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Synthesis and In Silico Analysis of Chalcone Derivatives as Potential Prostaglandin Synthetase Inhibitors

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ABSTRACT

Nine derivatives of chalcones were successfully synthesized using the Claisen- Schmidt condensation reaction between different derivatives of benzaldehyde and acetophenone at low temperature in the presence of potassium hydroxide (KOH) and ethanol. The compounds were obtained in high yield. The percentage yield ranges from 90.38 – 27.68%, with sample B having the highest yield while sample I gave lowest yield. Also, the infra-red and nuclear magnetic resonance (FTIR and NMR) spectroscopic analysis shows distinct spectrum across all molecules, indicating the presence of unique functional groups and chemical environments. All the synthesized chalcones derivatives showed appreciable protein binding affinity against the COX-1 and COX-2 enzymes. The synthesized compounds had higher binding affinity against the COX-1 protein, compared to diclofenac and celecoxib that were used as standards. Sample A showed the highest affinity (-7.24 kcal/mol), while E showed the lowest affinity at -6.11 kcal/mol, higher than diclofenac (-5.46 kcal/mol) and comparable to celecoxib (-6.19 kcal/mol). For COX-2, Celecoxib (selective COX-2 blocker) showed highest binding affinity of -10.55 kcal/mol, while the test compounds B had -8.84 (highest among the test samples) and I (-8.69 kcal/mol (lowest affinity), with diclofenac having -8.49 kcal/mol respectively. Compounds E (4-methoxy-4,6-diphenyl-2-thiopyrimidine) and B (para- chlorochalcone) from previous studies, displayed remarkable anti-inflammatory in an *in-vivo* animal model analysis. B showed the highest affinity against COX-2 and very high affinity towards COX-1 protein compared to the standard molecules. This shows that with adequate physiochemical and structural modifications, these compounds could serve as potential lead compounds in analgesic and anti-inflammatory pharmacology.

Keywords: Analgesic; Anti-Inflammatory; Chalcone Derivatives; Molecular Docking; Drug Design; *In-Silico*

Introduction

Prostaglandins (PGs) are biochemical endogenous lipids with autacoid functions, synthesized in- vivo from arachidonic acid [1]. PGs and other similar physiologically active compounds are collectively known as metabolites of eicosanoids [2]. PGs have long been reported to have sustained homeostatic roles and facilitate many pathogenic mechanisms in inflammation, gastrointestinal tract [1], muscle contraction, blood clotting [3], ocular protection [4,5], and regulation of the circulatory system [6,7]. These lipids are produced via the action of the cyclo-oxygenase (COX-1 and COX-2) isoenzymes, and their biosynthesis is antagonized by the nonsteroidal anti-inflammatory drugs (NSAIDs) [1]. Some vitamins, including D3 (cholecalciferol), and K2 (menaquinone) are also known to inhibit the actions and biosynthesis of PGs [8-10]. PGs mainly take part in vasodilation, conception, luteolysis, menstruation, parturition, blood pressure reduction, control of sodium reabsorption by the kidney, etc [11]. Studies have shown that excessive concentrations of PGs induce diarrhea that accompa-

nies medullary carcinoma of the thyroid or neural crest tumors and mediates several inflammatory responses [11], incoordinate hyperactivity of the uterine muscle leading to uterine ischemia, and menstrual cramps in women [12]. PG structural analogs like latanoprost, travoprost, and bimatoprost with antagonistic properties, are being used and well-tolerated for the reduction of intraocular pressure (IOP) in patients with primary open-angle glaucoma and ocular hypertension [7].

Previous reports have indicated that there are some correlations between high levels of PGs analog (PGFS) in tumors of the GI tract and the effectiveness of NSAIDs [13]. Thus, they can be used in the study, design, and discovery of antitumor agents. Cyclooxygenase 1 and 2 (COX-1 and COX-2) biologically transform arachidonic acid (AA) to prostaglandins H2 (PGH2), which is further biotransformed to various PGs, and other endogenous lipids like thromboxanes, leukotrienes, and hydroxyeicosateraenoic acids [14,15]. The names of these enzymes are derived from their catalytic cyclo-oxygenation that converts AA to prostaglandin G2 (PGG2), and peroxidation of PGG2 to PGH2, hence are also known as peroxidase enzymes as well [16]. The three COX isoforms, COX-1 COX-2, and COX-3, have been identified to share almost 60% amino acid sequence similarity but with much higher sequence homology in the catalytic sites (Figure 1) [17]. COX-1 is firmly expressed in many tissues, while COX-2 is strongly induced by various mitogens and plays imperative roles in many pathological conditions like inflammation [18,19]. There is also a COX-3 enzyme but reported to be not functional in humans. COX-3 isozyme is encoded by the same gene as COX-1, but COX-3 retains a particular nucleotide sequence (intron 94) that is not retained in COX-1 [20].

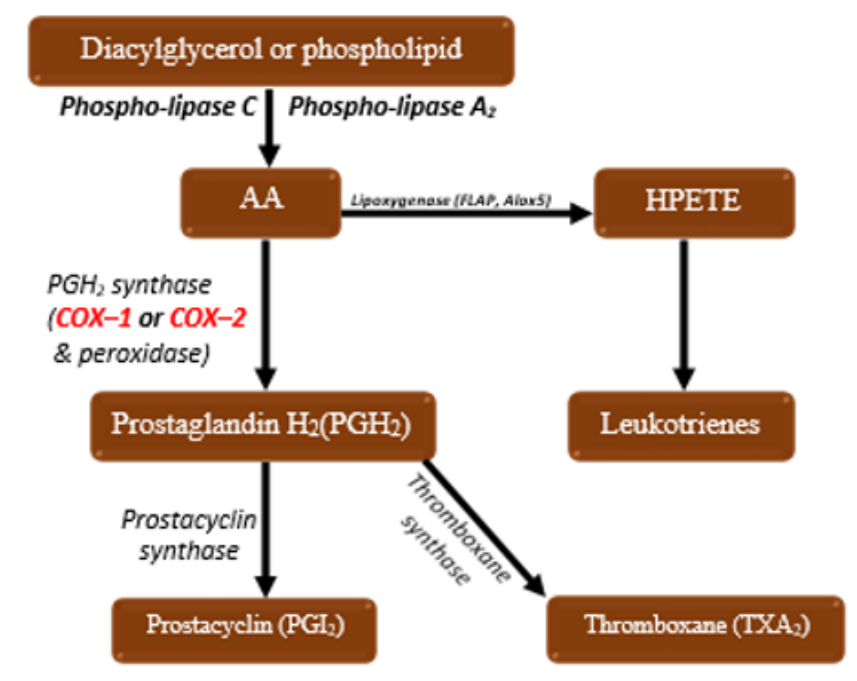


Figure 1: Biosynthetic scheme of prostaglandins [1]. HPETE - hydroperoxy- eicosatetraenoic acid; AA - Arachidonic acid, COX – Cyclooxygenase.

PGE2 increases gastric mucus secretion, uterus contraction (particularly during pregnancy), GI tract smooth muscle contraction, inhibition of lipolysis, autonomic neurotransmitters regulation, platelet response to agonists, and in-vivo atherothrombosis [21,22]. COX-1 enzyme regulates the baseline levels of PGs, while COX-2 synthesizes PGs via stimulation and significantly increases PGs levels during growth and inflammation, although both enzymes are located in the stomach, kidneys, and blood vessels [23]. Hence, inhibition of these agents is necessary for the optimal regulation of many biological functions, when in excessive amounts. NSAIDs inhibit the activities of COX-1 and COX-2 enzymes. There are non-selective (inhibits both COX-1 and COX-2), and COX-2 selective NSAIDs. These NSAIDs, while reducing inflammation caused by PGs, also inhibit platelet aggregation and increase the risk of GIT ulcers and intestinal bleeding [24]. COX-2 selective inhibitors promote thrombosis and increase the risk of heart attacks [25]. Due to these adverse reactions, coupled with the high etiology of vascular, and kidney disease complications, some COX-2 inhibitors are no longer in clinical use [26]. There are also reports that NSAIDs impair the production of erythropoietin, resulting in anaemia [27].

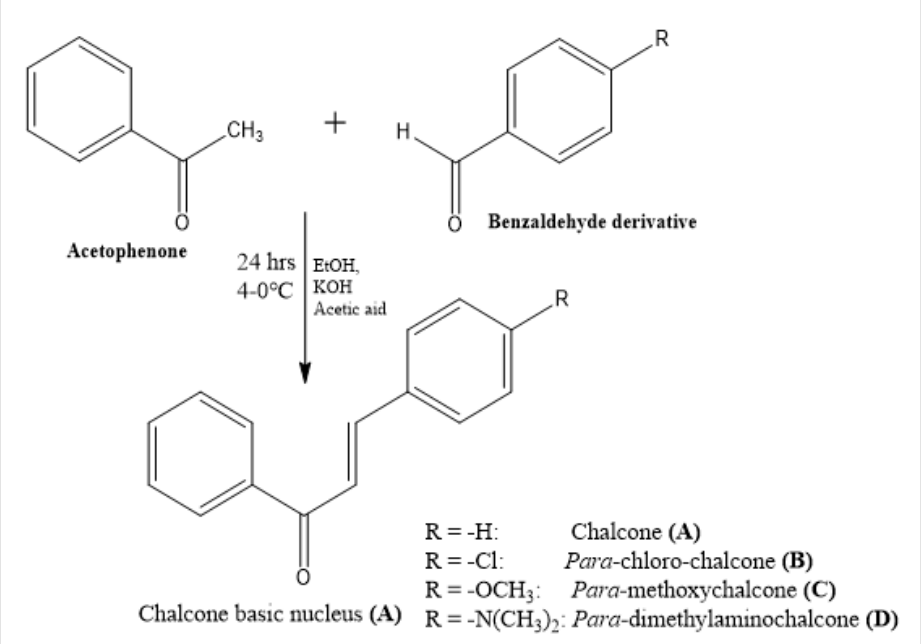
The long-term harmful effects of most NSAIDs outweigh the medical benefits. A study conducted a few years ago, observed a statistically significant increase in myocardial infarction incidence among patients on rofecoxib [28], and data from approved clinical trials, showed a significant relative risk of cardiovascular events that led to the global withdrawal of rofecoxib in 2004 [29]. Another study reported a significant increase in erectile dysfunction in men who frequently used NSAIDs [30]. NSAIDs are also associated with a doubled risk of heart failure in people who have not experienced cardiac disease in their lifetime [31]. Finally, the use of NSAIDs during late pregnancy can cause miscarriage [32], premature birth [33], constriction, and closure of fetal ductus arteriosus, leading to different blood-related congenital heart diseases in the fetus [34]. Acetaminophen, regarded as the safest, and well tolerated NSAID during pregnancy, was reported to cause male infertility in the fetus [35,36]. These advents call for the search for more effective, with minimal toxic molecules that can be used clinically to alleviate inflammatory conditions.

Chalcones chemically known as 1,3-diaryl-2-propen-1-ones, are flavonoids and isoflavonoids precursors, are chemical moieties present in many naturally compounds and are also prepared synthetically because of their convenient synthetic procedures [37]. Chalcone derivatives have been reported to possess antiproliferative [38], anti-inflammatory [39], antitumor [40], antimalarial [41], antibacterial [42], antiviral [43], antileishmanial [44], antifungal [45] properties, among others [46]. Molecular docking is a veritable tool used in the computational prediction of ligands and protein inhibitory affinity in the search for lead molecules [47], including characterized natural products [48]. Therefore, we conducted the synthesis and molecular docking of some chalones derivatives which biological properties were evaluated previously, that can serve as lead compounds in the design of anti- inflammatory and analgesic agents, especially as potential prostaglandin synthetase enzymes (COX-1 and COX-2) secretagogues inhibitors.

Method

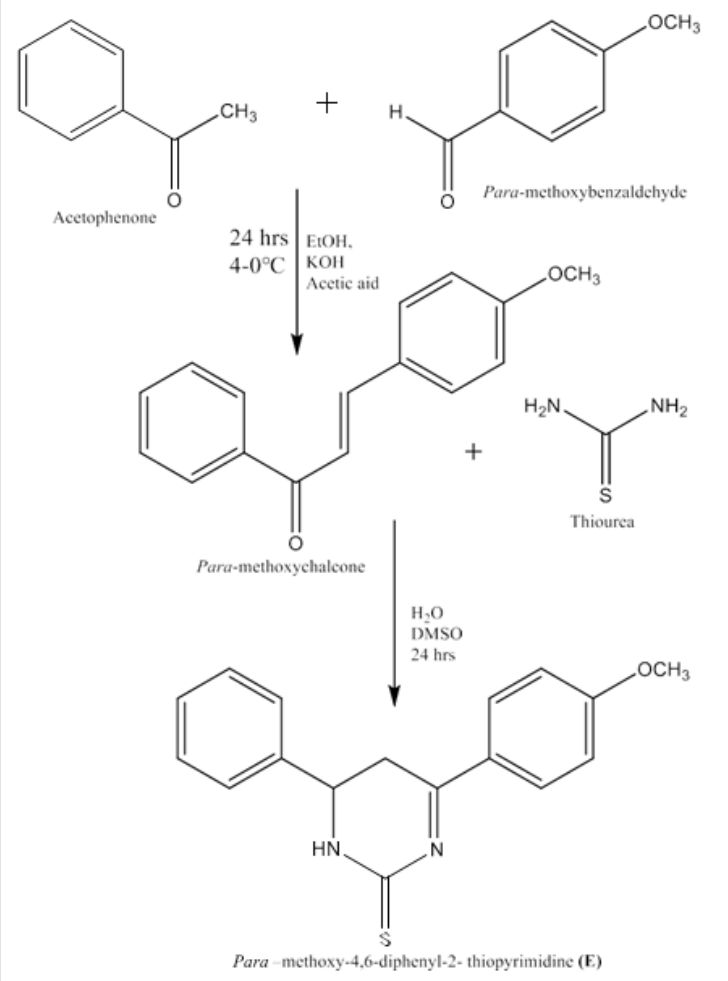
Synthesis

Scheme 1: Synthesis of Methoxy, Halogenated and Aminated Chalcone Derivatives: All reagents used in the synthesis and other analysis were of analytical grades. The IR data was obtained from the FTIR-8400S instrument, Shimadzu global links, North America, while Nuclear Magnetic Resonance (NMR) experiment was performed on a 400 MHz instrument, obtained from Varian Inc. Palo Alto, California, USA. An equivalent weight of 10.6 g benzaldehyde and 12.0 g acetophenone were weighed, into a 100 ml flask having 25 mL EtOH, and stirred on ice (4-0°C). 20 ml of KOH (20%) was added with continuous stirring for 20 minutes and allowed to stand for 24 hours. Ice chips were added, and the mixture was titrated with 25 mL of 20% acetic acid (4-0°C). Precipitates were formed, filtered under suction and recrystallized with ethanol, dried, the percentage yield and melting point were determined. This procedure was repeated with different benzaldehyde derivatives, including para-methoxybenzaldehyde, para-chlorobenzaldehyde and para-dimethylaminobenzaldehyde, giving rise to various derivatives of chalone (Scheme 1).



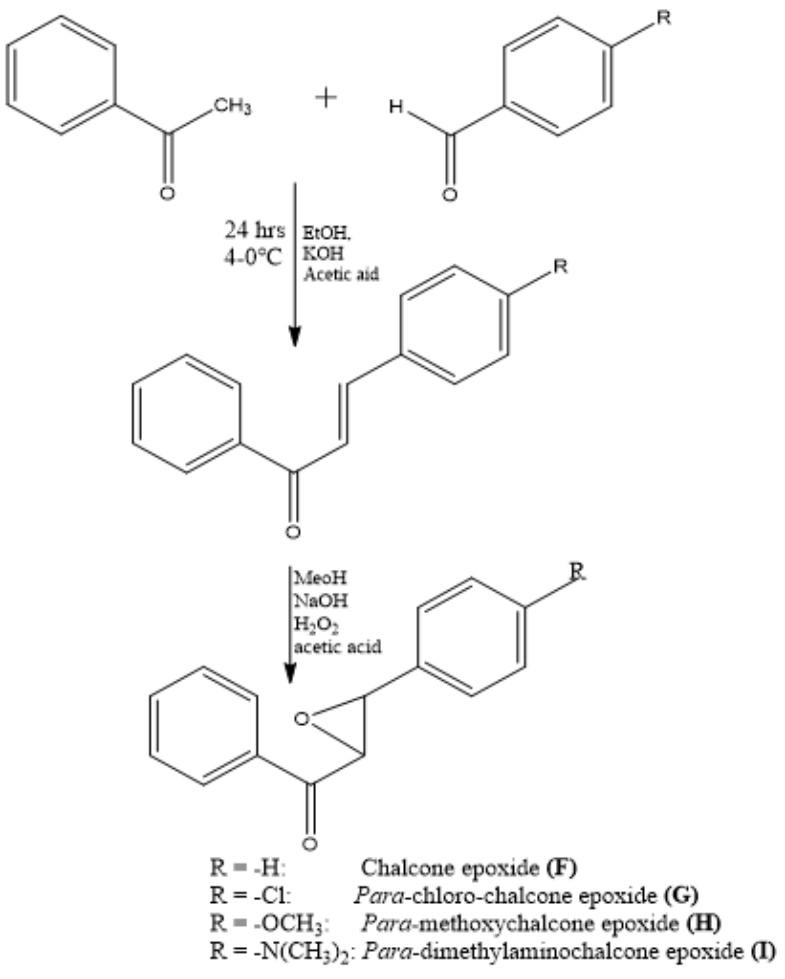
Scheme I: Synthesis of para-methoxy, p-chloro- and para-dimethylamino-chalcone derivatives

Scheme 2: Synthesis of 6-Diphenyl-2-Thiopyrimidine Chalcone Derivatives: From the initial 4-methoxy-chalone derivative obtained, an equivalent weight of 2.38 g 4- methoxy-chalone, 2.12 g sodium bicarbonate, and 1.52 g thiourea, were weighed into a flask having 30 mL DMSO. The mixture was refluxed under Nitrogen gas for about 2 hrs, using a Thin Layer Chromatographic plate to monitor the progress of the reaction. Water was added to the reaction medium at the end and was allowed to stand for 24 hours. Precipitates were formed, filtered under suction, the residues were recrystallized with diethyl-ether and petroleum spirit. The percentage yield and melting points of the crystals obtained were quantified, after drying (Scheme 2).



Scheme 2: Synthesis of 6-diphenyl-2-thiopyrimidine chalcone derivative.

Scheme 3: Synthesis of Epoxide Chalcone Derivatives: For the synthesis of epoxide derivatives, an equivalent weight of 5.16 g chalcone obtained previously was weighed into a beaker; 10 ml of 10% NaOH and 60 ml of MeOH were added respectively. The content of the beaker was dissolved with stirring via gentle heat, then 20 ml hydrogen peroxide H2O2) was added and stirred for 30 minutes. 5 ml of 10% acetic acid was used to acidify the medium. The resultant product was collected, and recrystallized with MeOH, filtered and dried. The percentage yield and melting points were respectively determined. This procedure was repeated with para-methoxychalcone, para-chlorochalcone, para- dimethylaminochalone, respectively, leading to the production of chalcone epoxide derivatives (Scheme 3).



Scheme III: Synthesis of epoxide chalcone derivatives

Molecular Docking

Molecular modeling and docking simulations of the binding protein and synthesized ligands were done using the Maestro software of OPLS3, 2018 Force field [49], and Pymol software [50]. The docking parameters and affinity were compared with the previously reported pharmacological profile of the chalcone derivatives. The human COX-1 crystal structure protein (6Y3C) [51], and 1PXX (COX- 2 crystal structure with diclofenac bound to the cyclooxygenase active site) [52], were obtained from the PDB website, and modeled with the Pymol and D3Pocket webserver [53,54], to obtain all possible binding pockets and utilize one(s) with the highest affinity using diclofenac and Celecoxib (a selective COX-2 inhibitor) as the standard molecules.

A. (E)-Chalcone.

B. Para-chlorochalcone [(E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one]

C. Para-methoxychalcone [(E)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one]

D. Para-dimethylaminochalcone [(E)-3-(4-(dimethylamino) phenyl)-1-phenylprop-2-en-1-one]

E. Para-methoxy-4,6-diphenyl-2-thiopyrimidine[4-(4-methoxyphenyl)-6-phenyl-5,6 dihydropyrimidine 2(1H)-thione]

F. Chalcone-epoxide [phenyl(3-phenyloxiran-2-yl) methadone]

G. Para-chlorochalcone-epoxide [(3-(4-chlorophenyl) oxiran-2-yl) (phenyl)methanone]

H. Para-methoxychalcone-epoxide [(3-(4-methoxyphenyl) oxiran-2-yl) (phenyl)methanone]

I. Para-dimethylaminochalcone-epoxide[(3-(4-(dimethylamino)phenyl)oxiran-2-yl)(phenyl)methanone]

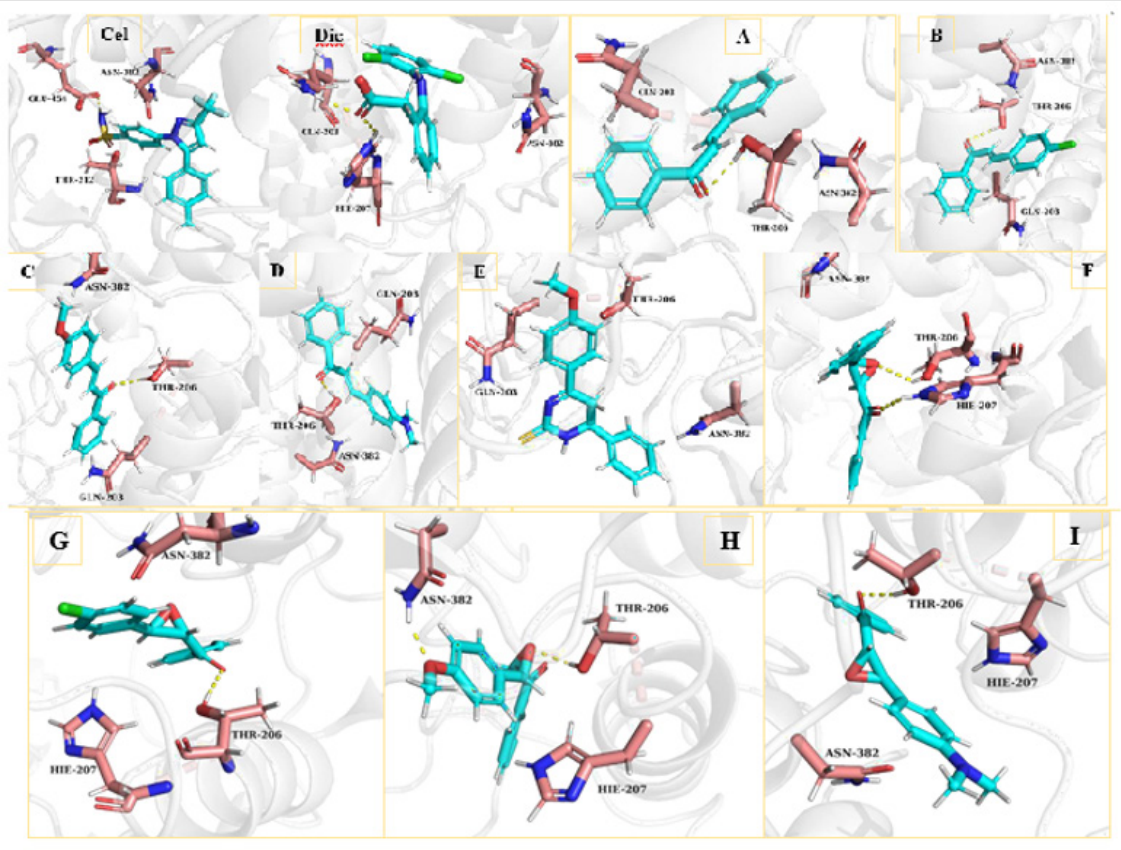
Discussion

The compounds were obtained in high yield after the synthetic processes (Schemes 1 & 2). The percentage yields of the compound ranged from 27.68 – 90.38%, with sample B having the highest yield while sample I gave lowest synthetic yield. Also, the spectroscopic (FTIR and NMR) analysis shows distinct spectrum across all molecules, indicating the presence of unique functional groups and chemical environments (Table 1). All the synthesized chalcones derivatives showed appreciable protein binding affinity against the COX-1 and COX-2 enzymes. Compared to the standard drugs, better protein-ligand affinity was observed with COX-2 enzyme. Diclofenac is known to inhibit both COX-1 and COX-2 enzymes [55]. The computational experiment showed that, some of the synthesized compounds had higher binding affinity against the COX-1 protein than both diclofenac and celecoxib. Compound A showed the highest affinity (-7.24 kcal/mol), while other compounds had affinity level of -7.21(C), -7.16 (B), -7.14 (I), -7.10 (D), -7.00 (H), -6.92 (G), -6.88 (F), and -6.11 kcal/mol(E), respectively. Whereas, the standard compounds (diclofenac and celecoxib) had -5.46 and -6.19 kcal/mol, respectively.

Table 1: Physiochemical and elemental analysis of Chalcone derivatives.

S/N	Chalconederivative	Percentage yield(%)	FTIR (cm^{-1})	^{1}HNMR (DMSO- *d6*) ppm	^{13}CNMR (DMSO-*d6*) ppm
1.	A	89.10	C=O: 1655.0, Ar-C=C: 1589.4, HC=CH: 3055.4	Ar-H: 7.5, 7.6, 7.7, 7.9–9.0, 7.9–8.0, 8.2–8.2: =CH: 7.7–7.8, 15.6,	C=O: 190, C=C: 123, Ar-C: 129-138, C=C: 144
2.	B	90.38	C=O 1645.3, Ar-C=C: 1543.10, C=C: 3084.3, C–Cl: 792.8	Ar-H: 7.5-8.17, HC-C: 6.7-6.9	C=O: 190, Ar-C=C: 110 – 130, -C=C: 140
3.	C	68.09	C=O: 1655.0, HC=CH: 3506, C=C: 1593.3, C-O:1018.5	H_3C-O: 3.8, HC=CH: 7.0-7.0, (Ar-H: 7.6-7.9	C=O:189, OCH_3:55, C=C:122, Ar-C:126-138,C=C144
4.	D	46.53	N-H: 3557.5, C=O: 1645.3, Ar-C=C: 1543.1,	H_3C- N-CH_3: 3.5, HC-O: 3.4, Ar-H: 6.8-7.5	H_3C-N-CH_3: 112, C=O: 189, C-O: 116, C-O: 122, Ar-C: 148-151
5.	E	56.33	N-H: 3034, C=S: 1655.0, C=N: 1587.5, C-N: 1319.4, C-O: 1005.0	N-H: 3.34, OCH_3: 3.82, Ar-H: 7.0-8.2	C=S: 189, OCH_3: 55, N-C: 144, C=N: 120, Ar-C: 127-144
6.	F	76.01	C=O:1682.0, Ar-C=C:1575.9 C=C: 3045.7, C–O: 1236.4	Ar-H: 7.4 – 8.0, H- CO: 4.2, H- CO: 4.8	C=O: 193, Ar-C=C: 126 – 137, C–O: 56 – 60
7.	G	58.90	C=O: 1656.9, C=C: 1579.8, C-O: 1093.7	HC-O: 3.3, 3.8, Ar-H: 7.4-8.0	C=O: 198, Ar-C: 128-135, C-O: 58, 60
8.	H	84.69	C=O: 1587.5, H-CO: 3441.1, 3045.7, H-C=C:1658.8, C-O:1244.1	Ar-H: 6.6-8.2, H-C-O: 3.8, H-C-O: 3.7, H_3C-O: 2.1	C=O: 189, OCH_3: 55, Ar-C:127-144
9.	I	27.68	N-H: 3757.5, C=O: 1645.3, C=C: 1543.1, H-C-O: 3055.4, C-O: 1163	H_3C- N-CH_3: 3.0, HC-O: 3.4, Ar-H: 6.8-8.1	H_3C-N-CH_3: 112, C=O: 189, C-O: 116, C-O: 122, Ar-C: 128-152

The protein-ligand interactions showed the actual protein residues in the COX-1 protein that compounds bound with (Figure 2). Also, the binding pocket and pose of the compound with highest affinity showed how it is well fitted into the protein pocket (Figure 3). Celecoxib, a selective COX-2 inhibitor showed highest binding affinity of -10.55 kcal/mol, while the test compounds had -8.55 (A), -8.84 (B) -8.50 (C), -8.79 (D), -8.24 (E) -8.13 (F), -8.50 (G), -8.22 (H), -8.69 (I), and diclofenac had -8.49 kcal/mol respectively (Table 2). The binding interactions of all molecules are shown in Figure 4, while binding poses of the molecules with the highest affinity is illustrated in Figure 5. Compounds E (4-methoxy-4,6-diphenyl-2-thiopyrimidine) and B (para-chlorochalcone) from previous studies, displayed remarkable anti-inflammatory in an in-vivo analysis using animal model [39]. E also showed the appreciable affinity against COX-1 protein more than the standard compounds, while lower affinity was observed against COX-2 protein. For compound B, it showed the highest affinity against COX-2 and very high affinity towards COX-1 protein compared to the standard molecules used in the analysis. This shows that with adequate physiochemical and structural modifications, these compounds could serve as potential lead compounds in analgesic and anti-inflammatory pharmacology, as pain and inflammation are associated with these enzymes in the biological system [16].



Note:

A. Chalcone.
B. Para-chlorochalcone.
C. Para-methoxychalcone.
D. Para-dimethylaminochalcone.
E. Para-methoxy-4,6-diphenyl-2-thiopyrimidine.
F. Chalcone-epoxide.
G. Para-chlorochalcone-epoxide.
H. Para-methoxychalcone-epoxide.
I. Para-dimethylaminochalcone-epoxide. The light blue carton represents the ligands, purple represents the protein residue and wedged yellow lines show ligand-protein interactions.

Figure 2: Ligand interaction of chalcone derivatives and COX-1 enzyme (6Y3C). Cel – celecoxib; Dic – diclofenac.

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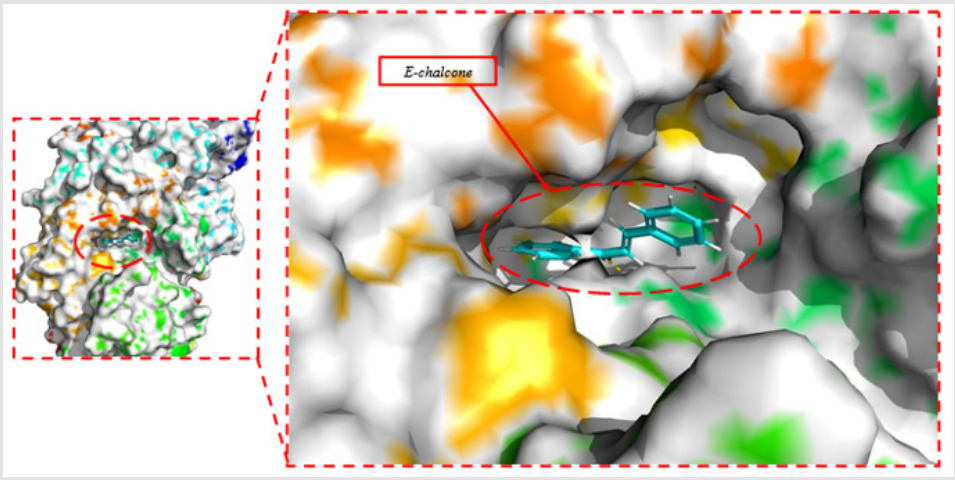
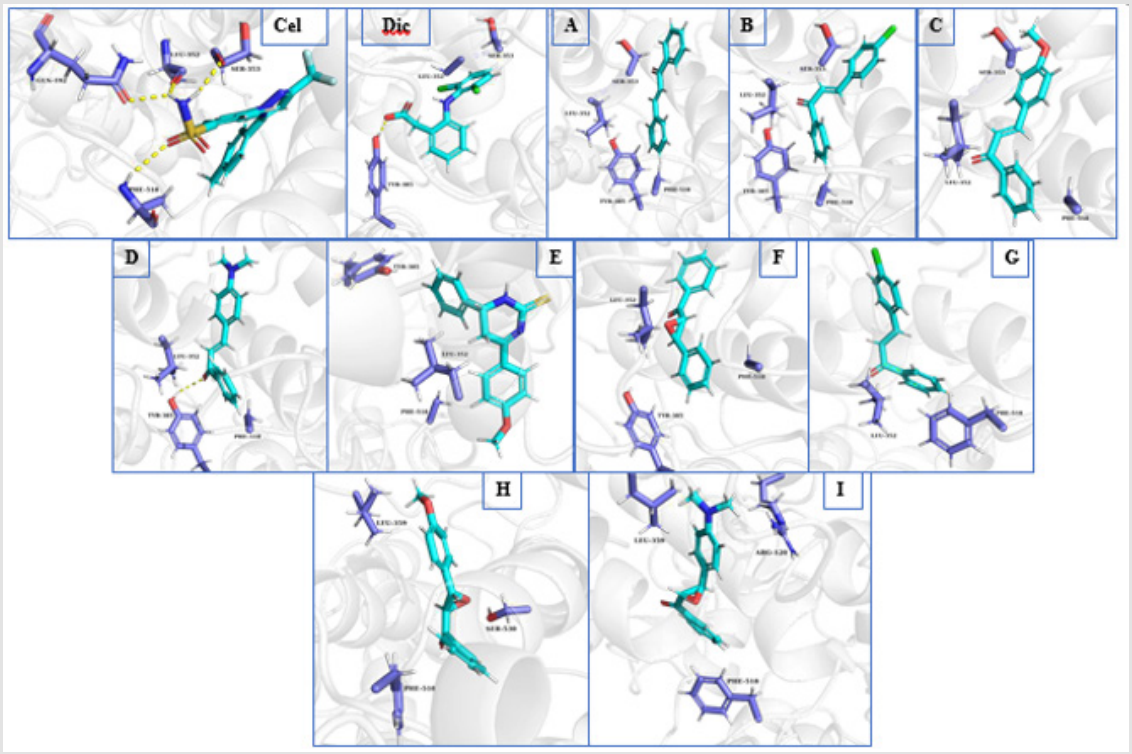


Figure 3: Binding pose of E-chalcone on 6Y3C protein surface that resulted in the highest affinity (-7.24 kcal/mol) more than the standard diclofenac (-5.46 kcal/mol), and celecoxib (-6.19 kcal/mol).



Note:

A. Chalcone.
B. Para-chlorochalcone.
C. Para-methoxychalcone.
D. Para-dimethylaminochalcone.
E. Para-methoxy-4,6-diphenyl-2-thiopyrimidine.
F. Chalcone-epoxide.
G. Para-chlorochalcone-epoxide.
H. Para-methoxychalcone-epoxide.
I. Para-dimethylaminochalcone-epoxide. The light blue carton represents the ligands, pink represents the protein residue and wedged yellow lines shows ligand-protein interactions.

Figure 4: Ligand interaction of chalcone derivatives and COX-2 enzyme (1PXX). Cel – celecoxib; Dic – diclofenac.

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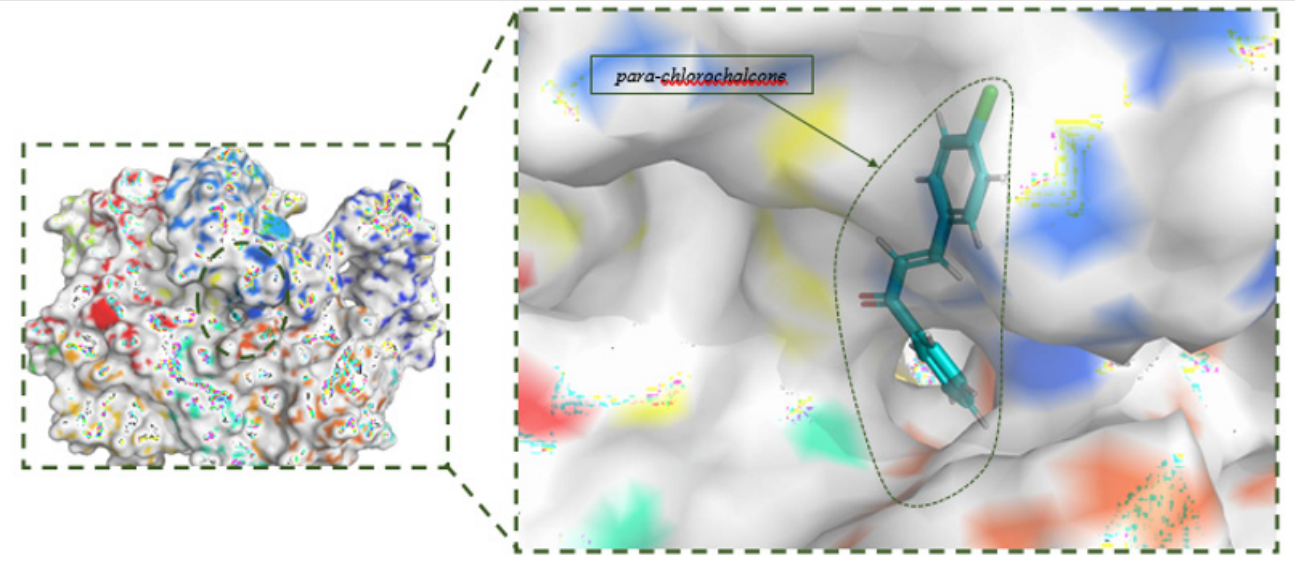
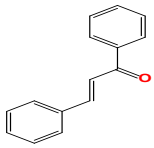
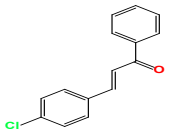
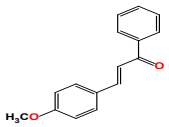
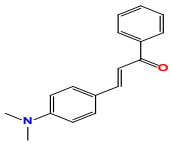
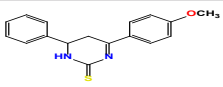
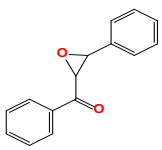
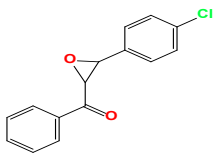
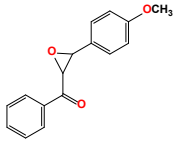
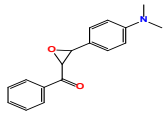
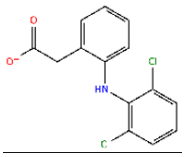
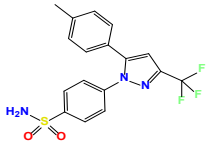


Figure 5: Binding pose of para-chlorochalcone [(E)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one] on 1PXX protein surface that resulted in the highest affinity (-8.84kcal/mol) more than the standard diclofenac (-8.49 kcal/mol), but less than celecoxib (-10.55 kcal/mol).

Table 2: Structural features and Molecular docking of the synthesized compounds.

S/N	Sample ID	Structure	PDB: 1PXX		PDB: 6Y3C	
			Docking Score (kcal/mol)	Glide emodel	Docking score (kcal/mol)	Glide emodel
	A		-8.55	-49.18	-7.24	-48.57
	B		-8.84	-54.69	-7.16	-49.69
	C		-8.50	-53.37	-7.21	-49.67
	D		-8.79	-48.62	-7.10	-51.63
	E		-8.24	-50.65	-6.11	-54.52
	F		-8.13	-52.65	-6.88	-51.44

	G		-8.50	-52.55	-6.92	-51.37
	H		-8.22	-50.07	-7.00	-52.66
	I		-8.69	-48.87	-7.14	-53.09
	Diclofenac		-8.49	-61.50	-5.46	-46.80
	Celecoxib		-10.55	-72.81	-6.19	-53.66

Conclusion

Analgesic and anti-inflammatory agents are used in the prevention of all kinds of pains, ranging from minor headaches to severe post-operative pains. The search for newer agents due to poor tolerability, adverse reactions and affordability of the existing ones is the focus of contemporary drug design and development. The compounds showed highly promising results in both in-vivo and computational molecular docking studies. Hence, the compounds reported in this study could be utilized and further modified structurally and physiochemically to achieve better analgesic and anti-inflammatory properties.

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Authors Contribution

SBJ: in silico studies, data analysis, manuscript original draft. OM: data curation, manuscript review. EVA: synthetic studies, preliminary in-vivo studies. DA: manuscript critical review. BA: supervision, conception, validation. COU: supervision, spectroscopic analysis, data interpretation, manuscript critical review and approval.

Conflict of Interests

The authors declare no conflict of interest.

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