Journal of Computational Methods in Molecular Design, 2015, 5 (1):1-14

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ISSN : 2231- 3176
CODEN (USA): JCMMDA

In silico study of chalcone binding to cyclooxygenase-1 (Cox-1) by HEX 6.3.

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ABSTRACT

The development of new drugs with potential therapeutic applications is one of the most complex and difficult process in the pharmaceutical industry. Millions of dollars and man-hours are devoted to the discovery of new therapeutical agents. Recently, impressive technological advances in areas such as structural characterization of molecules, computer sciences and molecular biology have made rational drug design feasible. The Protein- Ligand interaction plays a significant role in structural based drug designing. Chalcones and their derivates have been shown to have potency as anticancer. Chalcone is a flavonoid compound, analogs of this drug molecule were selected from published journals and docked with COX-1 (PDB ID: ICQE) using HEX software. Furthermore, these docking processes were obtained the lowest scoring value in chalcone-30. The substituent compatibility and then ADME properties of the Analogs was analyzed using Insilico. Analysis of the results of the docking softwares suggested that chalcone-30 can act as a potent COX-1 inhibitor, than the screened 50 chalcones.

Keywords: Chalcone, docking, COX-1, Arguslab, HEX 6.3

INTRODUCTION

Computational biology and Bioinformatics have the potential to speed up drug discovery processes, reducing the costs of the processes and changing the way the drugs are designed. Rational drug design facilitates and speeds up the drug designing processes that involves various method of identifying novel compounds. Thus computational biology or Insilico approach is developing day by day with refinement. It is becoming a promising field and with the help of this the time and cost of biological work related to drug discovery, molecular interaction is reducing. The computational techniques employed to aid the drug design process include virtual screening, docking, and scoring with the results or "hits" utilized by medicinal chemists. There are various tools, softwares and servers meant for docking calculations [1]. Docking is a technique of placing a drug candidate into the active site of a receptor. The docked pose of a ligand in the active site of a receptor can be scored using knowledge-, empirical, or physics-based methods with the latter being more expensive [2]. The compounds that make it through docking, scoring, and evaluation become drug leads, and are then passed on to undergo drug testing techniques by scientists in a wet lab, to ensure that only compounds with effects relatively unique to the target system and safe to the rest of organism are considered. However, the drug company has already saved much time and money up to this point by having computers do chemical screening, rather than human scientists [3].

Worldwide about 20 million people per year are diagnosed with cancer and more than 6 million mortalities are recorded and rate of cancer incidences increases every year. Till date large number of herbal products has been screened for their anticancer potential through various experimental models. This has caused the discovery of the

several drugs by the pharmaceutical and scientific communities [4]. Cancer is a leading cause of death in developed and developing countries. The current research in cancer is focused on the identification of new and unequivocal target for the development of novel anticancer agents. Cyclooxygenase (COX) enzymes are widely used to determine the anticancer effects of potential therapeutic products [5]. COX-1 and COX-2 are two isoforms of Cyclooxygenase, which are involved in the metabolism of prostaglandins by transforming arachidonic acid (AA) into PGH2. This enzyme bis-oxygenates AA to PGG2, which is subsequently degraded to vasoactive and inflammatory mediators such as prostaglandins (PGs), prostacyclin (PGI2), and thromboxane-A2. Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain.

Mainly isoform two of Cyclooxygenase (COX-2) is a major therapeutic target for inflammatory diseases since its selective inhibition has been shown to prevent prostaglandin synthesis at the inflammatory sites while producing reduced gastrointestinal and renal side effects. Indeed, the nonselective COX-2 drugs are inhibiting both the constitutive COX-1 isoform, which is involved in the gastrointestinal and renal homeostatic functions, and the inducible COX-2 enzyme expressed specifically during the inflammatory events. Most of the research going on selective inhibition of COX-2 over COX-1 is beneficial for treatment of inflammatory diseases with reduced ulcerogenic side effects. Therefore, selective inhibition of COX-2 over COX-1 is beneficial for treatment of inflammatory diseases with reduced ulcerogenic side effects.

But the recent reports shows that inhibition of both COX-1 and COX-2 is important in reduce the production 'Bad' prostaglandin. Specific inhibition of COX-2 has been extensively investigated, but relatively few COX-1 selective inhibitors have been described. Recent reports of a possible contribution of COX-1 in analgesia, neuroinflammation, or carcinogenesis suggest that COX-1 is a potential therapeutic target [6].

Chalcones are natural or synthetic trans-1,3- diaryl-2-propen-1-ones (Figure 1) belonging to the flavonoid family of natural products. Chemically, they contain an open-chain flavonoid skeleton in which two aromatic rings are linked by a three-carbon α,β-unsaturated carbonyl system [7].

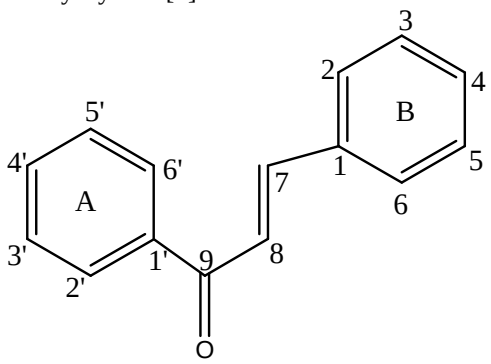

Fig.1 General chemical Structure of Chalcones

They have been reported to possess many useful properties including anti-inflammatory, antimicrobial, antioxidant and anticancer activities, therefore representing a class with enormous therapeutic potential. Anti-inflammatory activity of these compounds is manifested by their interaction with a number of targets; some of which include inducible nitric oxide synthase (iNOS), nuclear factor-κB (NF-κB), heme oxygenase (HO) and cyclooxygenase (COX). Among these, cyclooxygenase (COX), also known as prostaglandin H synthase (PGH synthase/PGHS/PHS) is a prominent and well studied protein catalyzing the conversion of arachidonic acid to prostaglandin H2 (PGH2), the committed step in prostaglandin (PG) biosynthesis [8]. The severe gastrointestinal (GI) side effects of the traditional non-steroidal anti-inflammatory drugs (NSAIDs) are attributed to their non- selective inhibition of COX [9].

HEX is an interactive molecular graphics program for calculating and displaying feasible docking modes of pairs of protein and DNA molecules. Hex can also calculate small-ligand/protein docking (provided the ligand is rigid), and it can superpose pairs of molecules using only knowledge of their 3D shapes. The HEX docking program was used to dock the chalcone molecule with COX-1 protein. The observed results are discussed in this paper.

MATERIALS AND METHODS

3.1. TOOLS AND BIOINFORMATICS SOFTWARE'S USED

The targeted protein (ID: 1CQE), having the resolution of 1.80 A^o was retrieved from the protein data bank (PDB) (www.rcsb.org/pdb). The softwares used for the docking studies were, ArgusLab 4.0.1, Chemsketch, Q-site finder, Hex 6.3, Discovery studio 4.0, Molinspiration Server, Osiris Property Explorer.

3.2. PROTOCOL FOLLOWED

3.2.1. Preparation of Protein

Retrieval of Protein (PDB ID: 1CQE) from RSCB Brookhaven protein data bank, then hetero atoms (Ligands), side chains and water molecule are removed from protein by using Discovery studio 4.0, then it is saved as modified 1cqe.pdb, active site was identified by Q-site finder. Active sites are selected and defined as binding site in Discovery studio 4.0. and saved as modified 1cqe.ds.

3.2.2. Preparation of Ligands

A collection of 50 Chalcones molecules from Published Journals, drug bank are selected and their 2D structure was drawn and converted into 3D structure in Chemsketch. The selected 3D chalcone was saved as ligand.mol format. Geometry and energy optimization were done by PM3 Method by using ArgusLab and saved the Optimized structure in Ligand.pdb format. The Protein was visualized in discovery studio 4.0.

3.2.3. Active Site Prediction by Q-site finder

Q-Site finder is a method for ligand binding site prediction; it works by binding hydrophobic (CH) probes to the protein, and finding clusters of probes with the most favorable binding energy. The URL for this database is http://www.modelling.leeds.ac.uk/qsitefinder/ [10]. The above URL was browsed. In the search option 1CQE name was typed, enter the 1CQE in PDB ID box. Treat as ligand selection will removes the ligand from the protein before binding site analysis, but retained in the final output, then submit the job.

3.2.4. Define Binding Site in Protein

Discovery studio 4.0 window was opened, open modified **1CQE.pdb. T**he molecule tree view tool of modified 1CQE was expanded (located on the left side on the screen) and open up the folder and Right-click on amino acids which is predicted by Q-site finder in the tree view and select the, "Make a Binding site Group from this Residue" option. Discovery studio 4.0 will construct a group underneath the Groups folder with the name "3 MOL" that is of type = Binding Site. File > Save as > Select Save as file type in the open dialog Discovery studio 4.0 file (*dsv,*.xml) > Type the File name = Modified 1CQE with Binding site.dsv > Save.

3.2.5. Preparation of Ligands

All the Chalcones (Ligands) used for docking study were selected from Published Journals. The structure of the 50 Chalcones was drawn by using ChemSketch (ACDLABS 12.0). The ChemSketch, chemically intelligent drawing interface freeware developed by Advanced Chemistry Development, Inc., (http://www.acdlabs.com) was used to construct the structure of the ligands [11]. ChemSketch window was opened and Ligand Structure was drawn. After this it is cleaned Tool > Clean Structure, followed by Tool > Generate > SMILES Notations, (By this operation, Smile notation of drawn structure will be generated and displayed below the drawn structure, it is used to determine the molecular properties by Molinspiration server.). Select the Generated Smile Notation > Cut (Ctrl+X) > Notepad new window was opened > paste (Ctrl+V) > Saved as word file. Tool > 3D Structure Optimization > Save > Select Save as file type in the open dialog [MDL Molfiles V2000 (*.mol)] > Type the File name = Ligand.mol > Save.

3.2.6. Geometry and Energy Optimization of Ligand

All the quantum mechanical calculations of Ligands and Molecular visualizations were carried out using Arguslab 4.0.1. i ArgusLab Window was opened, ii. File > Open > Select file type in the open dialog MDL MOL file (*mol) > Open, iii. Edit > Clean Geometry File > Calculation > Optimize Geometry... > Select. UFF Underneth MM > Start.. (UFF: The Universal Force Field of Rappe's and coworkers. This is a molecular mechanics (MM) force field and includes parameterization for the entire periodic table). After the UFF optimization, again ligand structure is optimized by PM3 method. Calculation > Optimize Geometry... > Click PM3, Molecular orbital and Dipole moment > Start. **(PM3:** The Parameterized Method 3 parameterization of the MNDO method. This is an NDDO Semi empirical Hamiltonian). Edit > Save As in both format Ligand.agl and Ligand.pdb [12].

3.2.7. DOCKING BY HEX 6.3

HEX 6.3 was used as the docking tool, which calculates intermolecular "energies" by adding up all intermolecular interactions (e.g. vander Waals, electrostatic) that occur between a ligand and protein target. HEX calculate protein - ligand docking, assuming that the ligand is rigid through spherical polar Fourier (SPF) correlations to accelerate the calculations in their 3D shapes. In Hex's docking calculations, each molecule is modelled using 3D expansions of real orthogonal spherical polar basis functions to encode both surface shape and electrostatic charge and potential distributions, it represents the surface shapes of proteins using a two-term surface skin plus vander Waals steric density model, whereas the electrostatic model is derived from classical electrostatic theory. (Protein Docking Using Spherical Polar Fourier Correlations Copyright 1996-2010 David W. Ritchie) [13]. Hex manual window was opened, from the file, both receptor and ligand separately were opened from the path location defined. By the option control, docking was selected and activated. Lastly the binding energy (AE) produced by docking action was saved carefully. The docking complex was saved from the file option in the .pdb format for future analysis.

3.2.8. MOLINSPIRATION

The URL for this database is http://www.molinspiration.com/cgi-bin/properties [14]. The above URL was browse, in the Enter SMILES box option, smiles of chalcones is pasted which is saved in Notepad. Enter Calculated Properties and Predict Bioactivity option. Properties of chalcones will be displayed & collect the data.

3.2.9. OSIRIS PROPERTY EXPLORER

The OSIRIS Property Explorer (March 26th, 2014: Version 2 has been published) lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color-coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green color indicates drug-conform behavior [15]. In certain cases, you must allow to run this applet - for example by clicking the "no entry" symbols. The updated version now predicts logP more accurately and converts SMILES strings and compound names into structures.

RESULTS AND DISCUSSION

4.2. MOLECULAR PROPERTIES PREDICTION

4.2.1. Molinspiration

The chemical names of selected 50 chalcones are tabulated in the table 1. Physicochemical parameter such as TPSA (Topological polar surface area), MW (Molecular weight), and Drug Likeness & LogP (octanols /water partition coefficient) was calculated by the methodology developed by *Molinspiration* software. These Parameters play a vital role in generation and determination of bioactivity of chemical entity.

The molecular descriptor study was performed on basis of "Lipinski's Rule of Five" using the *Molinspiration* server. Lipinski's Rule of Five is a rule of thumb to evaluate drug likeness or determine if chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A Lipinski. The Rule describes molecular properties important for a drugs pharmacokinetics in the human body, including their absorption, distribution, metabaolism and excretion ("ADME"). Lipinski's Rule of Five states that, in general, an orally active drug has [16]: 1. Not more than 5 hydrogen bond donors (OH and NH groups). 2. Not more than 10 hydrogen bond acceptors (notably N and O). 3. Not more than 15 Rotatable bonds (nrotb). 4. A molecular weight under 500 g/mol. 5. A partition coefficient log *P* less than 5.

Software Version: Molinspiration property engine v2013.09

The following result are obtained from molinspiration server. The table 2 shows that the calculated property of chalcones through molinspiration server. The calculated value of logP, TPSA, natom, MM (g/mol), Non, nOHNH, nviolation, Nrotb and Volume of reported. All the selected chalcones obey the liplnski rule and have drug likeness property. Where LogP- Octanal /water partition coefficient, natom- No.of atoms other than hydrogen, nOH- No.of hydrogen bond, nON-No. of hydrogen bond acceptor, nrotb-No. of rotatable bonds. TPSA - Topological polar surface area.

4.2.2. Drug Likeness

Drug likeliness is a qualitative means of analysis to check whether the given molecule is a drug or not and it is defined as a complex balance of various molecular properties and structural features which determine whether a

particular molecule is similar to the known drugs. Activity of all test compounds were analyzed under six criteria of known successful drug activity in areas of GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor by the molinspiration software [17]. Software Version: Molinspiration Bioactivity Score v 2011 The following result are obtained from Molinspiration server Table 3 shows that the bioactivity of 50 chalcones calculated by molinspiration bioactivity score v 2011.0.

4.2.3 OSIRIS Property Explorer

The OSIRIS Property Explorer is an integral part of Actelion's in-house substance registration system. It lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and colour coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green colour indicates drug- conform behaviour. The OSIRIS property explorer lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. The calculated drug -relevant property of 50 chalcones were tabulated in table 4 almost all the chalcones have drug-relevant property.

4.2.4. Molecular properties by ArgusLab

The orbital energies of frontier orbitals, namely, highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies of the compounds are critical for pharmacological activity. The prediction of the potential energies (E_{HOMO} and E_{LUMO}), geometry optimization of structures were performed by using Argus Lab software (Barua et *al.,* 2012, Peng *et al.,* 1995). The knowledge of the shape and electron density of a molecule helps to assess the nature of the binding of a drug to target site. The 3D structures of the compounds were geometry optimized using PM3 semi-empirical QM method. The Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO) energy values of 50 chalcones were estimated using PM3 method.

The table 5 shows the electronic parameters of optimized structures. All the chalcones have close relationship and drug likeness property. The highest energy gap the chalcone was chalcone-30 and the lowest one was chalcone-46. The chalcone-30 also have higher dipole moments than other chalcones.

RESULTS

The docking of chalcones with COX -1 (1CQE) receptor by Hex 6.3 software are tabulated (Table 6). The docking energy, no.of H-bonds formed and no.of rotatable bonds are calculated from the docking structure. The observed results shows that chalcone-30 have lowest docking energy. The chalcone-30 may be one of the best chalcone to inhibit COX-1 activity. These theoretical study may be helpful to clinical study of chalcone against COX-1. The order of chalcone docking energy with COX-1 was 30 > 45 > 36 > 31 > 7.

Table 7 shows the interaction site of chalcone with COX-1. the bond distances between the chalcone and the interaction COX-1 site were measured and tabulated in the table 7. The highest occupied molecular orbited (HOMO) value (-0.377902 a.u), and lowest unoccupied molecular orbital (LUMO) value (-0.086278 a.u) of chalcone-30 was reported. This energy value was critical for pharmacological activity.

In the drug bank the search is given for wound healing to find the drugs that are used to treat the disease, nearly 13 drugs were available (Table 1). Chalcone is the drug which binds on the 1CQE receptor. The chemical structure of the chalcones drug is retrieved from the NCBI PubChem compound. Chalcones has molecular weight of 208.26 g/mol, and 4 Hydrogen bond donor and 5 hydrogen bond acceptor. The chemical structure is then drawn in the chemsketch and the data is transferred to mol.page. In the mol.page the search is given to get the hits of the drug compound chalcones which are called as ligands. These compound are saved in the PDB - Extension in order to perform docking in Hex 6.3.

The docking control is done by using HEX-Tool (Fig: 2). The Hex Message showed the clusters formed and maximum and minimum energy during docking process. The maximum clusters are shown by the complex 1CQE and (2E)-1-(2,4- dihydrooxyphenyl)-3-(2-hydroxylphenyl)pro-2-en-1-one. (Table 1, Fig. 3) E-Value -223.70 Kcal/mol.

50 clusters formed during the docking process of the 1CQE and chalcones (Table 1, Fig 3). The docked complex were saved as PDB file. The docked complex is then opened in discovery studio 4.0 (Fig 2) and the color is selected by chain in order differentiate the helical structure of the 1CQE and chalcone.

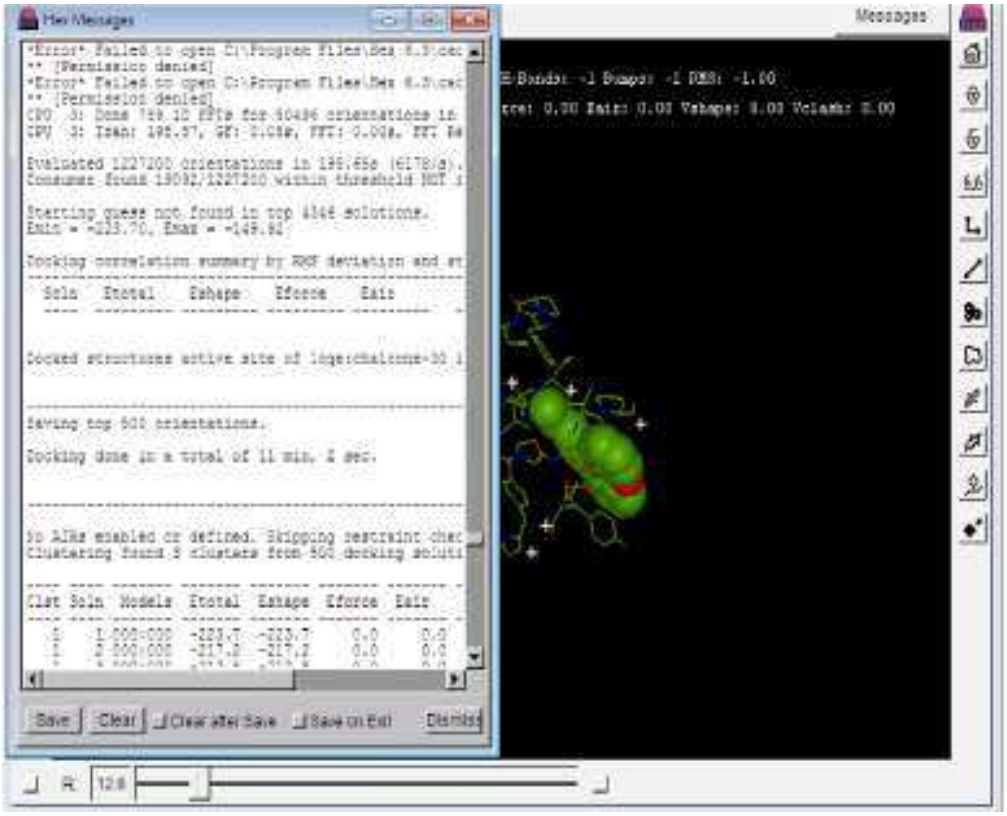

Fig: 2 The hex message after docking which shows the clusters formed and minimum and maximum energy of Chalcone-30 with COX-1 (1CQE).

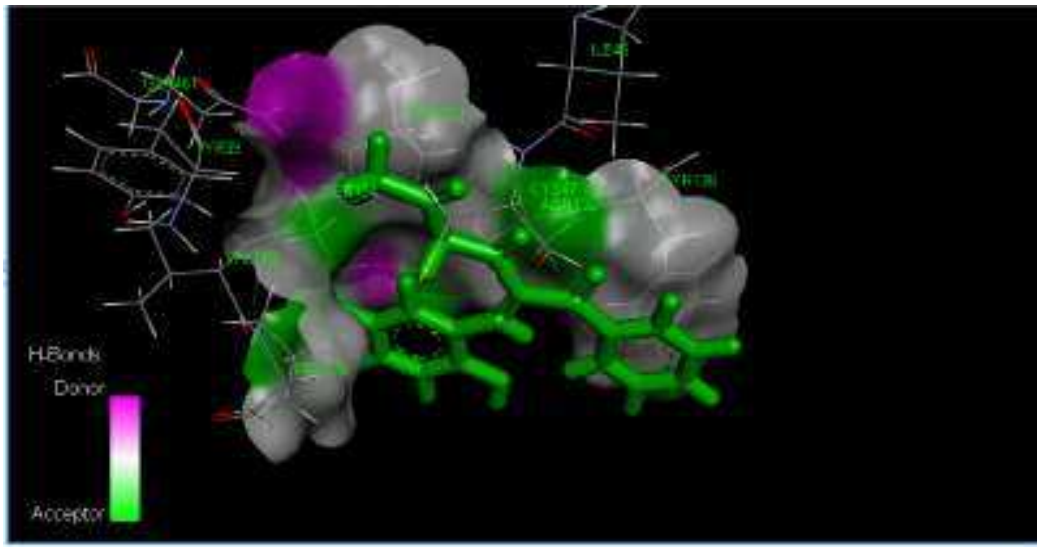

Fig: 3 The docked complex of Chalcone-30 with COX-1 (1CQE) showing the interacting amino acids by discovery studio 4.0.

Then the chalcone is selected and the search is given to find the interacting amino acids with the selected angstrom units. The Q SITE FINDER is the active site analysis tool (Table 3.1) the PDB -ID of the protein 1CQE is uploaded in the Q SITE FINDER. The 3D structure of the protein is viewed along with its binding pockets. This 1CQE protein contains binding pockets and the amino acids.

Docked pose of cyclooxygenase-1 (COX-1) enzyme with the standard chalcone-30 and 2 amino acid (154SER, 461GLN) was shown in Fig 3 which demonstrated the binding position of the ligand. The enzyme is yellow dotted line showing the polar interaction between ligand and enzyme active site. In most of the protein anti-inflammatory compounds have hydrogen bond. The potential binding sites of COX-1 (1CQE) was found that (154SER, 461 GLN) amino acid. This proves that the effective binding sites are presented in the selected Chalcone-30.

Table -1 The studied chemical structures of 50 chalcones

S.No.	IUPAC Name	S.No.	IUPAC Name
1	(2*E*)-1,3-diphenylprop-2-en-1-one	26	(2*E*)-1-(4-hydroxy-2-methylphenyl)-3-(5-methoxy-2-methylphenyl)prop-2-en-1-one
2	3-[(2*E*)-3-phenylprop-2-enoyl]benzoic acid	27	(2*E*)-1-[3-(2-amino-1-isocyanoethyl) phenyl] -3-(2-ethylphenyl)prop-2-en-1-one
3	(2*E*)-1-(naphthalen-2-yl)-3-(2,4,5-trimethoxyphenyl)prop-2-en-1-one	28	(2*E*)-1-(3-acetylphenyl)-3-(2-ethyl-6-methoxyphenyl)prop-2-en-1-one
4	(2*E*)-3-(2-hydroxyphenyl)-1-(naphthalen-2-yl)prop-2-en-1-one	29	methyl 3-[(1*E*)-3-(3-formylphenyl)-3-oxoprop-1-en-1-yl]-5-hydroxybenzoate
5	(2*E*)-3-(2,4-dimethoxyphenyl)-1-phenylprop-2-en-1-one	30	(2*E*)-2-(2-hydroxybenzylidene)-1-phenylhexane-1,3,5-trione
6	(2*E*)-3-(2,4-dimethoxyphenyl)-1-(naphthalen-2-yl)prop-2-en-1-one	31	(2*E*)-1-(1,1-diamino-1 5-pyridin-3-yl)-3-[(7*R*)-2-oxaspiro[5.5]undeca-3,8,10-trien-7-yl]prop-2-en-1-one
7	(2*E*)-3-(3-aminophenyl)-1-[6-(trifluoro methyl)naphthalen-2-yl]prop-2-en-1-one	32	{3-[(1*E*)-3-(2-aminophenyl)-3-oxoprop-1-en-1-yl]phenyl}sulfamic acid
8	3-[(2*E*)-3-(2-hydroxyphenyl)prop-2-enoyl]phenyl hydrogen sulfate	33	(2*E*)-1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one
9	(2*E*)-1-(3-aminophenyl)-3-(3-azidophenyl)prop-2-en-1-one	34	3-[(1*E*)-3-(3-aminophenyl)-3-oxoprop-1-en-1-yl]phenylthiocyanate
10	(2*E*)-1-(2-methoxyphenyl)-3-(naphthalen-2-yl)prop-2-en-1-one	35	(2*E*)-3-(4-hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)prop-2-en-1-one
11	(2*E*)-1-(2-ethenylphenyl)-3-phenylprop-2-en-1-one	36	(2*E*)-3-[4-(3-hydroxypropoxy)phenyl]-1-phenylprop-2-en-1-one
12	(2*E*)-1-(2-methylphenyl)-3-(3-methylphenyl)prop-2-en-1-one	37	(2*E*)-3-(3-ethenyl-4-methylphenyl)-1-(3-hydroxycyclohexa-1,5-dien-1-yl)prop-2-en-1-one
13	3-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]benzoic acid	38	(2*E*)-3-[4-(aminomethyl)-3-fluorophenyl] -1-phenylprop-2-en-1-one
14	3-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]benzaldehyde	39	(2*E*)-3-(1,3-dihydro-2-benzothiophen-5-yl)-1-phenylprop-2-en-1-one
15	3-[(2*E*)-3-(3-chlorophenyl)prop-2-enoyl]benzamide	40	ethyl 3-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]benzoate
16	4-chloro-3-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]benzenesulfonamide	41	(2*Z*)-1,3-diphenylpent-2-ene-1,4-dione
17	(2*E*)-1-phenyl-3-(5,6,7,8-tetrahy dronaphthalen-2-yl)prop-2-en-1-one	42	(2*E*)-1-(2,4-dihydroxyphenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one
18	(2*E*)-1-(3-chloro-4-nitrosophenyl)-3-phenylprop-2-en-1-one	43	1-(2,4-dihydroxy-6-methylphenyl)-3-(3-hydroxyphenyl)propan-1-one
19	*N*-{2-bromo-6-[(2*E*)-3-phenylprop-2-enoyl]phenyl}acetamide	44	3-chloro-4-methyl-5-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]phenyl cyanate
20	(2*E*)-3-phenyl-1-[4-(trifluoromethyl) phenyl]prop-2-en-1-one	45	(2*E*)-1-phenyl-3-[4-(tetrahydro-2*H*-pyran-2-yl)phenyl]prop-2-en-1-one
21	(2*E*)-1-(4-ethylphenyl)-3-phenylprop-2-en-1-one	46	*tert*-butyl 3-[(1*E*)-3-oxo-3-phenylprop-1-en-1-yl]benzoate
22	(2*E*)-1-(3-methoxyphenyl)-3-phenylprop-2-en-1-one	47	(2*E*)-3-(1-benzofuran-6-yl)-1-phenylprop-2-en-1-one
23	(2*E*)-3-(2-hydroxy-5-methylphenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one	48	(2*E*)-1-(3-ethynylphenyl)-3-phenylprop-2-en-1-one
24	(2*E*)-3-[4-(aminooxy)-2-hydroxy phe nyl]-1-(4-chlorophenyl)prop-2-en-1-one	49	(2*E*)-3-phenyl-1-[6-(trichloromethyl) pyridin-3-yl]prop-2-en-1-one
25	(2*E*)-3-[2-(aminomethyl)-5-chlorophenyl] -1-(3,4-dihydroxyphenyl)prop-2-en-1-one	50	(2*E*)-2-methyl-1,3-diphenylprop-2-en-1-one

Table - 2 : Molecular Properties calculation of chalcones by molinspiration server Molinspiration property engine v2013.09

Ligand	LogP	TPSA(A 2)	natom	MM(g/mol)	Non	nOHNH	nviolation	Nrotb	Volume
1	3.81	17.0	16.0	208.26	1	0	0	3	201.85
2	3.69	54.37	21.0	252.26	3	1	0	4	228.54
3	3.76	77.75	23.0	256.39	4	3	0	3	269.89
4	4.75	37.29	21.0	274.31	2	1	0	3	253.86
5	3.67	35.53	20.0	268.31	3	0	0	5	252.94
6	4.85	35.53	24.0	318.37	3	0	0	5	296.93
7	4.91	43.09	25.0	341.33	2	2	0	4	288.43
8	0.66	10.9	22.0	320.32	6	2	0	5	258.30
9	3.88	92.84	20.0	264.28	5	2	0	4	238.03
10	5.00	26.30	22.0	288.34	2	0	0	4	271.39
11	4.43	17.07	18.0	234.29	1	0	0	4	229.58
12	4.63	17.01	18.0	236.31	1	0	0	3	234.97
13	3.69	54.37	19.0	252.26	3	1	0	4	228.85
14	3.57	34.14	18.0	236.27	2	0	0	4	220.83
15	3.26	60.16	20.0	285.73	3	2	0	4	245.66
16	2.93	77.23	21.0	321.78	4	2	0	4	258.10
17	4.99	17.07	20.0	262.35	1	0	0	3	258.21
18	4.31	46.50	19.0	271.70	3	0	0	4	230.21
19	3.74	46.16	21.0	344.20	3	1	0	4	267.68
20	4.70	17.07	20.0	276.25	1	0	0	4	233.15
21	4.72	17.07	18.0	236.37	1	0	0	4	235.21
22	3.84	26.30	18.0	238.28	1	0	0	4	227.39
23	3.93	57.52	19.0	254.28	3	2	0	3	234.44
24	3.66	72.55	20.0	289.71	4	3	0	4	243.67
25	2.45	83.55	21.0	303.74	4	4	0	4	259.51
26	3.96	46.53	21.0	282.33	3	1	0	4	268.53
27	-3.58	47.45	23.0	304.39	3	2	0	6	302.22
28	4.38	43.37	7 30	308.37	3	0	0	6	296.30
29	3.19	80.67	0 310	310.30	5	1	0	6	273.38
30	2.49	71.44	23.0	308.83	4	1	0	6	281.12
31	-0.03	78.35	23.0	311.38	5	4	0	3	292.01
32	0.13	10.49	22.0	318.35	6	4	0	5	264.99
33	3.75	37.29	17.0	224.25	2	1	0	3	209.87
34	-2.95	21.43	18.0	233.27	2	0	0	3	223.94
35	2.68	97.98	20.0	272.25	5	4	0	3	233.92
36	4.80	26.30	20.0	270.37	2	0	0	6	278.10
37	3.34	37.29	20.0	266.34	2	1	0	4	260.37
38	3.08	43.09	19.0	255.29	2	2	0	4	234.87
39	4.06	17.07	19.0	266.36	1	0	0	3	242.4
40	4.33	43.37	21.0	280.32	3	0	0	6	263.1
41	2.86	34.14	19.0	250.29	2	0	0	4	237.39
42	3.00	77.75	19.0	256.25	4	3	0	3	225.39
43	3.09	77.15	20.0	272.30	4	3	0	4	248.65
44	4.43	50.09	21.0	297.74	3	0	0	4	257.79
45	4.66	26.30	22.0	292.37	2	0	0	4	284.03
46	5.10	43.37	23.0	308.37	3	0	0	6	296.00
47	4.11	30.21	19.0	248.28	2	0	0	3	227.41
48	3.55	17.07	18.0	232.28	1	0	0	3	224.11
49	4.46	29.96	20.0	326.61	2	0	0	4	254.80
50	4.35	17.07	17.0	222.28	1	0	0	3	218.41

Table - 3 Bioactivity Score of Chalcones by Molinspiration Server Molinspiration Bioactivity Score v 2011.0

Ligand	GPCR Ligand	Ion Channel modulator	Kinase Inhibitor	Nuclear Receptor ligand	Protease inhibitor	Enzyme Inhibitor
1	-0.43	-0.18	-0.66	-0.51	-0.60	-0.120
2	-0.17	-0.13	-0.43	-0.04	-0.30	0.06
3	-0.01	-0.12	-0.15	0.07	-0.13	0.08
4	-0.07	-0.12	-0.22	-0.01	-0.18	-0.07
5	-0.23	-0.27	-0.40	-0.23	-0.40	-0.10
6	-0.08	-0.22	-0.23	-0.04	-0.18	-0.04
7	-0.07	-0.04	0.01	0.04	0.03	0.10
8	0.23	-0.13	-0.31	-0.01	0.32	0.57
9	0.10	0.30	-0.00	-0.55	-0.16	0.39
10	-0.05	-0.19	-0.25	-0.05	-0.20	0.01
11	-0.19	0.02	-0.43	-0.21	-0.41	0.03
12	-0.20	-0.24	-0.54	-0.36	-0.50	-0.14
13	-0.17	-0.13	-0.43	-0.04	-0.30	-0.06
14	-0.38	-0.18	-0.51	-0.24	-0.68	-0.10
15	-0.12	-0.21	-0.21	-0.35	-0.23	-0.01
16	-0.28	-0.31	-0.49	-0.42	-0.10	-0.04
17	-0.03	-0.05	-0.35	-0.09	-0.19	-0.07
18	-0.49	-0.02	-0.25	-0.58	-0.51	-0.02
19	-0.32	-0.28	-0.41	-0.51	-0.46	-0.11
20	-0.07	-0.01	-0.25	-0.01	-0.24	-0.01
21	-0.26	-0.12	-0.55	-0.28	-0.41	-0.04
22	-0.34	-0.26	-0.54	-0.34	-0.52	-0.12
23	-0.21	-0.24	-0.43	-0.14	-0.39	-0.03
24	-0.09	-0.24	-0.1	-0.12	-0.13	-0.16
25	0.10	-0.04	-0.14	-0.27	-0.10	0.14
26	-0.10	-0.32	-0.32	-0.03	-0.32	-0.04
27	0.03	0.14	-0.32	-0.14	-0.13	-0.01
28	-0.12	-0.12	-0.42	-0.03	-0.28	-0.08
29	-0.24	-0.21	-0.34	-0.09	-0.42	-0.09
30	-0.32	-0.34	-0.68	-0.01	-0.38	-0.06
31	0.15	-0.01	-0.32	0.32	0.21	0.35
32	-0.18	-0.22	-0.32	-0.21	0.06	-0.60
33	-0.29	-0.14	-0.53	-0.23	-0.47	0.02
34	-0.38	-0.41	-0.38	-0.69	-0.53	-0.11
35	-0.11	0.02	-0.21	0.11	-0.21	0.13
36	-0.19	-0.32	-0.63	-03	-033	0.15
37	0.22	0.13	-0.32	0.38	-0.15	0.49
38	-0.05	-0.01	-0.21	-0.45	-0.04	-0.08
39	-0.19	-0.20	-0.56	-0.45	-0.49	-0.03
40	-0.29	-0.23	-0.48	-0.15	-0.39	-0.15
41	-0.30	-0.07	-0.57	-0.18	-0.19	-0.01
42	-0.14	-0.13	-0.3	-0.03	-0.32	-0.07
43	-0.01	-0.08	-0.32	-0.23	-0.16	0.20
44	-0.16	-0.18	-0.43	-0.04	-0.41	-0.05
45	0.17	-0.34	-0.13	-0.14	-0.05	-0.15
46	-0.07	-0.02	-0.29	0.06	-0.11	-0.01
47	-0.16	-0.07	-0.42	-0.29	-0.46	-0.04
48	-0.06	0.18	-0.21	-0.04	-0.25	0.16
49	-0.14	-0.15	-0.20	-0.29	-0.26	0.18
50	0.52	-0.27	-0.63	-0.42	-0.71	0.20

Table - 4 OSIRIS Property Explorer, 2001-2014

S.No	Mutagenic	Tumori-genic	Irritant	Reproductive effective	Clogp	Solubility	Drug likeness	Drug-Scroe
1	No	Yes	Yes	yes	3.3	-3.84	-2.88	0.25
2	Yes	Yes	Yes	Yes	2.79	-3.85	-4.08	0.41
3	Yes	Yes	Yes	Yes	2.27	-2.95	-1.98	0.45
4	Yes	Yes	Yes	Yes	4.15	-5.15	-1.79	0.34
5	Yes	Yes	Yes	Yes	3.16	-3.88	-0.48	0.55
6	Yes	Yes	Yes	Yes	4.36	-5.48	-3.21	0.28
7	Yes	Yes	Yes	Yes	3.92	-5.84	-2.57	o.29
8	Yes	Yes	Yes	Yes	1.0	-2.57	-0.52	0.62
9	Yes	Yes	Yes	Yes	2.9	-4.62	-3.27	0.38
10	Yes	Yes	Yes	Yes	4.43	-5.46	-1.55	0.32
11	Yes	Yes	Yes	Yes	4.01	-4.65	-7.15	0.34
12	Yes	No	Yes	Yes	3.99	-4.53	-0.23	0.4
13	Yes	Yes	Yes	Yes	2.79	-3.85	-2.76	0.43
14	No	Yes	No	Yes	3.24	-4.16	-3.44	0.25
15	Yes	Yes	Yes	Yes	3.0	-4.66	-0.39	0.5
16	Yes	Yes	Yes	Yes	2.67	-4.48	2.03	0.69
17	Yes	Yes	Yes	Yes	4.46	-4.93	-4.75	0.3
18	No	No	Yes	Yes	3.68	-5.09	-2.85	0.12
19	Yes	Yes	Yes	Yes	3.68	-4.73	0.91	0.52
20	Yes	Yes	Yes	Yes	3.4	-4.15	-1.56	0.45
21	Yes	Yes	Yes	Yes	4.06	-4.43	-4.1	0.35
22	Yes	Yes	Yes	Yes	3.23	-3.86	-1.95	0.45
23	Yes	Yes	Yes	Yes	2.96	-3.59	-0.17	0.6
24	No	Yes	Yes	Yes	2.38	-5.31	3.5	0.39
25	Yes	Yes	Yes	Yes	2.22	-3.94	-0.46	0.56
26	Yes	Yes	Yes	Yes	3.58	-4.25	-2.39	0.4
27	Yes	Yes	Yes	Yes	3.45	-3.02	-2.37	0.23
28	Yes	Yes	Yes	Yes	3.86	-5.04	-2.47	0.34
29	No	Yes	No	Yes	2.8	-4.01	-2.08	0.25
30	Yes	Yes	Yes	Yes	2.82	-3.78	-8.89	0.29
31	Yes	Yes	Yes	Yes	2.3	-3.78	-8.89	0.29
32	Yes	Yes	Yes	Yes	0.09	-3.5	-1.1	0.26
33	Yes	Yes	Yes	Yes	2.96	-3.54	0.68	0.7
34	Yes	Yes	Yes	Yes	2.63	-3.92	-1.28	0.5
35	Yes	Yes	Yes	Yes	1.92	-2.66	0.75	0.75
36	Yes	Yes	Yes	Yes	4.51	-3.84	-2.22	0.38
37	Yes	Yes	Yes	Yes	4.0	-4.69	-3.02	0.35
38	Yes	Yes	Yes	Yes	2.41	-4.11	-4.25	0.41
39	Yes	Yes	Yes	Yes	4.13	-5.43	-2.21	0.32
40	Yes	Yes	Yes	Yes	3.22	-3.98	-6.42	0.39
41	Yes	Yes	Yes	Yes	2.93	-3.49	1.75	0.47
42	Yes	Yes	Yes	Yes	2.39	-2.82	-1.21	0.55
43	Yes	Yes	Yes	Yes	2.61	-3.3	0.61	0.71
44	Yes	Yes	Yes	Yes	4.25	-4.92	0.66	0.52
45	Yes	Yes	Yes	Yes	4.28	-4.72	-2.03	0.35
46	Yes	Yes	Yes	Yes	3.22	-3.98	-5.35	0.39
47	Yes	Yes	Yes	Yes	3.53	-4.21	1.49	0.68
48	Yes	Yes	Yes	Yes	4.06	-4.34	0.19	0.54
49	Yes	Yes	Yes	Yes	2.7	-3.41	0.44	0.69
50	Yes	Yes	Yes	Yes	0.31	-3.96	-0.71	0.5

Table - 5: PM3 Optimized formation energy, HOMO, LUMO, Energy gap and Dipole moments of chalcones

Chalcones	ΔHf (Kcal/mol)	HOMO(eV)	LUMO(eV)	Energy gap(eV)	Dipole moment (Debye)
1	-33.64	-0.278790	-0.174999	0.103791	2.550953
2	-54.77	-0.341274	-0.139516	0.201758	2.437448
3	-78.06	-0.318498	-0.031199	0.287299	3.109350
4	-16.50	-0.296348	-0.171305	0.125143	0.125143 2
5	-26.59	-0.361925	-0.084795	0.27713	0.858642
6	-91.15	-0.235126	-0.153595	0.081531	2.578658
7	-45.67	-0.332726	-0.145576	0.18715	5.452380
8	-91.14	-0.326370	-0.112110	0.21426	2.129281
9	-126.80	-0.338028	-0.158382	0.179646	3.442248
10	-18.59	-0.313120	-0.119628	0.193492	4.738250
11	-54.01	-0.355986	-0.081550	0.274436	2.120210
12	-23.29	-0.250303	-0.157824	0.092479	1.615520
13	-54.77	-0.380651	-0.103845	0.276806	2.682996
14	-10.02	-0.333064	-0.121529	0.211535	5.450866
15	-14.95	-0.339870	-0.116891	0.222979	3.234436
16	-47.36	-0.280545	-0.202318	0.078227	2.298701
17	-215.44	-0.272726	-0.191873	0.080853	1.695944
18	-48.73	-0.272896	-0.198113	0.074783	3.580324
19	-102.47	-0.283959	-0.183619	0.10034	3.834756
20	-25.29	-0.283803	-0.206743	0.07706	3.838540
21	-35.28	-0.206754	-0.129599	0.077155	2.925652
22	-41.37	-0.278633	-0.174920	0.103713	2.382405
23	-56.12	-0.318481	-0.186852	0.131629	1.801943
24	-12.80	-0.345215	-0.128962	0.216253	2.856004
25	-68.55	-0.280192	-0.189647	0.090545	3.354541
26	-27.50	-0.322039	-0.137167	0.184872	1.402617
27	-94.24	-0.343672	-0.142678	0.200994	2.869612
28	-13.58	-0.358624	-0.091192	0.267432	4.743726
29	-124.39	-0.267384	-0.152478	0.114906	1.512335
30	-70.48	-0.377902	-0.086278	0.291624	9.437332
31	-193.67	-0.282407	-0.165860	0.116547	2.212802
32	-32.02	-0.331676	-0.110946	0.22073	0.430831
33	-60.68	-0.278107	-0.190501	0.087606	2.750078
34	-77.17	-0.347951	-0.124933	0.223018	1.431386
35	-136.29	-0.326732	-0.180090	0.146642	5.748661
36	-109.44	-0.263380	-0.210652	0.052728	3.702630
37	-204.43	-0.283258	-0.208560	0.074698	4.456464
38	-114.55	-0.300507	-0.185276	0.115747	3.518350
39	-33.97	-0.285612	-0.204924	0.080688	3.254241
40	-35.26	-0.261511	-0.206491	0.05502	4.300598
41	-26.38	-0.349916	-0.101741	0.451657	2.182341
42	-98.26	-0.315033	-0.177427	0.137612	2.816507
43	-31.47	-0.346250	-0.155200	0.19105	3.677993
44	-45.55	-0.265856	-0.156310	0.109546	5.432599
45	-72.49	-0.301029	-0.076889	0.22414	0.898030
46	-137.56	-0.241209	-0.199005	0.042204	5.516168
47	-21.66	-0.306854	-0.188051	0.118803	2.787110
48	-85.09	-0.296964	-0.201768	0.095196	2.611681
49	-84.48	-0.295339	-0.207325	0.088014	8.924567
50	-119.40	-0.336557	-0.096477	0.24008	1.025770

Table - 6: Docking Score of 50 chalcones against COX-1 Receptor by HEX 6.3.

Chalcone No	Energy kcal/mol	No.of H-bonds	No.of rotatable bonds
1	-182.17	6	3
2	-190.95	9	3
3	-207.57	13	7
4	-189.81	5	3
5	-197.64	8	4
6	-181.99	9	4
7	-208.40	6	5
8	-177.72	11	7
9	-198.95	7	6
10	-194.13	4	4
11	-183.3	6	5
12	-169.02	3	3
13	-177.77	9	5
14	-176.29	3	4
15	-184.31	12	4
16	-198.15	6	4
17	-187.23	9	3
18	-194.44	9	4
19	-198.54	7	4
20	-194.06	4	4
21	-182.35	4	4
22	-174.31	8	3
23	-183.48	Is)	3
24	-188.10	14	4
25	-191.24	10	7
26	-181.44	7	Is)
27	-204.19	8	6
28	-204.00	3	4
29	-196.48	5	5
30	-223.70	3	3
31	-208.43	3	3
32	-197.90	5	4
33	-183.99	5	3
34	-188.17	1	7
35	-195.05	9	Is)
36	-210.06	4	6
37	-192.38	6	4
38	-184.28	7	4
39	-179.19	9	3
40	-199.88	8	6
41	-179.64	6	4
42	-166.11	11	3
43	-171.81	5	Is)
44	-198.02	7	5
45	-214.78	3	4
46	-207.79	10	6
47	-178.23	3	3
48	-181.74	10	4
49	-186.42	12	3
50	-174.74	8	4

Table - 7: List of Hydrogen bonds between chalcones and COX-1 receptor

Chalcone	**Interaction site**	**Hydrogen Bond Between Chalcone & Protein**	**Bond Distances (A^0)**	**No. of Hydrogen Bonds**
7	154 residue of ser 461 residue of gln 47 residue of gys	154 SER 461 GLN 47 GYS	2.141 2.058 2.277	3
30	**154 residue of ser 461 residue of gln**	**154 SER 461 GLN**	**2.141 2.058**	**2**
31	154 residue of ser 461 residue of gln	154 SER 461 GLN	2.141 2.058	2
36	461 residue of gln	461 GLN	2.058	1
45	83 residue of arg 83 residue of arg 122 residue of asn 123 residue of leu 124 residue of ile	83 ARG 83 ARG 122 ASN 123 LEU 124 ILE	2.117 2.053 2.263 2.286 2.436	5

CONCLUSION

In the present work, we describe the naturally available chalcones to prove the importance of the various functionalities by in silico docking method with regard to selective inhibition of COX-1 (PDB ID: 1CQE). Naturally available chalcone compounds are selected and their docking energy and other parameters are investigated. Among the selected 50 chalcones the lowest docking energy was -223.70 Kcal/mol [table 1, fig. 3]. It was concluded that naturally available chalcone-30 to inhibit COX-1 than the other selected chalcones.

Cyclooxygenases (COX-1 and COX-2) catalyze the oxygenation of arachidonic acid (AA) to form prostaglandins and thromboxane, which mediate a range of physiological and pathophysiological responses. COX-1 dependent prostaglandin synthesis has been implicated in many pathophysiological processes including atherosclerosis, endothelial dysfunction, neuroinflammation, preterm labor, pain, and cancer. Earlier results indicate that COX-1 is a major source of pro-inflammatory PGs in the brains of both LPS-treated mice and mice treated with the Parkinsonism-inducing compound. Therefore, COX-1selective inhibitors represent, a potentially useful class of drugs that has not been extensively investigated.

COX activity is the main therapeutic target for non-steroidal anti-infammatory drugs. Some inhibitors of COX-1 and COX-2 would be less elective at more infamed sites, since the supply of arachidonic acid can determine their effectiveness. Chalcone derivatives able to control NO and PG production by mechanisms other than enzyme inhibition have a potential role in modulating the inflammatory process. In summary, this study suggests that growth inhibitor effect of chalcones against cancer was supported by theoretical results. The Protein-Ligand interaction plays a significant role in structure based drug design. The main reason of the computational approach is the reduction of cost and time in drug discovery process. Aim of this project was to investigate which was the best chalcones that inhibit activity against COX-1 (cyclooxgenase-1). The best binding chalcones identified by best binding energies obtained in docking studies of chalcones with COX-1 (PDB ID: 1CQE).

In the present work of Chalcone-30 (1,3-diarylprop-2-en-1-one) have been introduced as selective cyclooxygenase inhibitors. Chalcone-30 have the lowest binding energy (-223.70Kcal/mol) among the investigated chalcone, which is the best inhibitory activity against COX-1 (PDB ID: 1CQE).

Cancer is the main cause of death in the world. One of the promising strategies in controlling cancer progression is considered cancer chemoprevention by taking dietary factors. Chalcones are the main precursor for the biosynthesis of flavonoids, which are frequent components of the human diet. Recent studies on biological evaluation of chalcones revealed some to be anticancer, anti-inflammatory, antimitotic, anti-tubercular, cardiovascular, cell differentiation inducing, nitric oxide regulation modulatory and antihyperglycemicagents.

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