Tropical Journal of Pharmaceutical Research November 2022; 21 (11): 2419-2427
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i11.22

Original Research Article

Effects of anti-cyclooxygenases (COX-1 and COX-2), structure activity relationship, molecular docking and in silico ADMET of some synthesized chalcones

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Sent for review: 5 June 2022 *Revised accepted: 13 October 2022*

Abstract

Purpose: *To develop effective cancer chemopreventive and anti-inflammatory agents, a series of chalcones were prepared by reacting suitable aromatic aldehyde with appropriate acetophenones.*
Methods: *Twenty-four synthesized chalcones (namely, 1 - 24) were assessed for their in vitro anti-cyclooxygenase-1 (COX-1) and anti-cyclooxygenase-2 (COX-2) activity in a COX catalyzed prostaglandin synthesis bioassay. Molecular docking was done to investigate the ligand-protein interactions, and selectivity on both enzymes. ADMET (absorption, distribution, metabolism, excretion, toxicity) modeling and software were also used.*
Results: *The compounds inhibited both COX-1 and COX-2. Two compounds (3 and 19) demonstrated more marked COX-2 inhibition than compound 1. Indomethacin as a standard anti-cyclooxygenase shows unselective inhibition of 81.44 ± 6.5 and 91 ± 9.5, respectively. The in silico data revealed that a chalcone skeleton with C=O at 4-position, C2–C3 double bond and OH at 5-position are necessary properties for anti-cyclooxygenase effects. It was also revealed that the propenone moiety comprises of an appropriate scaffold which proposes a new acyclic 1,3-diphenylprop-2-en-1-ones with selective anti-COX effects. A molecular modeling investigations where these chalcones 1, 3 and 19 were docked in the active site of COX-2 depicted that the p-CH3 substituent on the C-4- phenyl ring A are oriented in the vicinity of the COX-2 secondary pocket Phe381, Gly526, Tyr385 and Val349.*
Conclusion: *Based on the screening for oral bioavailability, in silico ADMET, and toxicity risk assessment, this study shows that these compounds could be a cornerstone for the development of new pharmaceuticals in the battle against COX-associated inflammatory disorders.*

Keywords: *Chalcones; cyclooxygenase enzymes: docking; in silico ADMET*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Inflammation is considered an important cellular phenomenon and a significant step in the pathogenesis and cure for most human ailments. Thus, the modulation of inflammatory mediators using anti-inflammatory agents is considered as the chief therapeutic aim for a new drug design

for the cure of inflammation-related sicknesses. Cyclooxygenases (COX) are major enzymes that interfere with the prostaglandin metabolic pathway, and contributes to the progression of inflammation and tissue injury [1]. COX-1 and COX-2 enzymes can be activated by various intercellular initiators and are involved in acute and chronic inflammatory disorders and carcinogenesis [2]. Thus, inhibitors of COX enzymes are potential anti-inflammatory and cancer chemopreventive drugs [3]. Clinical uses of anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) are associated with some unwanted side-effects [4]. Variability in patients' response to NSAIDs and their unwanted side-effects led biomedical researchers to search for new anti-COX agents [5].

Chalcones are a group of chemical compounds demonstrating encouraging therapeutic usefulness for several diseases. [6]. Scientific literature reported structural modifications of the chalcone template, and diverse pharmacological activities have been reported, including cytotoxic, anti-inflammatory, anti-plasmodial, antitumor, immunosuppression, and antioxidant activities [7]. The anti-inflammatory effect of chalcones *per se* has been tested and shown to correlate with the inhibition of inflammatory pathways, such as tumor necrosis factor and nitric oxide. There were a few reports on the synthesis of chalcones as potential inhibitors for COX enzymes [7,8].

Therefore, this current research was designed to investigate the anti-inflammatory activities of some synthesized chalcones and their *in silico* properties.

EXPERIMENTAL

Synthesis and identification of chalcones

Chalcones were prepared according to the methods described and summarized in a previous published work [9]. Spectroscopic data and chemical properties of these compounds are available in the same previously published paper [9].

In vitro evaluation of COX-1 and COX-2 inhibitory activities

COX-inhibitor screening kit is an enzyme immunoassay (EIA assay) and was used according to the supplier's guidelines (Cayman Chemical, USA). The biochemical basis of this EIA assay is based on the bio-production of prostaglandin (PGF2α) generated by $SnCl_2$ in the presence of prostaglandin H2 at 37 °C [10]. The stock solutions of the synthesized compounds were diluted in dimethyl sulphoxide (DMSO) with final concentration of 200 µM. Indomethacin was used as a positive control. Components of the kit as described by the supplier's guidelines were distributed in background, activity and sample tubes. The tubes were incubated in a water-bath (37 °C) for 15 min before the addition of arachidonic acid. The reaction was stopped using concentrated HCl and the samples were added to mouse anti-rabbit IgG in a 96-well plate provided with the kit. The enzymatic reaction was incubated at ambient temperature for 18 h and washing buffer was used 5 times after this incubation period. Ellman's Reagent was used to develop the reaction. Microplate spectrophotometer was used to obtain readings at 410 nm. The percentage of inhibition (50 %) for the individual cyclooxygenase enzymes was obtained using GraphPad software based on three-point curves.

Molecular docking

The purpose of this *in-silico* computational method is to understand the binding and interactions between the active sites of the cyclooxygenase enzymes and the tested compounds. 3D structures of cyclooxygenase enzymes (COX-1 and COX-2) were downloaded from the Protein Data Bank website (https://www.rcsb.org). The 3D structures of both enzymes were prepared for molecular docking by separating all heteroatoms including H_2O molecules and the molecules that are associated with crystallization buffers. Enzymes were pre-treated for polar and non-polar hydrogen atoms, and Kollman charges. Default parameters were allocated for solvation parameters. Chalcones structures were prepared using HyperChem Professional and ChemBioDraw Ultra software, with PM3 indicators using the conjugate gradient (Polak-Ribiere) and steepest descent algorithms. AutoDock Tools computer software (version 1.5.4) was used to prepare docking files. Gasteiger charges, non-polar hydrogen atoms and all related bonds were considered prior to the docking using AutoDock 4.2 software package based on the Lamarckian genetic algorithm (LGA). A population size of 150 and $2.5*10^6$ energy assessments were utilized for $1*10^2$ search runs. A grid spacing (0.375Å) was used and placed in the centre of the grid box at the active sites of the enzymes. The configuration of the docking tests was investigated and visualized using the Discovery Studio 3.0 (http://www.accelrys.com). Discovery Studio 3.0 was also used to visualize Van der Waals interactions and H-bonds between the enzymes and chalcones.

ADMET modeling

For this study, *ADMET (absorption, distribution, metabolism, excretion, toxicity)* modeling was performed *in silico*. The solubility of the chalcones (1-24) at ambient temperature was predicted and ranked in comparison to a set of drug molecules. Human Intestinal Absorption (HIA) and classification of absorption level was predicted after oral administration. Parameters for blood brain barriers were also predicted in this study and bilateral penetration of the compounds were classified and reported according to previous method [11,12]. Indomethacin, ibuprofen and declofenic were used as standard drugs in this ADMET study.

Statistical analysis

Each experiment was replicated three times (n = 3) and the data were analyzed by are presented as mean ± standard deviation (SD).

RESULTS

COX enzyme activities

The synthesized chalcones were assessed for their *in vitro* inhibitory activities against COX-1 and COX-2 enzymes implicated in inflammation using catalyzed-prostaglandin synthesis bioassay. As shown in Table 1, the compounds inhibited both COX-1 and COX-2 enzymes in various manners. Compound **22** showed the highest inhibition rate on COX-1 enzymes. Indomethacin as a standard COX-1 and COX-2 inhibitor displayed an inhibition level of 81.44±6.5 and 91±9.5 respectively.

Docking results

For the *in silico* study, compounds 1, 3 and 19 were chosen. Compound **1** was observed to bind with COX-1 active site with an interaction energy of -5.93 kcal/mol, creating one H-bond with Tyr355 into the binding site of COX-1 and showing a bonding distance of 1.859 Å between OH of **1** and H of Tyr355. Both ring A and B of compound **1** were enclosed by the amino acids binding site (Gly526, Val349, Ser358, Val116, Ala527, Arg120, Trp387 and Leu531) as shown in Figure 1. An effective docking of compound **1** into the COX-2 binding site was also observed with a binding energy of 6.70 kcal/mol.

The bonding distance between C=O (carbonyl group) of **1** and the oxygen (O) of Tyr385 amino acid of COX-2 was observed to be 2.790 Å (H...O). The trans C=C olefinic bond was enclosed by Gly526, Ala 527 and Val 523. The ring A and B of 1 were also enclosed by the binding site amino acid residues: Met522, Gly526, Leu352, Leu531, Ser530 and Tyr385, respectively (Figure 2).

Table 1: Inhibitory effects of the chalcones on COX-1 and COX-2 enzymes

Compound		Inhibitory effect on COX enzymes	
No.	*Chemical name*	*COX2-*	*COX-1*
1	1, 3-Diphenyl-propenone	39.58±2.37	40.54±2.43
2	3-(4-Hydroxy-phenyl)-3-phenyl-propenone	34.98±2.10	59.38±3.56
3	3-Phenyl-1-*p*-tolyl-propenone	42.61±2.56	34.24±2.05
4	1-(4-Methoxy-phenyl)-3-phenyl-propenone	31.67±1.90	66.00±3.96
5	3-(2-Chloro-phenyl)-1-phenyl-propenone	46.57±2.79	49.38±2.96
7	3-(2-Chloro-phenyl)-1-(4-hydroxy-phenyl)-propenone	40.54±2.43	46.42±2.78
8	3-(2-Chloro-phenyl)-1-P-tolyl-propenone	40.06±2.40	56.66±3.40
9	3-(2-Chloro-phenyl)-1-(4-methoxy-phenyl) propenone	43.45±2.61	47.25±2.84
10	1-Phenyl-3-*m*-tolyl-propenone	44.57±2.67	51.34±3.08
11	1-(4-Hydroxy-Phenyl-3)-*m*-tolyl-propenone	38.53±2.31	52.39±3.14
12	3-*m*-Tolyl-1-*p*-tolyl-propenone	35.21±2.11	44.56±2.67
13	1-(4-Methoxy-phenyl)-3-*m*-tolyl-propenone	42.26±2.54	49.72±2.98
14	3-(4-Methoxy-phenyl)-1-phenyl-propenone	40.50±2.43	60.98±3.66
15	1-(4-Hydroxy-phenyl)-3-(4-methoxy-phenyl) propenone	41.71±2.50	56.56±3.39
16	3-(4-Methoxy-phenyl)-3-*p*-tolyl-propenone	41.75±2.50	45.90±2.75
17	1,3-Bis-(4-methoxy-phenyl)-propenone	40.39±2.42	47.90±2.87
18	3-(4-Dimethylamino-phenyl)-1-phenyl-propenone	45.46±2.73	55.09±3.31
19	3-(4-Dimethylamino-phenyl)-1-(4-hydroxy-phenyl)-propenone	40.60±2.44	30.34±1.82
20	3-(4-Dimethylamino-phenyl)-1-*p*-tolyl-yl-propenone	41.20±2.47	50.35±3.02
21	3-(4-Dimethylamino-phenyl)-1-(4-methoxy-phenyl)-propenone	37.28±2.24	39.66±2.38
22	3-(2-Hydroxy-phenyl)-1-phenyl-propenone	37.10±2.23	97.89±5.87
23	3-(2-Hydroxy-phenyl)-1-*p*-tolyl-propenone	42.79±2.57	65.64±3.94
24	3-(2-Hydroxy-phenyl)-1-(4-methoxy-phenyl) propenone	37.64±2.43	27.04±3.39
25	Indomethacin	81.44±6.5	91±9.5

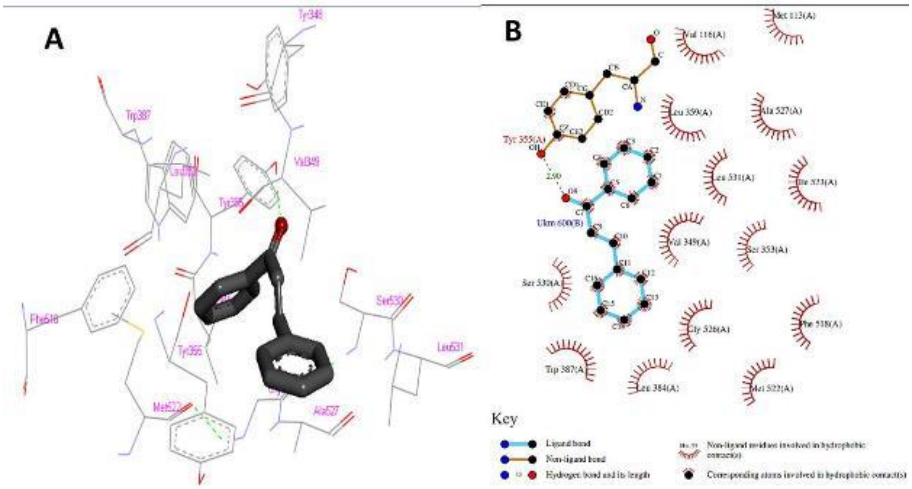

Figure 1: Depictions of the molecular modeling of the docking created between compound **3** and COX-1. (a) 3D represents the ligand-enzyme binding biochemical interactions. Compound **3** is shown in grey colour and hydrogen bonds as green lines; (b) 2D represents the hydrophobic interactions and H-bonding

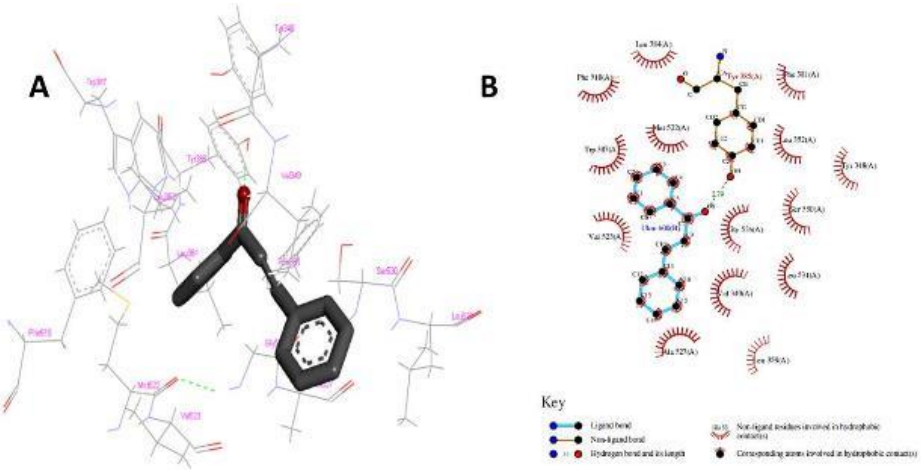

Figure 2: Depictions of the molecular modeling of the docking created between compound **3** and COX-2. (a) 3D represents the ligand-enzyme binding biochemical interactions. Compound 3 is shown in grey colour and hydrogen bonds as green lines; (b) 2D represents the hydrophobic interactions and H-bonding

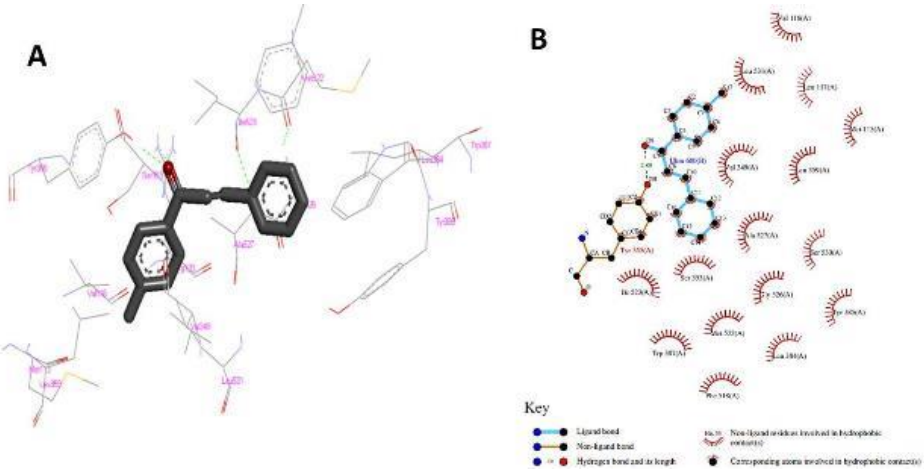

Figure 3: Depictions of the molecular modeling of the docking created between compound **1** and COX-1. (a) 3D represents the ligand-enzyme binding biochemical interactions. Compound **1** is shown in grey colour and hydrogen bonds as green lines; (b) 2D represents the hydrophobic interactions and H-bonding

Compound **3** was shown to dock into the binding sites of both enzymes (COX-1 and COX-2) with an interaction energy of 6.29 and 7.32 kcal/mol respectively. Compound **3** formed a hydrogen bond of Tyr355 with COX-1, and the bonding distance between the hydroxide of compound **3** and hydrogen of Tyr385 was 1.894 Å. The ring A and B of **3** were enclosed by amino acid residues: Val349, Ser358, Val116, Ala527, Arg120, Gly526, Trp387 and Leu384, respectively (Figure 3) in the binding site of COX-1. The carbonyl double-bond of the central α,β –unsaturated–carbonyl moiety was sloping in the direction of the entrance to the COX-2 active site (Val344, Val349, Phe205 and Tyr348). The *trans C=C* olefinic chemical bond which was enclosed by Ser530 and Leu534. The ring A and B of 3 were enclosed by the binding site amino acid residues (Val349, Tyr 385, Leu352, Gly526, Trp,387, Phe205, Gly533 and Ser530) as depicted in Figure 4. Interaction energy of -5.79 kcal/mol was observed between compound **19** and the binding site of COX-1 enzyme with both ring (A and B) were enclosed in the binding site. Figure 5 shows the interaction of **19** and the active site amino acid residues (Ser530, Val349, Leu534, Tyr385, phe381 & Ser353).

Compound **19** was observed to dock effectively into the binding site of COX-2 with binding energy of -6.35kcal/mol. This could be explained by the stronger binding of this compound and H-bond with Tyr385. The bonding distance between the carbonyl double-bond of **19** with O of Tyr385 3.042 Å (H...O) of COX-2 was observed. The carbonyl double-bond of the central α,β-unsaturated-carbonyl moiety was oriented in the direction of the entry of the COX2 active site (Arg 120 and Tyr 355). The trans C=C olefinic bond which is enclosed by Gly526, Ala 527 and Met 522, positions the *C4* 4-tolyl accompaniment towards the apex of the COX-2 binding site (Arg120, Leu 359, Tyr355, Vall116 and Met113). The C-4 *p*- dimethyl amine accompaniment was within vander Waal's range of Tyr355, Leu359 and Leu531 (distance<5Å). The methyl group at C-4 at ring A is directed toward the COX-2 pocket (Phe518, Met522 and Leu384). Both ring A and B of **19** were enclosed by the active site amino acid residues (Gly526, Met522, Leu352, Leu531, Ser530 & Tyr355) as shown in Figure 6. Table 2 depicts docking results for the compound 1, 3 and 19. ADMET findings for compounds 1, 3 and 19 are listed in Table 3.

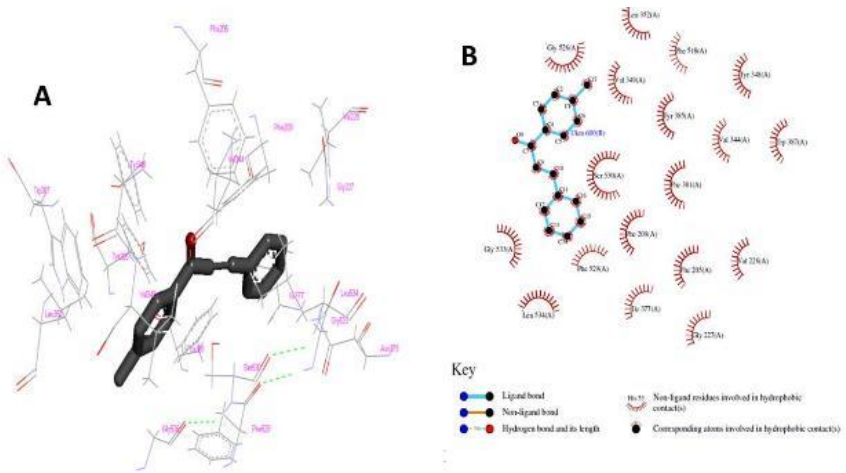

Figure 4: Depictions of the molecular modeling of the docking created between compound **1** and COX-2. (a) 3D represents the ligand-enzyme binding biochemical interactions. Compound **1** is shown in grey colour and hydrogen bonds as green lines; (b) 2D represents the hydrophobic interactions and H-bonding

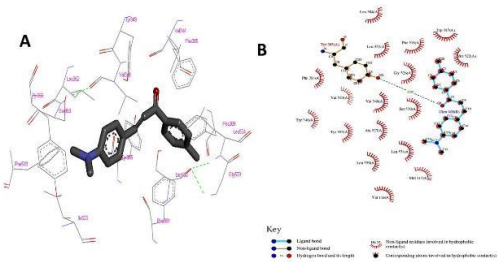

Figure 5: Depictions of the molecular modeling of the docking created between compound **19** and COX-1. (a) 3D represents the ligand-enzyme binding biochemical interactions. Compound **19** is shown in grey colour and hydrogen bonds as green lines; (b) 2D represents the hydrophobic interactions and H-bonding

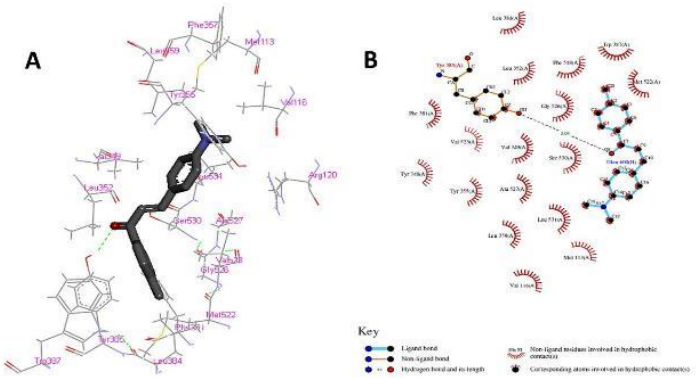

Figure 6: Depictions of the molecular modeling of the docking created between compound **19** and COX-2. (a) 3D represents the ligand-enzyme binding biochemical interactions. Compound **19** is shown in grey colour and hydrogen bonds as green lines; (b) 2D represents the hydrophobic interactions and H-bonding

Table 2: Docking result of the compounds and indomethacin against COX2 and COX1 enzymes*

Compound	Docking parameter			
	COX-1		COX-2	
	Lowest binding energy	***H-Bond***	***Lowest binding energy***	***H-Bond***
1	-5.93	TYR355:HH_ 1:O8 GLY526:HN- MET522:O ALA527:HN- ILE523:O SER530:HN- GLY526:O	-6.70	TYR385:OH_ TYR348:OH TYR385:OH_ 1:O8 GLY526:N- MET522:O
3	-6.29	TYR355:HH_ 3:O9 GLY526:HN- MET522:O ALA527:HN- ILE523:O SER530:HN- GLY526:O	-7.32	TYR385:OH_ TYR348:OH SER530:HN- GLY526:O GLY533:N- SER530:O LEU534:N- SER530:O
9	-5.79	GLN192:HE22- LEU352:O SER353:HN-VAL349:O GLY533:HN- SER530 LEU534:HN- SER530:O	-6.35	TYR385:OH_ 19:O8 TYR385:OH_ TYR348:OH GLY526:N- MET522:O SER530:HN- GLY526:O
Indomethacin	-6.53	GLN192:HE22- LEU352:O SER353:HN-VAL349:O TYR385:HH-indo:O23 LEU531:HN-ALA527	-8.15	ARG120:NH1-indo O23 ARG120:NH1-indo O24 GLY526:N- MET522:O

*The COX-1, COX-2 inhibitory of 1 and its derivatives prompted us to perform molecular docking studies to understand the ligand-protein interactions, and COX-1/COX-2 selectivity in detail. The docking studies *were carried out using autodock 4.2.* The crystal structures of COX-1 (1EQG)[22] and COX-2 (1PXX)[23] complexed with ibuprofen and diclofenac respectively were used for docking. *autodock 4.2*, an automated docking program, was used to dock these compounds into the active sites of COX-1 and COX-2 enzyme and the most stable conformation based on the best lowest binding energy

Table 3: ADMET properties of the compounds*

Compound	Absorption level	Solubility level	Brain blood ratio level	ADMET-PSA-2D*	ADMET-AlogP98
Indomethacin*	Good	Yes, Low	Medium	67.699	3.418
Ibuprofen*	Good	Yes, Good	high	38.116	3.607
Diclofenac*	Good	Yes, Low	high	50.926	4.373
1	Good	Yes, Low	Very high penetrant	17.3	3.702
3	Good	Yes, Low	Very high penetrant	17.3	4.188
19	good	Yes, low	Very high penetrant	20.653	4.35

*Bioavailability of test compounds 1, 3 and 19 as well as the drugs was assessed using ADMET (absorption, distribution, metabolism, excretion, and toxicity) prediction methods (table 2). Polar surface area (PSA) is a key property that has been linked to drug bioavailability

DISCUSSION

The present study was intended to examine the anti-cyclooxygenase (COX-1 and COX-2) effects, as well as molecular docking, and *in silico* ADMET of some synthesized chalcones. Abundant research has been conducted on the pharmacological properties of naturally occurring and synthetic chalcones [13]. The use of *in vitro* inhibitory activity testing of various enzymes, implicated in inflammations using COXs catalyzed prostaglandin synthesis bioassay, is extensively observed. Compound **22** showed the highest inhibition rate on COX-1 enzymes. Previous results suggest that chalcone derivatives act as inhibitor of both COX enzymes and show anti-inflammatory effects [14,15].

The anti-COX-1 and COX-2 activities of the synthesized chalcones was an encouraging sign to carry out molecular docking studies to recognize the compound-enzymes interactions, and COX-2/COX-1 specificity. The crystal 3D structures of both enzymes [COX-2 (1PXX) and COX-1 (1EQG)] were utilized for docking. *Autodock 4.2* was utilized for the docking of these chalcones into the binding sites of both enzymes, and the mainly stable configuration was done based on the best minimum binding energy. The three compounds (**1, 3** and **19**) that were selected for in silico investigations were chosen based on their chemical composition. They give a general idea of all compounds because they contain the chemical groups used in the synthesis of the other twenty-four compounds that were examined in this study, which includes the tolyl, diphenyl and dimethylamino groups.

Compound **1** was observed to bind with COX-1 and COX-2 active sites with various interaction energies. Compound **3** was also shown to dock into the binding sites of both enzymes (COX-1 and COX-2) with an interaction energy of 6.29 and 7.32 kcal/mol, respectively. Although compounds **2, 4, 14, 22** and **23** showed inhibitory effects towards both COX enzymes, there were still more powerful and selective inhibitors towards COX-1. Integration of *p*-OMe and OH substituents brought in a remarkable augmentation of COX-1s inhibition with compound 14 ($C4^{-}$ = OH, C4=OCH3) and compound 22 ($C4^{-}$= CH_3, C2=OH), revealing a selective and potent inhibition of the COX-1 isozymes. The amino acid Ser530 is very crucial in the reaction of the binding sites of COX-1 and COX-2 enzymes as explained earlier [16]. The reaction of these enzymes with arachidonic acid is regulated by Tyr385 [17].

Compound **3** and **19** showed selective inhibition to COX-2, and this could be explained by the absence of the H-bonding interaction with Ser530 in COX-1. Furthermore, the lowest binding energy of **3** and **19** with COX-2 proposes these compounds as the favored inhibitors for COX-2 than COX-1, and therefore justifies the selective inhibition of these chalcones. As it was observed that COX-2 and COX-1 enzymes have almost comparable binding site residues and varieties falls in its binding site size, COX-2 has bigger binding site volume- 417 Å3; while COX-1 has lesser active site volume-366 Å3) [18]. It also demonstrates that the selective inhibitors of COX-1 can uniformly affect COX-2, which is considered as equi-potency. While the bigger sized compound appears to be more discriminatory towards COX-2 due to its augmented size of the binding site [19]. It is also significant to consider that the style of binding of compound **3** and **19** in both COX enzymes is somewhat dissimilar due to its variation in the binding site volumes [20], and the selectivity matter was further sustained by our data demonstrating enhanced inhibitory effects towards COX-2 (Table 1) [21].

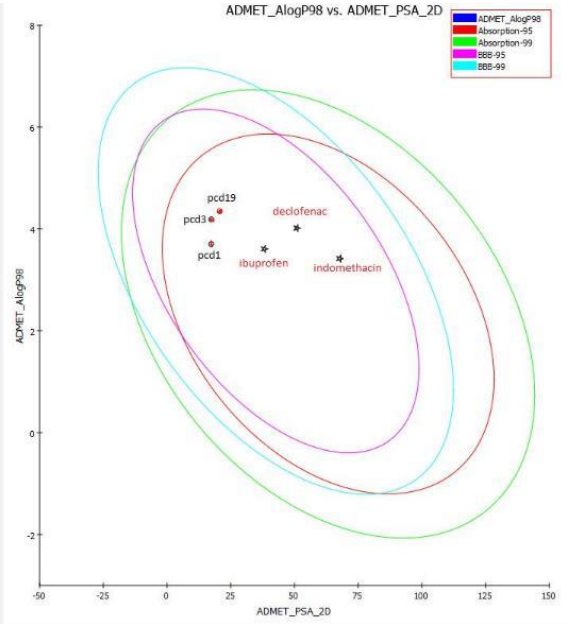

Figure 7: ADMET characteristics of the compounds. PSA-2D: polar surface area; ALogP: lipophilicity [AlogP98: logarithm of the octanol-water partition coefficient [values in parentheses were obtained based on a Simulations Plus model (S + log P)]

CONCLUSION

The synthesized chalcones exhibit varied anti-cyclooxygenases properties. Chalcone skeleton

with C=O at 4-position, C2–C3 double bond, and hydroxyl group at 5-position are necessary assets for cyclooxygenase inhibition. Thus, propenone moiety constitutes an appropriate scaffold for the design of novel acyclic 1,3-diphenyl prop-2-en-1-ones with discriminating COX-1 or COX-2 inhibitory property. *In silico* ADMET forecasting might be significant preliminary steps toward the discovery of novel pharmaceuticals in the fight against inflammation-related ailments.

DECLARATIONS

Acknowledgements

This work was supported by the Deanship of Scientific Research, Jazan University, Kingdom of Saudi Arabia (Initiatives' Program).

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. SIA, MA and MMET designed the study and wrote the manuscript. MMET and SIA collected the samples. MMET performed the experiments. SAI, MA, KH, HA, MMET and AF reviewed the manuscript.

REFERENCES

1. *Wang D, DuBois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene 2009; 29:781-788.*
2. *Rouzer CA, Marnett LJ. Cyclooxygenases: structural and functional insights. J Lipid Res 2009;50: S29-S34.*
3. *Guo W, Kong EH, Meydani M. Dietary polyphenols, inflammation, and cancer. Nutr & Cancer 2009; 61:807-810.*
4. *Sehajpal S, Prasad DN, Singh RK. Prodrugs of non-steroidal anti-inflammatory drugs (NSAIDs): a long march towards synthesis of safer NSAIDs. Mini Rev Med Chem 2018; 18:1199-1219.*
5. *Somasundaram C, Nath RK, Perkinson J, Somasundaram SG, Bjarnason I. NSAID-induced gut inflammation and vasoconstriction: Causes and potential reversal with beta-CGRPA hypothesis. Biosci. Hypotheses 2009; 2:290-294.*
6. *Yadav VR, Prasad S, Sung B, Aggarwal BB. The role of chalcones in suppression of NF-KapapB-mediated inflammation and cancer. Int Immunopharmacol 2011; 11:295-309.*
7. *Batovska DI, Todorova IT. Trends in utilization of the pharmacological potential of chalcones. Fundam Clin Pharmacol 2010; 5:1-29.*
8. *Huang Z-H, Yin L-Q, Guan L-P, Li Z-H, Tan C. Screening of Chalcone Analogs with Anti-depressant, Anti-inflammatory, Analgesic, and COX-2–inhibiting Effects. Bioorg Med Chem Lett 2020; 30:127173.*
9. *Syam S, Abdelwahab SI, Mohan S. Synthesis of Chalcones with Anticancer Properties. Molecules 2012; 17:6179-6195.*
10. *Wessel MD, Jurs PC, Tolan JW, Muskal SM. Prediction of human intestinal absorption of drug compounds from molecular structure. J Chem Inf Comput Sci 1998; 38:726-735.*
11. *Geerts T, Vander Heyden Y. In silico predictions of ADME-Tox properties: drug absorption. Comb Chem High Throughput Screen 2011; 1:339-361.*
12. *DÍAZ-TIELAS C, GRAÑA E, REIGOSA MJ, SÁNCHEZ-MOREIRAS AM. Biological activities and novel applications of chalcones. Planta Daninha 2016; 34:607-616.*
13. *Jantan I, Bukhari SNA, Adekoya OA, Sylte I. Studies of synthetic chalcone derivatives as potential inhibitors of secretory phospholipase A2, cyclooxygenases, lipoxygenase and pro-inflammatory cytokines. Drug Des Devel Ther 2014; 8:1405-1418.*
14. *Bukhari SN, Jantan I, Jasamai M. Anti-inflammatory trends of 1, 3-diphenyl-2-propen-1-one derivatives. Mini Rev Med Chem 2013; 13:87-94.*

15. Selvam C, Jachak SM, Gnana Oli R, Thilagavathi R, Chakraborti AK, Bhutani KK. A new cyclooxygenase (COX) inhibitory pterocarpan from Indigofera aspalathoides: structure elucidation and determination of binding orientations in the active sites of the enzyme by molecular docking. Tetrahedron lett 2004; 45:4311-4314.
16. Kurumbail RG, Kiefer JR, Marnett LJ. Cyclooxygenase enzymes: catalysis and inhibition. Curr Opin Struc Biol 2001; 11:752-760.
17. Zubieta C, Krishna S, Kapoor M, et al. Crystal structures of two novel dye decolorizing peroxidases reveal a barrel fold with a conserved heme-binding motif. Proteins 2007; 69:223-233.
18. Smith WL, DeWitt DL, Garavito RM. Cyclooxygenases: structural, cellular, and molecular biology. Annu Rev Biochem 2000; 69:145-182.
19. Marnett LJ, DuBois RN. COX-2: a target for colon cancer prevention. Annu Rev Pharmacol 2002; 42:55-80.
20. Zernov VV, Balakin KV, Ivaschenko AA, Savchuk NP, Pletnev IV. Drug discovery using support vector machines. The case studies of drug-likeness, agrochemical-likeness, and enzyme inhibition predictions. J Chem Inf Model 2003; 43:2048-2056.
21. Tareq Hassan Khan M. Predictions of the ADMET properties of candidate drug molecules utilizing different QSAR/QSPR modelling approaches. Curr Drug Metab 2010; 11:285-295.
22. Amir-Aslani A. Toxicogenomic predictive modeling: Emerging opportunities for more efficient drug discovery and development. Technol Forecast Soc Change 2008; 75:905-932.
23. Leeson PD, Springthorpe B. The influence of drug-like concepts on decision-making in medicinal chemistry. Nat Rev Drug Discov 2007; 6:881-890.
24. Abraham MH, Ibrahim A, Zissimos AM, Zhao YH, Comer J, Reynolds DP. Application of hydrogen bonding calculations in property-based drug design. Drug Discov Today 2002; 7(20):1056-1063.