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CHALCONES AS INOS AND COX-2 INHIBITORS; INSIGHTS FROM MOLECULAR DOCKING STUDIES

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ABSTRACT

In the present study, a series of ring substituted chalcones were docked into the binding sites of COX-2 and iNOS enzymes. These enzymes exhibit similarities in terms of pathophysiological activities and are mostly co-expressed in cancer tissues. Dual inhibition of these enzymes has been proposed as a promising therapeutic tool in the treatment of various types of diseases, especially for antiiniflammatory and antinociceptive drug development. Results of docking experiments revealed that these structurally simple molecules have good binding affinity for the enzymes and electronic effects have profound influence on the binding interactions. Trifluoro methyl substituted chalcone, (C12) was found to have highest binding affinity among the chalcones studied, indicating the importance of strong electron withdrawing effect at this position. Predicted molecular properties of these compounds demonstrated good oral bioavailability and CNS permeability.

KEY WORDS

Chalcones; COX-2; iNOS; Molecular docking; Schrödinger

INTRODUCTION

Chalcones (1,3-diaryl-2-propen-1-one) are the most familiar molecules among natural as well as synthetic chemists for their diverse set of biological and enzyme inhibitory activities [1,2]. The compounds with the backbone of chalcone structure have been reported to possess various biological activities such as anti-cancer [3-4], antifungal [5], antileishmanial [6], antiiniflammatory [7], antimalarial [8], antiplatelet [9], antihyperglycemic [10], antitubercular [11], antiviral [12] and antimicrobial activities [13]. Chalcones and their derivatives have gained high interest due to their antioxidant properties [14-16]. Antinociceptive activities of chalcones were also reported in the literature [17-19]. The α,β-unsaturated ketone group in chalcone is responsible for their enzyme inhibitory activity including xanthine oxidase, aldose reductase, soluble epoxide hydrolase, protein tyrosine kinase, quinonone reductase and mono amine oxidase [13].

Compounds containing this type of unsaturated system are considered as potential drug candidates due to their ability to act as Michael acceptors with the protein functional groups, especially the sulfhydryl group of cysteines in proteins plays a major role in Michael-addition-based activation process [20-21]. Despite their simple substitution patterns, chalcones exert antinociceptive actions in different models of pain and were more potent than some of the well-known anti inflammatory and analgesic drugs [22-24]. Chalcones possessing aryl or hetero aryl ring demonstrated significant in vitro inhibition of inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) enzymes. Presence of halogens, electron releasing groups such as hydroxy, alkoxy groups and side chains such as prenyl, geranyl and dimethylamino groups were found to enhance the in vitro inhibitory activity of chalcones [25-27]. Dual inhibition of these enzymes appears as a promising therapeutic tool in the treatment of various types of diseases, especially

for antiinflammatory and antinociceptive drug development [28-30].

In view of the potent in vitro iNOS and COX-2 inhibitory activities of the chalcones, we performed docking studies to analyse in silico binding affinity of these ligands against these enzymes. Chalcones bearing various electron withdrawing and donating groups present on ring A were selected, to analyse their binding poses in the respective enzyme active pockets.

MATERIALS AND METHODS

Protein preparation: Crystal co-ordinates of proteins were downloaded (PDB ID: 2Y37 for iNOS and 3LY1 for COX-2) from the Protein Databank (PDB) (http://www.pdb.org/). They were imported into the Schrödinger Maestro suite 2013 (Schrödinger, LLC, New York, NY, 2013) for preparation, minimization and docking studies. Proteins were prepared for docking using protein prep wizard of Schrödinger. Hydrogen atoms, charges were added to protein structure and missing animoacids were taken care by using Prime module of Schrödinger. Finally, grid co-ordinates were calculated based upon the co-crystal ligands in PDB. Grid co- ordinates were set to X: 20.78; Y: -68.94; Z: 32.87 for iNOS and X: 30.67, Y: -22.53, Z: -16.06 for COX-2 to generate the grid box. Glide SP docking was used to carry out docking calculations.

Ligand preparation: A series of ring substituted chalcones were selected as ligands for docking studies. Molecular docking study of these chalcones has been carried out using Glide, module of Schrödinger suite 2013. Ligand molecules were sketched and optimized using LIGPREP wizard and 10 conformations were generated for each compound.

Prediction of Molecular and ADME descriptors: Molecular descriptors, such as log P (partition coefficient), molecular weight (MW), the acceptors and donors for hydrogen bonding in a molecule and polar surface area (PSA) were calculated using the online software (http://www.molinspiration.com/). These descriptors are strongly associated with membrane permeability and oral bioavailability (The "Lipinski rule" states that the compounds are more likely to be orally bioavailable if they obey the rule and fulfil following criteria: log p ≤ 5, molecular weight ≤500, hydrogen bond acceptors ≤10, and hydrogen bond donors ≤5). The percentage of absorption was estimated using the equation: % ABS = 109 − (0.345 × TPSA) [31]. Absorption, distribution, metabolism and excretion (ADME) properties of molecules were predicted using the preADMET online server (http://preadmet.bmdrc.org/). This program calculates the human intestinal absorption, in vitro Caco-2 cell permeability, Maden Darby Canine Kidney (MDCK) cell permeability, skin permeability, plasma protein binding, blood brain barrier penetration, and carcinogenicity. The blood brain barrier permeability was also estimated using Log BB value, which can be calculated using PSA value with the clark equation Log BB= (-) 0.0148PSA+0.152 Log P+0.139 [32].

RESULTS AND DISCUSSION

Molecular docking studies using iNOS enzyme:

To determine the importance of various steric, polar and electronic effects of substituent groups at the active sites of COX-2 and iNOS, a series of ring substituted chalcone derivatives (Fig.1) were selected for docking studies. Met368, Glu371 and Asp376 were the critical amino acids of iNOS, having key interactions with standard inhibitor 2Y37_A54, 2-[(1R)-3-amino-1-phenylpropoxyl]-4-chlorobenzonitrile and the glide score for this inhibitor was found to be -8.68 kJ mol^{-1}. Within the amino acids surrounding the active site of iNOS, NH proton of Met 368 form strong hydrogen bonding with triply bonded nitrogen of benzonitrile group present in standard inhibitor. Amino functionality linked to phenylpropoxy group of standard compound, found to participate in important hydrogen bonding interactions with amino acid residues Asn 376 and Glu 371.

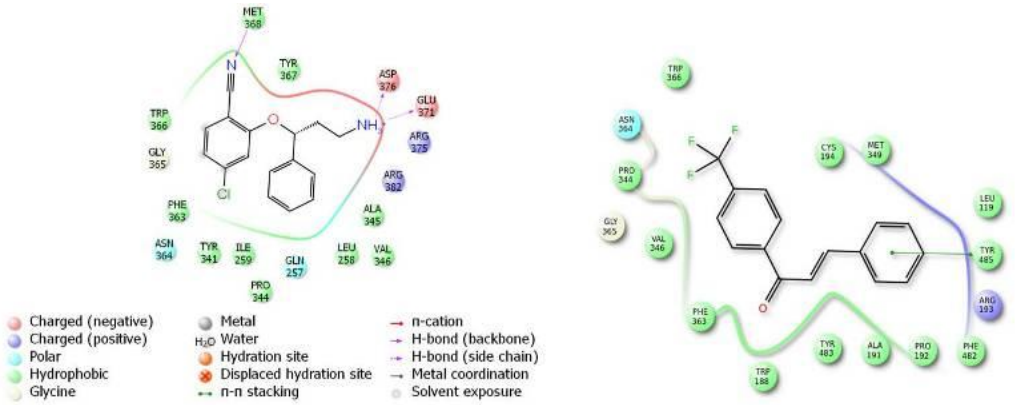

Figure 1: Binding conformation of standard inhibitor (A) and compound 12 (B) within the active site of iNOS:

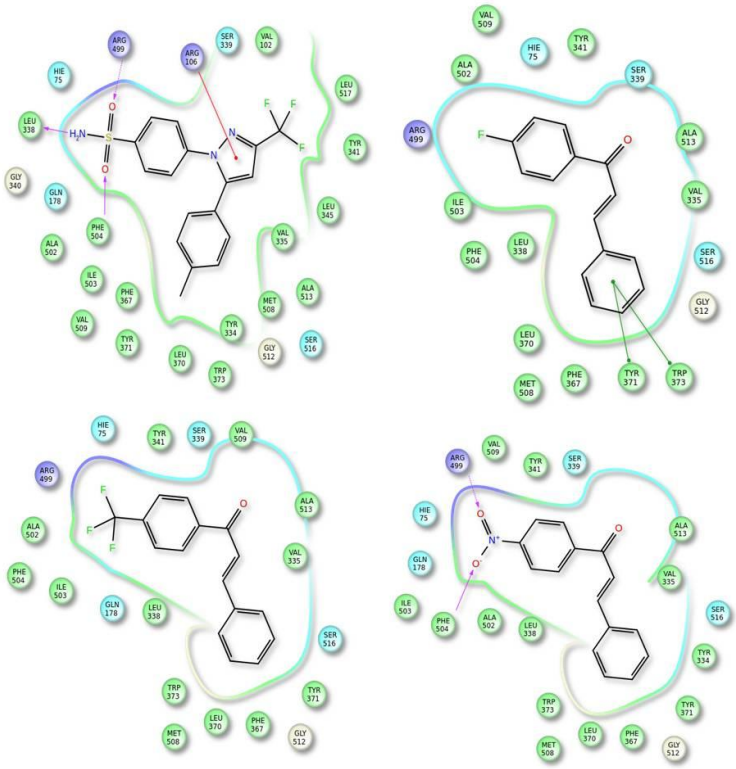

Figure 2: Best docking poses of standard inhibitor (A) and chalcones C2,C5 and C12 (B,C and D) as obtained using GLIDE at COX-2 enzyme

Binding free energies obtained for chalcones with respect to iNOS (Table.1) suggest that unsubstituted chalcone has significant binding affinity for this enzyme (-7.39 kJ mol^{-1}), indicating that chalcone motif has essential features to bind with iNOS enzyme. Introduction of halogens increased the binding affinity for this enzyme. Highest docking score was observed with halogen containing trifluoro methyl substituted chalcone (C12), which is -7.847 kJ mol^{-1} comparable to standard inhibitor -
8.68 kJ mol^{-1}, implying that halogens enhance binding ability of chalcone towards this enzyme.

Table 1: Interaction energies of ring substituted chalcones (C1- C12) with iNOS and COX-2 enzymes using GLIDE

Compd.	R	Interaction Energy (kJ mol^{-1}) for iNOS	Interaction Energy (kJ mol^{-1}) for COX-2
Standard		-8.68	-11.875
C1	H	-7.391	-8.644
C2	4-F	-7.526	-8.875
C3	4-Cl	-7.329	-8.989
C4	2,5-$(Cl)_2$	-7.364	-8.753
C5	4-NO_2	-6.746	-9.096
C6	4-OH	-5.722	-8.970
C7	4-OCH_3	-6.455	-8.000
C8	3,4-$(OCH_3)_2$	-6.615	-8.696
C9	3,4,5-$(OCH_3)_3$	-7.082	-8.783
C10	4-CH_3	--6.827	-8.423
C11	4-$C(CH_3)_3$	-7.521	-8.121
C12	CF_3	**-7.847**	**-9.259**

Table 2: Calculated ADME descriptors for the chalcones (C1-C12)

Compd	R	Absorption		Distribution	
		Caco-2 cell (nm sec^{-1})	%HIA	PPB (%)	BBB
C1	**H**	54.59	100.00	94.83	1.51
C2	**4-F**	57.75	100.00	96.64	1.42
C3	**4-Cl**	56.98	100.00	100.00	2.97
C4	**2,5-$(Cl)_2$**	56.65	100.00	100.00	2.33
C5	**4-NO_2**	22.35	98.608	93.35	0.01
C6	**4-OH**	53.54	96.035	91.87	1.15
C7	**4-OCH_3**	57.99	100.00	91.40	0.34
C8	**3,4-$(OCH_3)_2$**	57.45	98.073	90.21	0.09
C9	**3,4,5-$(OCH_3)_3$**	54.55	97.64	90.69	0.09
C10	**4-CH_3**	54.59	100.00	93.16	3.36
C11	**4-$C(CH_3)_3$**	54.98	100.00	95.90	8.21
C12	**CF_3**	40.44	100.00	94.57	5.49

$CaCO_2$ (nm/sec), $CaCO_2$ cell permeability in nm/sec; HI A (%), Percentage human intestinal absorption; PPB (%), *in vitro* plasma protein binding (percentage); BBB (C brain/C blood), in vivo Blood-Brain Barrier penetration.

Table 3: Calculated theoretical molecular descriptors for the chalcones (C1 - C12)

Compd	R	miLog P	PSA	MW	HBA	HBD	LogBB	nrotb	%ABS	MV
C1	**H**	3.81	**17.07**	208.26	1	0	0.466	3	103.11	201.85
C2	**4-F**	3.98	**17.07**	226.25	1	0	0.491	3	103.11	206.78
C3	**4-Cl**	4.49	**17.07**	242.71	1	0	0.569	3	103.11	215.39
C4	**2,5-$(Cl)_2$**	4.92	**17.07**	277.15	1	0	0.634	3	103.11	228.92
C5	**4-NO_2**	3.77	**62.90**	253.26	4	0	-0.070	4	87.29	225.19
C6	**4-OH**	3.33	**37.30**	224.26	2	1	0.093	3	96.13	209.87
C7	**4-OCH_3**	3.87	**26.30**	238.29	2	0	0.338	4	99.92	227.40
C8	**3,4-$(OCH_3)_2$**	3.46	**35.54**	268.31	3	0	0.139	5	96.73	252.94
C9	**3,4,5-$(OCH_3)_3$**	3.44	**44.77**	298.34	4	0	0.142	6	93.56	278.49
C10	**4-CH_3**	4.26	**17.07**	222.29	1	0	0.534	3	103.11	218.41
C11	**4-$C(CH_3)_3$**	5.52	**17.07**	264.37	1	0	0.726	4	103.11	268.04
C12	**CF_3**	4.71	**17.07**	276.26	1	0	0.602	4	103.11	233.15

miLogP: Logarithm of partition coefficient between n-octanol and water PSA: polar surface area; MW: molecular weight; HBA: Hydrogen bond acceptors; HBD: Hydrogen bond donors; nrotb: Number of rotatable bonds; % ABS: Absorption; MV: Molecular volume ; Log BB; Blood brain barrier permeability.

Presence of strong electron withdrawing group, $–NO_2$ decreases the affinity of chalcones for iNOS (-6.746 kJ mol^{-1}) when compared to unsubstituted chalcone (-7.39 kJ mol^{-1}) indicating that factors other than electron withdrawing effects may be responsible for high affinity at this position.

Substitution with electron releasing group such as 3, 4, 5- trimethoxy or bulky group like tert-butyl seem to retain the binding ability (-7.08 and-7.521 kJ mol-1) whereas introduction of 4-hydroxyl group decreased the binding affinity (-5.72 kJ mol^{-1}).

Molecular docking studies using COX-2 enzyme:

The COX-2 enzyme (Table.1) consists of three independent folding units: an epidermal growth factor-like domain, a membrane binding site, and an enzymatic domain. NSAIDS bind reversibly with tyrosine 385 amino acid residue and inhibit the enzymatic action and PGE_2 production [33]. Celecoxib, 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide, was used as standard inhibitor for docking studies involving COX-2, which was highly interactive with amino acid residues Leu 338, Arg499, Phe 504 and Arg 106 with the glide score of -11.87 kJ mol^{-1}. Sulfonamide moiety was found to have three hydrogen bonding interactions, two of which involve oxygen atoms present on sulfonyl group and another is from amino proton. In addition, π-π interactions were found to exist between pyrazole ring of celecoxib and Arg 106 amino acid.

Molecular docking results obtained for COX-2 enzyme, indicate that unsubstituted chalcone (C1) has good affinity for this enzyme, with the interaction energy of -8.644 kJ mol^{-1}. Thus structural features of chalcones are also suitable for interaction with the active site of COX-2 enzyme. Introduction of electron withdrawing groups enhanced the binding affinity of chalcones. Highest binding score was obtained for trifluoromethyl substituted chalcone (C12) that is -9.259 kJ mol^{-1}. Binding modes of chalcones bearing halogens or $-CF_3$ were similar in the in the binding pocket of COX-2 and were shown to participate in hydrophobic interactions with tyrosine residues situated at 371 and 373 positions in enzyme. With the presence of nitro group at 4^{th} position (C5) improved the binding affinity of the parent molecule (-9.096 kJ mol^{-1}). Nitro group seems to mimic the sufonyl moiety of celecoxib at the receptor binding site and interacts with Arg 499 and Phe504 amino acid residues.

Presence of hydroxyl group at 4^{th} position of chalcone (C6), binding free energy is increased (-8.970 kJ mol^{-1}) when compared to unsubstituted chalcone (-8.644 kJ mol^{-1}). Replacement of hydroxyl group with methoxy

group led to chalcone with reduced binding affinity for COX-2 (-8.000 mol^{-1}), indicating the importance of hydrogen bonding donor ability of hydroxyl group at this position, which is diminished upon methoxylation. The strong hydrogen bonding ability of the substituent might be playing an important role at the COX-2 binding site.

When 3, 4, 5-trimethoxy groups were introduced, binding affinity of chalcone was retained, whereas introduction of alkyl groups decreased the affinity.

Interpretation of the results of iNOS and COX-2 docking studies reveals that

i) Electronic effects influence the binding affinities of chalcones. Introduction of trifluoromethyl group was found to be the most favourable at the binding sites of iNOS and COX-2.
ii) Effect of nitro and hydroxyl groups is opposite. In case of COX-2 enzyme, this group has enhanced the binding affinity whereas for iNOS, presence of this moiety decreased the binding affinity.

Prediction of Molecular and ADME descriptors:

In the chalcones, except for the 4-tert-butyl derivative (C11), all the other derivatives have obeyed the Lipinski rules of five, suggesting that these compounds were predicted to have good oral bioavailability. Predicted ADME descriptors for these chalcones denote that they have good Pharmacokinetic profile (Table.2).

In general, ligands targeted at the CNS tend to have lower PSA (60–70 Å), higher Log BB and BBB values (>0.3 and >0.1). Results of molecular and pharmacokinetic descriptors revealed that most of the chalcones (C1-C4 and C7-C12) have suitable descriptor values for good CNS penetration. These chalcones contain PSA values lesser than 70 Å (17.07 -62.90 Å) Log BB values higher than 0.3 (0.34 -0.72) and BBB values higher than 0.1 (0.15- 8.21) which predict positive CNS permeability. Among all the chalcones, tert-butyl derivative (C11) was predicted to have excellent CNS penetration with optimal PSA, LogBB and BBB descriptor values (17.07, 0.72 and 8.21).

CONCLUSION

Docking studies of a series of ring substituted chalcones revealed that electronic effects play an important role for binding, with trifluoromethyl group being most favourable for binding. Molecular properties prediction demonstrated that these compounds possess good oral bioavailability and CNS permeability

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