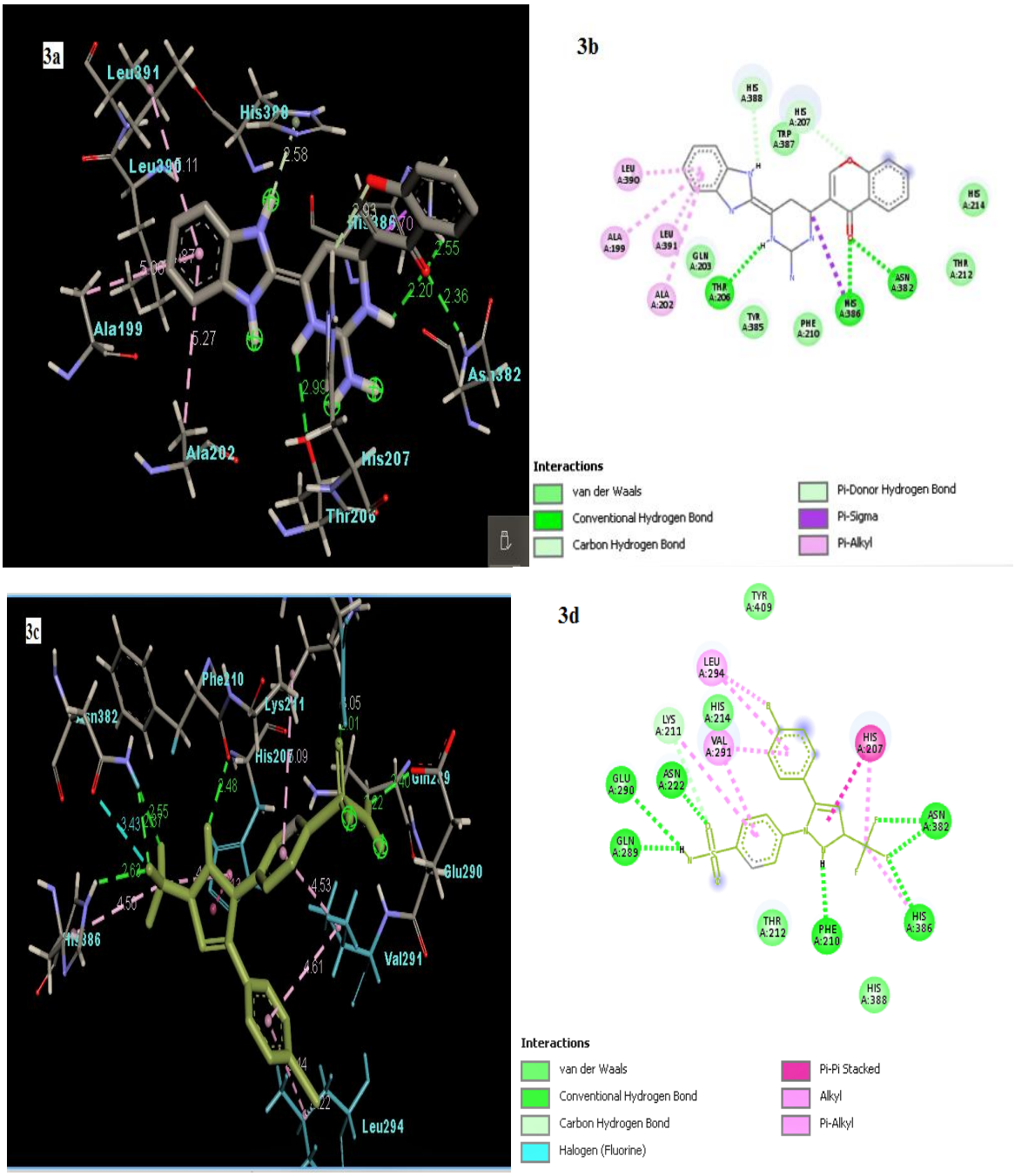

Fig. 3a and 3b. 3D and 2D binding interactions of compound 6a with 5Kir COX-2 protein (Binding energy -9.8kcal/mol)
Fig. 3c and 3d. 3D and 2D binding interactions of COX-2 inhibitor SC-588 with 5Kir COX-2 protein

On the basis of the data obtained from Swiss ADME (Table-4) all the compounds were found to follow Lipinski rule of five signifying the compound to have drug likeness. The absorption was found to be in the range of 55.48 to 82.79%. The compound 3a, 3b, 3c showed the highest absorption (82.79%) whereas the compounds 4d, 5d and 6d ($R=NO_2$) were showing low gastrointestinal absorption. The nitro group appears to decrease the oral bioavailability of the compound. The result was also supported by the data obtained by Osiris Property tool in which drug-likeness model score of 3d, 4d, 5d and 6d was negative, which shows that these

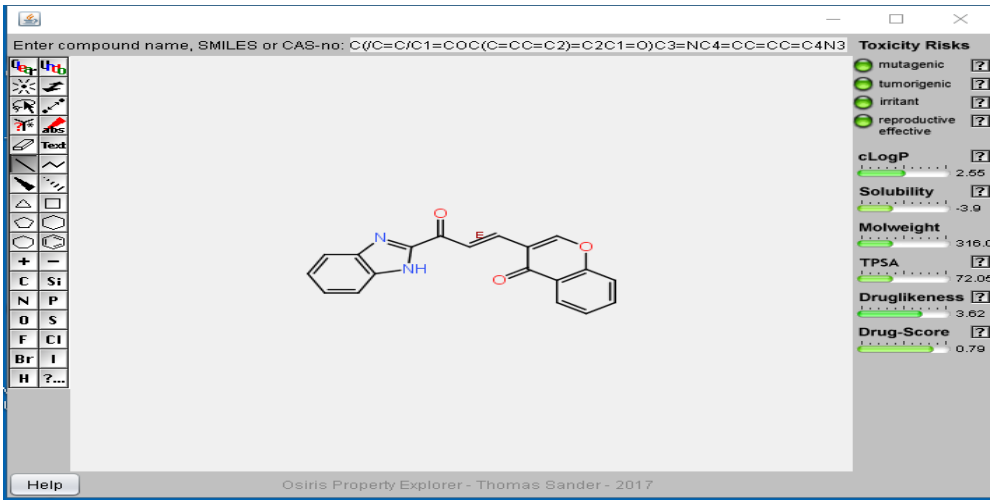

Fig. 4. Screenshot of Osiris software showing Drug likeness and Drug score of compound 3a

compounds are not adequate to be treated like candidate drugs. Some of the compounds having R=H i.e 3a, 5a, 6a have favorable drug likeness and drug score. Osiris screenshot (Fig. 4) shows good drug likeness and drug score of compound 3a.

Table 6. PASS data of the selected compounds

Compound Code	Antineoplastic	
	Pa	Pi
3a	0.321	0.016
3b	0.287	0.020
3c	0.300	0.026
4a	0.635	0.038
4b	0.586	0.048
4c	0.503	0.071
5a	0.530	0.062
5b	0.487	0.075
5c	0.393	0.107
6a	0.700	0.026
6b	0.654	0.034
6c	0.581	0.049

As per PASS prediction the selected compounds have more probability of acting as anti-neoplastic compound and compounds such as 6a, 6b and 6c have higher probability of anticancer activity.

5. CONCLUSION

The present study can be summarized as the designing of novel COX-2 selective inhibitors and analysis of the compounds through ADMET filters and molecular docking studies. From a library of designed compounds 16 compounds were chosen which had binding energy more negative than -9.0 kcal/mol and having interactions similar to selective COX-2 inhibitors. The compounds were having more negative binding energy and hydrogen bond distance less than 3Å showing more binding affinity of compounds towards the receptor. The results of ADMET showed that the designed compounds followed Lipinski rule of five. Compounds having R=H, 6-$CH_3$and 6-Cl were having better drug likeness, drug score and good oral absorption whereas compounds having R=6-NO_2 did not comply with the drug likeness parameters and were also showing low absorption. Therefore compounds 3d, 4d, 5d 6d were excluded from further PASS prediction study. A number of compounds had bioactivity scores between -0.50 and 0.00 against various receptors and enzyme inhibitors showing moderate activity. After summation of overall result it can be concluded that compound 3a, 3c, 5a, 5c and 6a have similar binding interactions in comparison to SC-558, good oral bioavailability, favorable bioactivity score, adequate drug likeness, drug score and higher probability that they can possess anti-cancer activity. Few of the selected compounds could serve as lead compound for the development of newer COX-2 inhibitors which can act as potent anti-cancer agents

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of

knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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