Synthesis, anti-inflammatory, molecular docking and ADME studies of new derivatives of ketoprofen as cyclooxygenases inhibitor

Mustafa M. Allawi*, Monther F. Mahdi**, Ayad M. R. Raauf ***
*Department of Pharmacy, Uruk University College, Baghdad, Iraq.
**Department of Pharmacy, Ashur University College, Baghdad, Iraq.
***Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mustansiriyah, Baghdad, Iraq.

Abstract:

The synthesis of new selective COX-2 enzyme is an approach for obtaining potent, anti-inflammatory drugs that have fewer side effects. Ketoprofen has a very low selectivity toward COX-2 enzyme and has a serious GIT side effects because it induces gastric ulcer. A new series of 4-thiazolidinones bearing ketoprofen moiety was designed, synthesized, and then evaluated as a new inhibitor of cyclooxygenase-2 (COX-2). Characterization and identification of the synthesized compounds were established by determination of ^{1}H-NMR spectra, ^{13}C-NMR spectra, FT-IR spectroscopy, and physical properties.

These newly synthesized compounds have been evaluated in vivo for their anti-inflammatory efficiency and in silico selectivity toward COX-2 throughout molecular docking by using GOLD.suite.v.5.6.2. All the tested. compounds via molecular. docking showed significant. activities when compared. With ketoprofen and diclofenac as references drugs, the results were consistent with the study of in in vivo acute. anti-inflammatory activity.

Also, ADME studies had been accomplished in order to predict the absorption sites, bioavailability, topological polar surface Area (TPSA), and also drug-likeness. The ADME results reported that. All the synthesized. compounds can be absorbed by the GIT.

Key words: ketoprofen, docking, ADME, GOLD, Lipinski rule.

تخليق والدراسات المضادة للالتهابات والجزيئات و **ADME** لمشتقات جديدة من الكيتوبروفين كمثبط للإنزيمات الأكسدة الحلقية

مصطفى ماهر علاوي*، منذر فيصل مهدي**،اياد محمد رشيد رؤوف***
*فرع الكيمياء الصيدلانية/ كلية الصيدلة/ جامعة اوروك
**فرع الكيمياء الصيدلانية/كلية الصيدلة/كلية اشور الجامعة
***فرع الكيمياء الصيدلانية/كلية الصيدلة /الجامعة المستنصرية

الخلاصة:

تخليق مثبطات COX-2 الانتقائية الجديدة هي طريقة للحصول على أدوية فعالة مضادة للالتهابات لها آثار جانبية أقل. يحتوي كيتوبروفين على انتقائية منخفضة للغاية تجاه COX-2 وله آثار جانبية خطيرة في الجهاز الهضمي لأنه يسبب قرحة المعدة. تم تصميم وتوليف وتقييم سلسلة جديدة من مثبطات ٤-ثيازولدين التي تحمل مركب الكيتوبروفين كمثبطات إنزيم حلقية جديدة.(COX-2).

تم تحديد خصائص المركبات المركبة وتحديدها من خلال تحديد أطياف H-NMR¹و C-NMR ¹³ و مطيافية FT-IR والخصائص الفيزيائية.

تم تقييم هذه المركبات المركبة حديثًا في الجسم الحي للتأكد من كفاءتها المضادة للالتهابات وفي انتقائية السيليكو تجاه COX-2 من خلال الالتحام الجزيئي باستخدام GOLD suite v.5.6.2. أظهرت جميع المركبات المختبرة عبر الالتحام الجزيئي أنشطة مهمة عند مقارنتها بالديكلوفيناك والكيتوبروفين كعقاقير مرجعية ، وكانت هذه النتائج متوافقة مع دراستهم للأنشطة المضادة للالتهابات الحادة في الجسم الحي.

أيضا ، تم إنجاز دراسات ADME من أجل التنبؤ بمواقع الامتصاص ، والإمكانيات الحيوية ، ومساحة السطح القطبي الطوبوغرافية (TPSA) ، وكذلك تشابه الدواء. ذكرت نتائج ADME أن جميع المركبات المركبة يمكن امتصاصها من قناة الجهاز الهضمي.

الكلمات المفتاحية: الكيتوبروفين ، الالتحام ، ADME، GOLD suite program ، قاعدة Lipinski

Introduction

Cyclooxygenase considers as a rate-limiting. Enzyme that catalyzes the biosynthesis of arachidonic acid into thromboxanes and prostaglandins. These, bioactive metabolites give an important role in managing of the physiological. processes, such that mucosal secretions and contraction of smooth. Muscle, and in the regulation of pathological conditions such.as, allergic diseases and rheumatoidarthritis (1,2). Two isoforms of cyclooxygenase. COX-1 and COX-2, have been recognized (3,4,5). COX-1 is.constitutively.expressed.in.most.human.tissues.and.functions.as a house keeping gene.whereas.COX-2.is.an.immediate-early.gene.and.is.provided.by.oncogenes, growth factors. cytokines, endotoxins and phorbolesters.[6,7,8].Overexpression.of.CO-2. Had been resulted in chronic inflammation, angiogenesis and carcinogenesis[9].

Non- steroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used drugs in the world because it contains anti-inflammatory, anti-fever and analgesic properties [10,11]. However, their common use results in serious gastrointestinal problems in approximately 1: 4 of their users [12].

In recent years, medical studies indicate that NSAIDs are also neuroprotective agents

, that the prolong uses of NSAIDs decrease the chance of Alzheimer disease [14].

Moreover, medical studies have shown the discovery of NSAIDs derivatives are promising to give anticancer activity [15].

The most common side effects of using NSAIDs are ulcers in the stomach or intestines. Thus, patients who use these drugs have a three-fold incidence of ulcer than those who do not [16, 17]. As a result, we need anti-inflammatory drugs and pain relievers that are free of digestive problems [18].

The NSAIDs have different chemical properties, because almost are organic acids. Regardless of having structural diversity, NSAIDs possess a typical mode of action, that inhibit prostaglandin (PG) which is synthesized mostly through their COX enzyme inhibition, that catalyzes the bioconversion of arachidonic acid into prostaglandins and thromboxanes [19].

Ketoprofen is one of the propionic acid class of nonsteroidal anti-inflammatory drugs (NSAID) with analgesic and antipyretic effects. It acts by inhibiting the body's production of prostaglandin[20].

In order to increase the suppressive effect of ketoprofen on the COX-2 enzyme, some ketoprofen derivatives were synthesized by adding new functional groups to the ketoprofen scaffold. For this purpose, medicinal chemists use different tools to optimize the potency, unwanted property and selectivity of a given lead drug structure toward a given targeted COX-2 enzyme.

There are several biological active molecules that contain various heteroatoms like nitrogen, sulfur and oxygen, always have the attention of chemist over the years mainly due to their biological importance. Thiazolidinones are thiazolidine derivatives, that have an atom

of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at positions 2, 4, or 5 [21].

Thiazolidinone, a saturated form of thiazoles with carbonyl group on fourth carbon, has been considered as a moiety of choice as it possesses a broad spectrum of pharmacological activities [22].

These new synthesized compounds would demonstrate the potency of anti-inflammatory agents and show higher selectivity with COX-2 enzyme because of their larger size than their parent ketoprofen compound, however, the actual fact of the presence of the side pocket close to the base of the COX-2 binding site makes its site 20% larger than that of COX-1, therefore, the active center of COX-2 can receive larger structures in comparison with those that are capable of fitting the active site of COX-1[23].

Materials and Methods

General

All the used reagents and anhydrous solvents, were from annular type and they received from the commercial suppliers (Merck, Germany, Reidel-De Haen, Germany, Sigma-Aldrich, Germany and BDH, England). Ketoprofen had been supplied by the GK Bio-Technology Company, China. Melting points has been determined by capillary method on Bamstead/Electro¬thermal 9100 an electrical melting point apparatus (England). The identification of compounds has been done using a FT- IR spectrum and recorded on a FTIR-spectrophotometer FT-IR-6100 Type A as KBr disks. ^{1}H-NMR determined by H-NMR device Instrument Model: Bruker 300 MHz-Avanc III. ^{13}C-NMR determined by C-NMR device Instrument Model: Bruker 75.65 MHz-Avanc III.

Typical procedure for the reactions
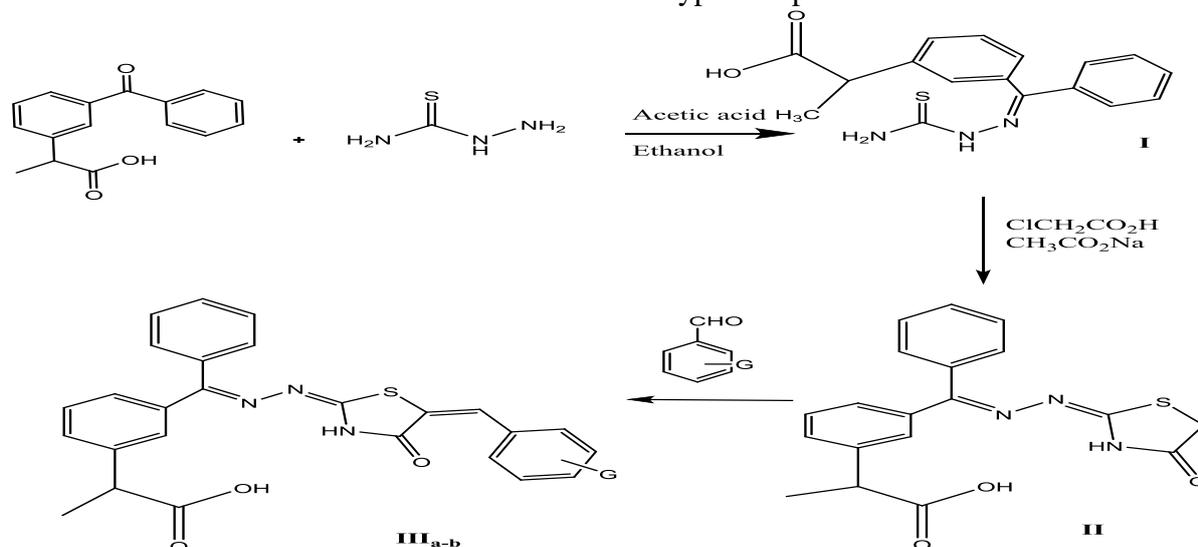
G= H (a), OCH$_3$ (b)

 Scheme 1: The synthesis of target compounds (III$_{a-b}$) was achieved following procedures

Synthesis Ketoprofen thiosemicarbazone derivative, compound(I):

Ketoprofen thiosemicarbazone was synthesized by mixing ketoprofen (0.254g, 0.001mole) and thiosemicarbazide (0.091g, 0.001mole) both dissolved in methanol (10 mL) with one drop of concentrated hydrochloric acid and bringing the reaction mixture to a reflux on the water bath for two hours. A white colored microcrystalline product separated out when the mixture was allowed to cool, filtered and then washed with ether and dried in vacuum [24].

Synthesis_of_2-(3-((E)-(((E)-4-oxothiazolidin-2-ylidene) hydrazono)(phenyl)methyl) phenyl) propanoic acid, compound (II):

A mixture consists of compound I (3.27g, 0.01mole) in an absolute ethanol (10mL) that contain chloroacetic acid (0.01mole) with fused sodium acetate (0.03mole) had been refluxed to 6 hrs. The final product obtained was then poured onto ice-water (100mL) and the formed precipitate had been filtered off, then washed with water and dried, finally recrystallized from ethanol. [25].

General procedure for the synthesis of compounds (III_a-b):

To a solution of compound II (0.01 mile) mixed with anhydrous sodium acetate (0.015 moles) in the solvent glacial acetic acid (10 mL) had been added the benzaldehyde (0.01 mile). This mixture was then refluxed to 6hrs with continuous stirring. The mixture has been left for cooling, then poured onto crushed ice with stirring. The separated precipitate had been filtered, then washed with water and dried, finally recrystallized from ethanol [26].

(Z)-2-(3-((2carbamothioylhydrazono)(phenyl)methyl)phenyl)propanoic acid(I): Off-white crystals (84% yield); mp 166-168°C; IR (KBr) v (cm^{-1}): 3429 (NH$_2$-C=S), 3159 (NH), 1732 (C=O), 1589 (C=N), 927 (C=S); ^{1}H-NMR (DMSO-d$_6$,

300 MHz): δ 7.25 (s, 1H, SH), δ 8.40 (d, 2H, NH$_2$-C=S), δ 8.44 (s, 1H, NH-C=S), δ 12.39 (br. s, 1H, OH); ^{13}C-NMR (DMSO-d$_6$, 75.65 MHz): δ 174.39 (1C, C=N), δ 175.50 (1C, C=O), δ 178.35 (1C, C=S).

2-(3-((E)-(((E)-4-oxothiazolidin-2-ylidene)hydrazono)(phenyl)methyl)phenyl)propanoic acid (II): Off-white crystals (88% yield); mp 91-92°C; IR (KBr) v (cm-1): 3452 (NH), 1728 (C=O carboxylic acid), 1653 (C=O amide), 1589 (C=N); ^{1}H-NMR (DMSO-d6, 300 MHz): δ 3.58-3.62 (doublet of doublet, 2H, S-CH2-C=O), δ 8.44 (s, 1H, NH-C=O), δ 12.39 (br. s, 1H, OH); ^{13}C-NMR (DMSO-d6, 75.65 MHz): δ 33.35 (C-S), δ 161.65 (1C, C=N of Thiazolidinone ring), δ 166.47 (1C, C=N), δ 166.66 (1C, C=O of 4-thiazolidinone), δ 174.55 (1C, C=O of carboxylic acid).

2-(3-((E)-(((E)-5-((E)-benzylidene)-4-oxothiazolidin-2-ylidene)hydrazono)(phenyl)methyl)phenyl)propanoic acid (IIIa): Yellow powder (70% yield); mp 80-82°C; IR (KBr) v (cm^{-1}): 3452 (NH), 1728 (C=O carboxylic acid), 1654 (C=O amide), 1585 (C=N); ^{1}H-NMR (DMSO-d6, 300 MHz): δ 7.78 (s, 1H, CH vinyl group), δ 8.65 (s, 1H, NH-C=O), δ 10.20 (br. s, 1H, OH); ^{13}C-NMR (DMSO-d6, 75.65 MHz): δ 33.48 (C-S), δ 142.43 (1C , C=C vinyl group), δ 162.86 (1C, C=N of ring), δ 166.88 (1C, C=N), δ 174.69 (1C, C=O of 4-thiazolidinone), δ 175.86 (1C, C=O of carboxylic acid).

2-(3-((E)-(((E)-5-((E)-4-methoxybenzylidene)-4-oxothiazolidin-2-ylidene)hydrazono)(phenyl)methyl)phenyl)propanoic acid (III$_b$): Pale yellow crystals (70% yield); mp 73-74°C; IR (KBr) v (cm^{-1}): 3452 (NH), 1730 (C=O carboxylic acid), 1654 (C=O amide), 1527 (C=N); ^{1}H-NMR (DMSO-d6, 300 MHz): δ 3.89 (s,1H, OCH$_3$), δ 7.44 (s, 1H, CH vinyl group), δ 8.42 (s, 1H, NH-C=O), δ 12.00 (br. s, 1H, OH); ^{13}C-NMR (DMSO-d6, 75.65 MHz): δ 33.27 (C-S), δ 52.30 (1C, methoxy), δ 141.46 (1C , C=C vinyl group), δ 161.83 (1C, C=N of ring), δ

166.17 (1C, C=N), δ 174.33 (1C, C=O of 4-thiazolidinone), δ 174.49 (1C, C=O of carboxylic acid).
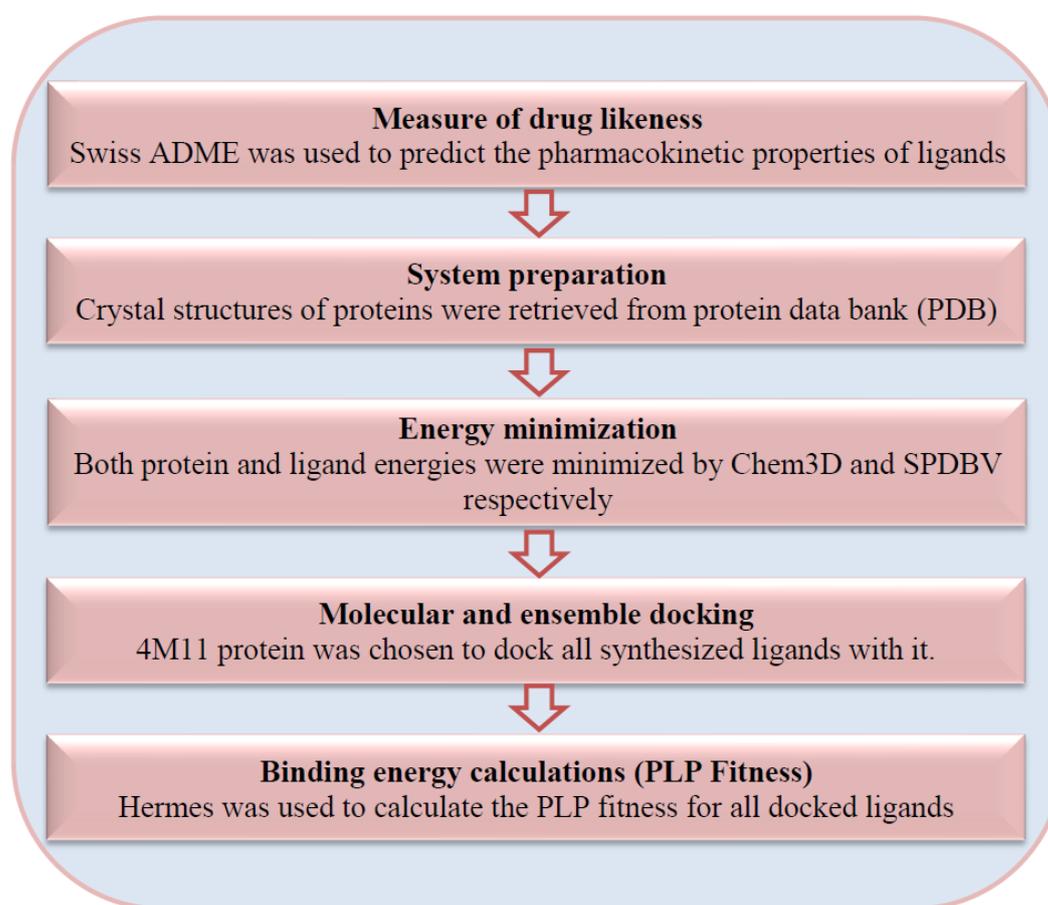
Computational Method

The application of computational method performed in our work is reported in (**Figure 1).**

CCDC GOLD Suite (*v. 5.6.2*) had been utilized for achieving the study of molecular docking for all the tested ligands. CCDC visualizer software (Hermes *v. 1.9.2*) had been utilized for visualizing: the protein used, tested ligands, interactions of hydrogen bonding, the short contacts, and finally the bonds length calculations. These ligands chemical structures had been drawn with ChemBioOffice (*v. 17.1*) software.

The pharmacokinetic profiles, i.e., ADME of the new synthesized compounds were reported by using the swiss ADME server [27].

Measure of drug likeness
Swiss ADME was used to predict the pharmacokinetic properties of ligands

System preparation
Crystal structures of proteins were retrieved from protein data bank (PDB)

Energy minimization
Both protein and ligand energies were minimized by Chem3D and SPDBV respectively

Molecular and ensemble docking
4M11 protein was chosen to dock all synthesized ligands with it.

Binding energy calculations (PLP Fitness)
Hermes was used to calculate the PLP fitness for all docked ligands

(Figure 1): Computational protocol outlines

ADME procedures:

All the synthesized ligands (IIIa, IIIb) had been drawn by Chem Sketch (v.12), then converted to the SMILE name using the tool (Swiss ADME) that estimates the physicochemical parameters and also the pharmacokinetic characteristics. BOILED EGG has been used to predict the polarity and lipophilicity report for the small molecules [28].

Preparation of the tested ligands and protein receptor:

The crystallin structure for the enzyme COX-2 [PDBID: 4M11] had been obtained from the Protein Data Bank (PDB), and then their missing atoms had been inserted by the using of Swiss PDB Viewer (SPDBV) (v. 3.7). The crystallin structure for our COX-2 protein has been prepared by deleting all the water molecules, then the addition of hydrogen atoms for

achieving the correct state of ionization and tautomeric for the amino acid residues. CheBio3D (v. 17.1) had been utilized for energy minimization of our new synthesized ligands via application of MM2 force field.

Docking procedures:

The full licensed version of Genetic Optimization for Ligand Docking (GOLD) (v. 5.6.2) had been utilized for the process of molecular docking [29,30]. The visualizer software (Hermes) used within the GOLD Suite for setting up the COX receptors to the docking process. The binding sites utilized in GOLD docking were reported that all the protein residues inside the 10 A^o for the referenced ligands which hold within the COX protein structure complexes. Five COX-2 proteins had been downloaded from the PDB website (1pxx, 4m11, 3LN1, 3KK6 and 5kIR) for performing the molecular docking process [31]. Therefore, 4m11 had been selected for the docking process of the tested compounds.

The cavity and the active sites had been demonstrated by utilizing CCDC hermes. The reference ligands of the choosed protein had been applied for determination the radius (10 A^o) for the active sites. Chemscore kinase had been utilized as a configuration template. ChemPLP has been applied to the scoring function. The parameters values that were utilized during the docking process were kept to the default, and all the solutions were scored referring to Piecewise Linear Potential (CHEMPLP) fitness function. According to the CHEMPLP, the steric complementary within the protein and ligand was determined while the bond distance and hydrogen angle-dependent are assessed. The docking results, i.e., the binding mode, pose docked, and the binding free energy was determined for estimating the interaction between the amino acid residues of COX-2 proteins and our synthesized compounds.

Results and Discussion

Chemistry:

The first step of the reaction is the removal of a proton from NH by sodium acetate which resulted in the conversion of the resulting intermediate to a partially or totally thiol form.

The second step exhibits a nucleophilic attack by thiol on a carbon atom that bears a good leaving group (CH-Cl) that will result in the formation of new S-C bond. This step is followed by a nucleophilic attack by NH2 on the carbon atom of the carbonyl group resulted in the formation of a five-member heterocyclic ring. The carbonyl group at position 4 of the heterocyclic ring may be formed by losing one molecule of water.

Thiosemicarbazone and benzaldehyde derivatives which involve the following steps: [32]

Step 1: Formation of enolate ion (acid-base reaction): Is an acid-base reaction. Hydroxide acts as a base that removes an acidic α-hydrogen giving a reactive enolate.

Step 2: Alkoxide formation (nucleophilic addition): The nucleophilic enolate attacks the carbonyl carbon of benzaldehyde in a nucleophilic addition process giving an intermediate alkoxide.

Step 3: Protonation of alkoxide: The alkoxide deprotonates a water molecule producing a hydroxide ion and a β-hydroxy ketone, the aldol product.

Step 4: Dehydration: The hydroxide functions as a base that removes an acidic β-hydrogen giving the reactive enolates. The electrons bear a negative charge of the enolate are used to form a carbon-carbon double bond (C=C) and displace a leaving group, regenerating the hydroxide giving the final product, the conjugated ketone [33].

Pharmacology:

Many irritant agents had been used in the paw-edema method such as egg-white, dextran and carrageenan solution. The egg-white intraplanar injection into rat hind paw exhibit progressive edema. To ensure

the validity of the method (paw-edema) used for the evaluation of the new synthesized anti-inflammatory compounds, ketoprofen was used as a refrence drug of known anti-inflammatory activity profile, as shown in Table 1 and Fig. 2. Non-

identical superscripts (IIIa and IIIb). Numbers are stated in mm paw width as mean ± SEM. n = number of rats. Time (0) is the i.p. injection time of tested compounds. Time [30] is the egg-white injection time.

Table 1. The anti-inflammatory action of synthesized compounds (III$_a$ and III$_b$), ketoprofen and control on egg-white induced paw edema in rats

compounds	Time(min)			Versus	Paw thick.	in(mm)	
	0	30	60	120	180	240	300
control	2.53±0.06	5.85±0.04	6.65±0.07	6.84±0.04	6.34±0.04	6.19±0.05	5.88±0.04
ketoprofen	2.57±0.04	5.84±0.08	6.64±0.05	6.54±0.05*a	5.84±0.05*a	4.85±0.03*a	3.88±0.06*a
III$_a$	2.47±0.03	5.88±0.02	6.63±0.04	5.72±0.03*b	4.91±0.06*b	3.46±0.03*b	2.60±0.08*b
III$_b$	2.46±0.05	5.86±0.06	6.77±0.07	5.66±0.05*b	3.77±0.04*c	3.13±0.06*c	2.54±0.06*c

Duration (min)
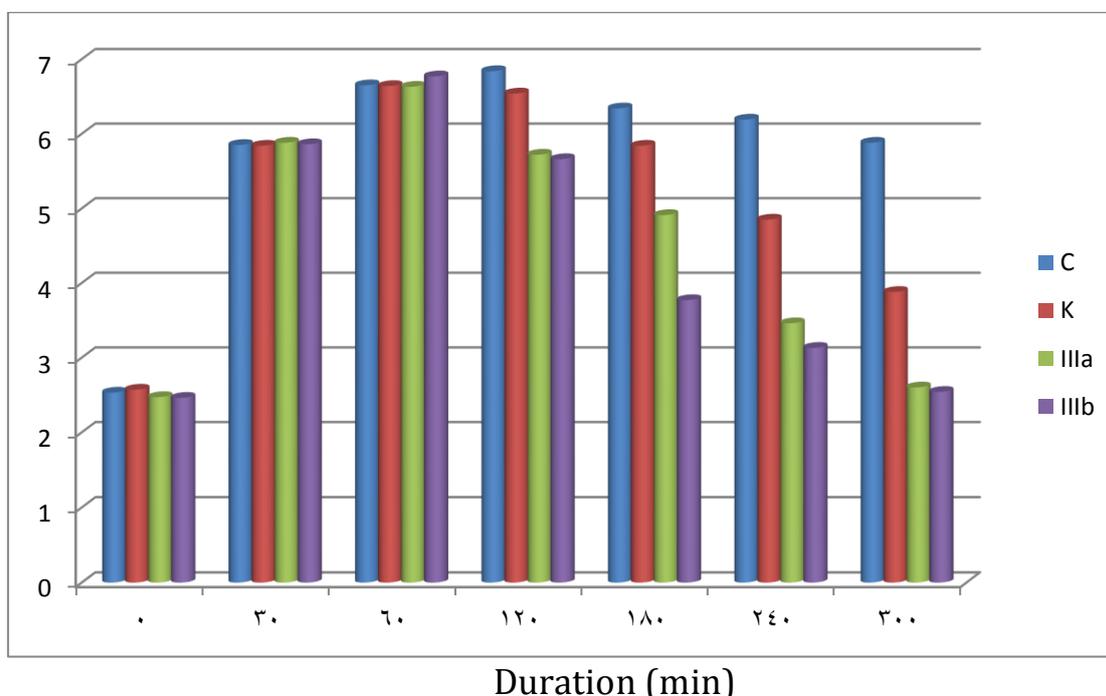
(Figure 2) Effect of propylene glycol, ketoprofen, com¬pounds (IIIa and IIIb) on egg-white induced paw edema in rats.

Molecular Modeling

GOLD is considered as a "genetic algorithm to dock flexible ligands into protein binding sites" (34). GOLD was widely verified and was showed excellent rendering for the pose predictions and superb docking results for the virtually screening (35). It was supplied in the GOLD Suite, that has further software components, such as GoldMine, Hermes, Mercury, and Isostar and Conquest, etc.….

Minimization of energy of the ligands and proteins can be fixed the twisted geometries via shifting atoms to show internal constraints. After the energy minimization, the geometries are fixed that mean minimum energy has been accomplished.

To expect the energy of selectivity and binding for the new synthesized compounds to COX -2, docking studies were carried out by the help of GOLD Suite software for studying the molecular

interactions involved between the synthesized compounds (IIIa & IIIb) and active binding sites of the targeted protein. The COXs inhibition action of the compounds IIIa, IIIb, diclofenac, and ketoprofen had been ranked on the basis of their PLP fitness that involved at the active sites during the complex formation. The docking PLP fitness of all tested compounds on COX 2 was found in the range of 77.20 to 81.66, respectively in table (2).

There was a superb consistency for our docking results and the experiment's results (In vivo study). Ensemble docking is so important because it decreases the risk of accidentally choosing of inappropriate protein model, improving in pose expectations, virtually screening improvements, and for ensuring that the docking process is in a true direction, this is why we started the first step with ensemble docking by involving five diverse COX-2 proteins.

Docking analysis reported that Arg120, Tyr355, Ser530, Met522, Val349, Ala527, Gly526, Trp387, listed in the table (2) of this enzyme, involved interaction by hydrogen bonding and also short contacts for our tested ligands library.

The distance of these hydrogen bonds and short contacts between our synthesized ligands and a specific protein atom is reported by GOLD and all the bonds length less than 3A° [36].

The short contacts can be defined as other interaction forces like van der Waals, electrostatic, steric, pi-pi stacking, dipole-dipole, and others.

All the synthesized ligands having very well docking results with COXs, fitting in the COX-2 active site as shown in (figures 3to 6) COX- 1 binding results reported lower binding energy because COX-2 active site is larger than COX-1 active site, and the new synthesized ligands have a big structure that makes difficult insertion within COX-1 enzyme pocket.

Compound IIIb show the best docked PLP fitness, that was 81.66 within COX-2, there was one H-bond contacts with Tyr385&Ser530 and short contact with Tyr355 as in (figure 5&6). Little hydrophobic contacts report low biological activity, when increses the number of hydrophobic contacts, the biological activity will also be higher because these contacts will outweigh the H-bonding contacts and these bonds play a major role in the binding of a pose to an active site [37].

(Table 2): The binding energies for ketoprofen derivatives and references NSAIDs docking with COX-2.**

Compounds	COX-2 Binding Energy (PLP Fitness)	AminoAcids Included in H-bonding	Amino Acids Included in Hydrophobic Interactions
III$_a$	77.20	Arg120&Ser530	Arg120&Val349
III$_b$	81.66	Tyr385&Ser530	Tyr355
Diclofenac	71.7	Ser530 &Tyr385	Ala527, Val349, Gly526 &Trp387
Ketoprofen	67.5	Tyr355&Met522	Gly526
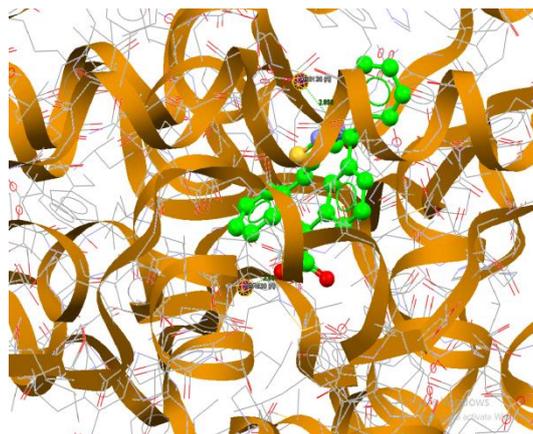
(Figure 3): Hydrogen bond interaction profile for the compound III_a. The interaction between compound III_a and amino acid residues Arg120&Ser530. [III_a: Ball and stick style, amino acid residues in Ball and stick style and the active site pocket in purple color].
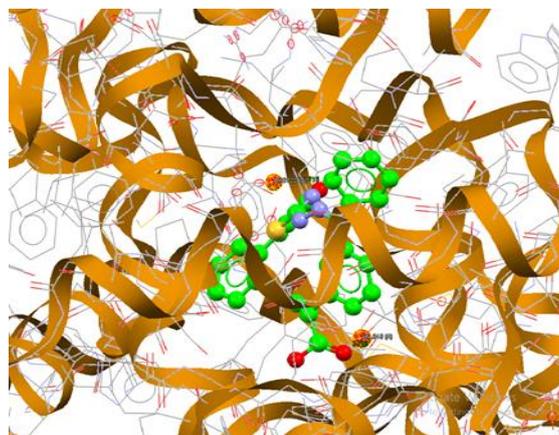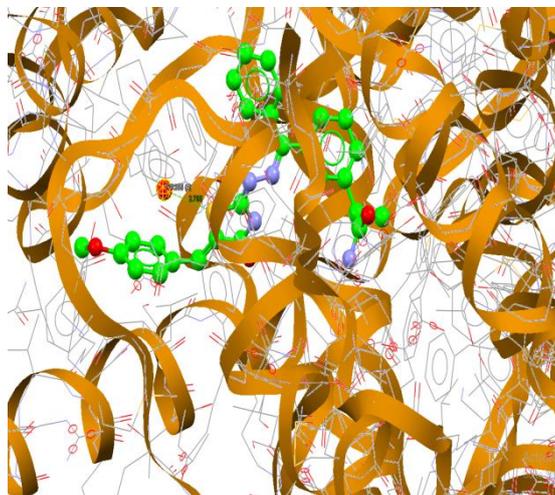

(Figure 4): Short contact interaction profile for the compound III_a. The interaction between compound III_a and amino acid residues Arg120&Val349. [III_a: Ball and stick style, amino acid residues in Ball and stick style and the active site pocket in red color].
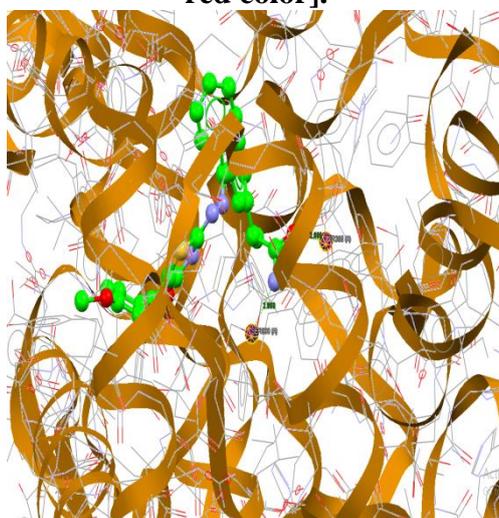
(Figure 5): Hydrogen bond interaction profile for the compound III_b. The

interaction between compound III$_e$ and amino acid residues Tyr385&Ser530. [III$_e$: Ball and stick style, amino acid residues in Ball and stick style and the active site pocket in purple color].

(Figure 6): Short contact interaction profile for the compound III$_b$. The interaction between compound III$_e$ and amino acid residues Tyr355. [III$_e$: Ball and stick style, amino acid residues in Ball and stick style and the active site pocket in red color].

ADME Studies

The ADME studies results for our synthesized analogues had been reported by Swiss ADME server to demonstrate which is the safer and potent drug candidate(s), for excluding the tested compounds that may fail in the next stages of the drug development because of the uncomplimentary ADME results.

We exposed all the synthesized compounds to ADME (adsorption, distribution, metabolism, excretion) method. Briefly, Lipinski rule related to the oral administration of the drugs that should have ≤ 5 hydrogen bonds donor, $\leq$ 10 hydrogen bond acceptor, LogP ≤ 5 and molecular weight (M.Wt.) ≤ 500 to be given orally [38].

Also, the topological polar surface area (TPSA) was calculated, because it considers as a very important characteristic that was associated with the bioavailability of the drugs. As a result, the passively absorbing molecules within a TPSA >140 A^o are considered to have lower oral bioavailability (39). Our study results reported that all synthesized compounds had TPSA < 140, that are in the range (106-115) and the bioavailability results were 0.55 for all ligands this means that all ligands can reach the systemic circulation. Compounds IIIa and IIIb fulfilled Lipinski rule, (Figures7 to 9) respectively. In addition, they also fulfilled the topological description and fingerprints of molecular drug-likeness structure keys such as LogP and Log S.

The GI absorption result score is an amount of absorption of a molecule by the intestine after the oral administration. The absorption would be maximum if the result was high. For our study, the absorption of GI for all synthesized ligands was higher than expectations to be well absorbed by the intestine.
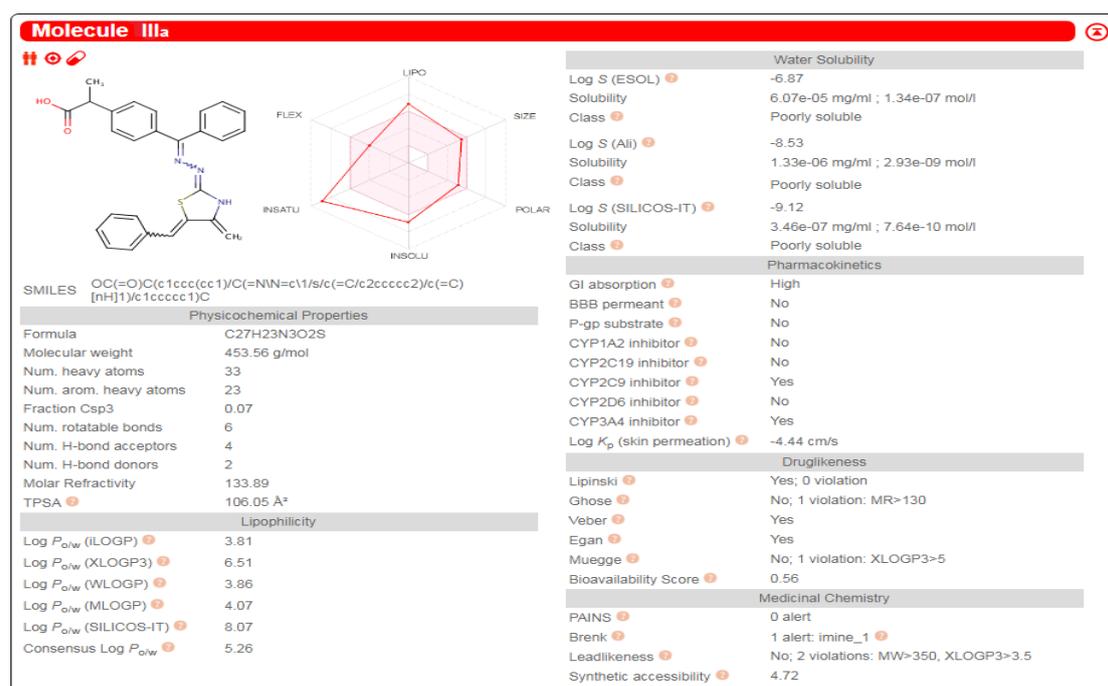
(Figure 7): ADME study of Compound (III$_a$)
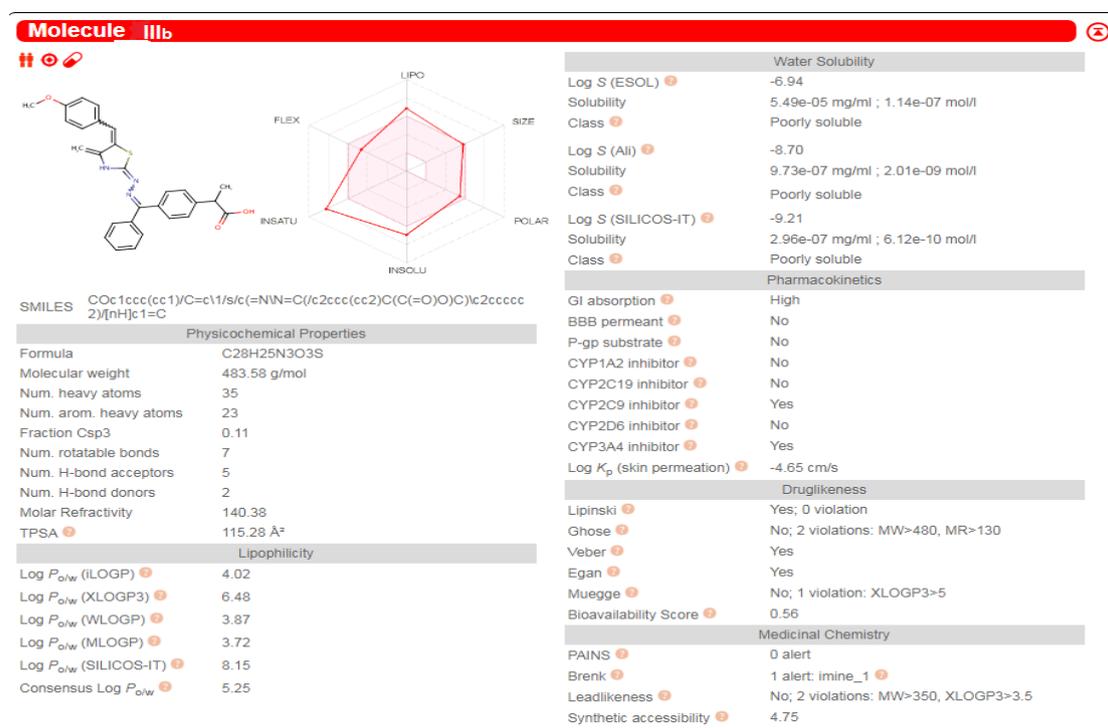
(Figure 8): ADME study of Compound (III$_b$)
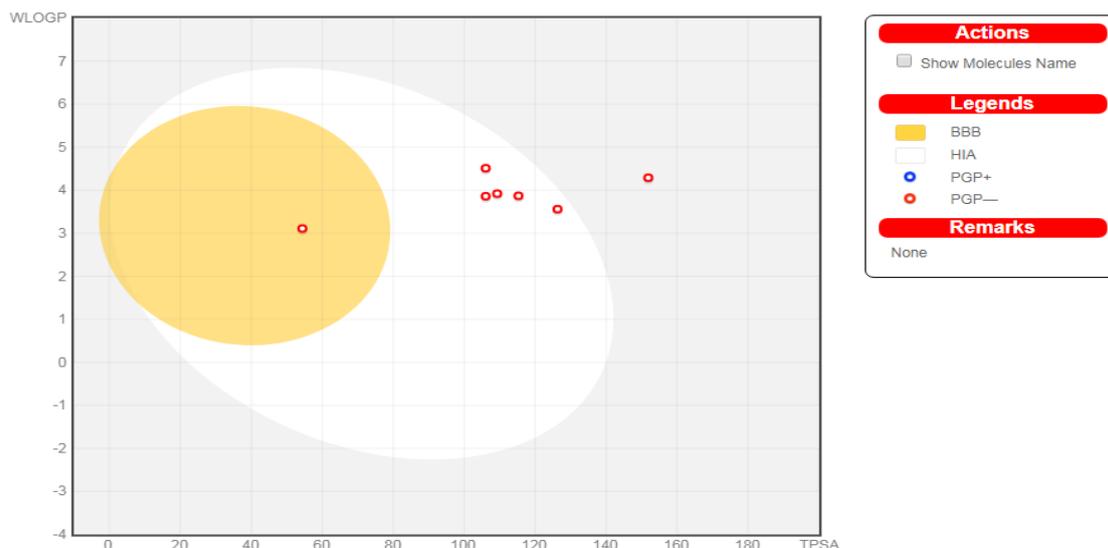
(Figure 9): BOILED EGG – for ketoprofen and final compounds.

Yellow ovule (yolk): are molecule predicted to passively permeate through blood-brain barriers.

White ovule (white): are molecule predicted to passively absorbed by the GIT.

PGP+: Blue dots are for molecules predicted to be effluated from the CNS by the P-glycoprotein.

PGP-: Red dots are for molecules predicted not to be effluated from the CNS by the P-glycoprotein

Conclusion

The anti-inflammatory evaluation of the final products gives an indication that the insertion of 4-thiazolidinone pharmacophore into ketoprofen enhanced its anti-inflammatory activity.The study of ADME reported that compounds IIIa and IIIb fulfilled the Lipinski rule, and all the synthesized compounds absorbed by GIT.The study of Docking reported a perfect consistency with In vivo study of compounds (IIIa and IIIb).The Preliminary study of anti-inflammatory efficiency reported that compound (IIIb) have a higher anti-inflammatory impact than all the other compounds.anti-inflammatory impact than all the other compounds.

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