

## Design, Synthesis, and Acute Anti-inflammatory Assessment of New 2-methyl Benzoimidazole Derivatives Having 4-Thiazolidinone Nucleus

Abdul Muhaimen Amjed Adnan\*, Monther Faisal Mahdi\*\*, Ayad kareem Khan\*\*\*

\* Department of Pharmacy, Baghdad College of Medical Science, Baghdad, Iraq.

\*\*Department of pharmaceutical Chemistry, Ashur University College, Baghdad, Iraq.

\*\*\*Department of pharmaceutical Chemistry, College of Pharmacy, University of Mustansiriyah, Baghdad, Iraq.

DOI: <https://doi.org/10.32947/ajps.19.04.0427>

### Article Info:

Received 25 Aug 2019

Accepted 28 Oct 2019

Published 1 Nov 2019

Corresponding Author email:

[ayad@uomustansiriyah.edu.iq](mailto:ayad@uomustansiriyah.edu.iq)

### Abstract:

New two derivatives of 2- methyl benzoimidazole were designed, synthesized and evaluated as a potential cyclooxygenase-2 [COX-2] inhibitors. The synthesized compounds have been recognized according to their spectral FT-IR, <sup>1</sup>H-NMR data and physical pro-

erties. The newly synthesized compounds were investigated in vivo for their anti-inflammatory activities using egg-white stimulated paw edema method with respect to the effect of propylene glycol 50% v/v [control group] and the ibuprofen [10mg/kg i.p.] was selected as a reference ligand. New compounds showed a significantly higher in vivo anti-inflammatory activity compared with ibuprofen as a reference drug. COX-2 selectivity evaluation through molecular docking via GOLD suite [v. 5.6.2.]. The new compounds via molecular docking showed significant higher activities when compared with ibuprofen as referenced drugs because of having hydrogen bonding interaction toward the key amino acids within COX-2 structure and all these results were compatible with the study of in vivo acute anti-inflammatory activities for tested compounds. ADME studies were performed to predict absorption, bioavailability, topological polar surface area, and drug-likeness. The results of ADME studies showed that all synthesized compounds absorbed from the gastrointestinal tract.

**Key words:** 2-methyl benzoimidazole, 4-thiazolidinone, Anti-inflammatory activity, ADME, GOLD

تصميم ، توليف ، والتقييم لمضادات للالتهابات الحادة لمشتقات ٢-ميثيل بنزوإميازول الجديدة والتي تحتوي على نواة ٤-ثيازوليدونون

عبد المهيمن امجد عدنان\*، منذر فيصل مهدي\*\*، اياد كريم خان\*\*\*

\*قسم الصيدلة ، كلية بغداد للعلوم الطبية ، بغداد ، العراق.

\*\*قسم الكيمياء الصيدلانية ، كلية عاشور الجامعة ، بغداد ، العراق.

\*\*\*قسم الكيمياء الصيدلانية ، كلية الصيدلة ، الجامعة المستنصرية ، بغداد ، العراق

الخلاصة:

تم تصميم وتحضير وتقييم مشتقان جديان من ٢- ميثيل بنزوإميازول كمثبطات لإنزيم سيكلو اوكسجينيز ٢-[COX-2]. تم التعرف على تراكيب المركبات المصنعة وفقاً لطريقة الاشعة تحت الحمراء الطيفية وبيانات الرنين النووي المغناطيسي للبروتون والخصائص الفيزيائية. تم فحص المركبات المصنعة حديثاً في الجسم الحي بسبب أنشطتها المضادة للالتهابات باستخدام طريقة ذمة مخلب البيض المحفز بالبيض الأبيض فيما يتعلق بتأثير البروبيلين غليكول ٥٠% v / v (المجموعة الضابطة) وتم اختيار الإيبوبروفين [١٠ ملغم / كلغ] كمرجع للمقارنة. أظهرت المركبات الجديدة ارتفاعاً ملحوظاً في النشاط المضاد للالتهابات في الجسم الحي مقارنة بالإيبوبروفين كدواء مرجعي. تقييم انتقائية COX-2 من خلال الالتحام

الجزيني عبر [v. 5.6.2] GOLD suite أظهرت المركبات الجديدة عبر الإرساء الجزيني أنشطة اعلى بكثير عند مقارنتها الإيبوبروفين كدواء مرجعية بسبب تكون الاصرة الهيدروجينية مع الأحماض الأمينية الرئيسية داخل تركيب COX-2 وكانت جميع هذه النتائج متوافقة مع دراسة الأنشطة المضادة للالتهابات الحادة في الجسم الحي للاختبار. أجريت دراسات ADME للتنبؤ الامتصاص ، والتوافر البيولوجي ، مساحة سطح القطبية الطوبوغرافية ، وتشبه الدواء. أظهرت نتائج دراسات ADME ان جميع المركبات المصنعة تمتص من الجهاز الهضمي.

**الكلمات المفتاحية:** ٢-ميثيل البنزيميدازول ، ٤-ثيازوليدون ، نشاط مضاد للالتهابات ، ADME ، GOLD

## Introduction

Inflammation is a basic way in which the body interacts with infection, irritability, the main characteristic is redness, warmth, swelling, and pain. Inflammation is now recognized as a type of non-specific immune response [1]. Inflammation can be classified as either acute or chronic. Acute inflammations describe the rapid response of innate immune components to a challenge. Acute inflammation starts rapidly and quickly becomes severe like acute bronchitis, sore throat from a cold or flu, acute appendicitis, acute dermatitis, acute tonsillitis, and acute sinusitis. While chronic inflammation may arise because of susceptibility in the individual to continue the inflammatory response, failure to eradicate the agents or factors triggering inflammation [e.g. foreign body embedded in injured tissue], persistent microbial infection [e.g. TB, or continuing tissue damage] and pro-inflammatory stimuli, such as those encountered in the atherosclerotic plaque [2-3].

The NSAIDs exert their therapeutic action by inhibiting of cyclooxygenase [COX-1], and [COX-2], which are responsible for the biosynthesis of the pro-inflammatory prostaglandins [PGs]. It was believed that blocking COX-2 will lead to the antipyretic, analgesic and anti-inflammatory effects and in addition NSAIDs blocks COX-1 that lead to side effect [4]. Side effects depend on the specific drug but largely include an increased risk of gastrointestinal ulcers and bleeds, heart attack and kidney [5].

Benzoimidazole is a heterocyclic aromatic organic compound. The synthesis of benzoimidazole took attention of pharmacists from the last few decades as it plays an important role as pharmacophore in medicinal chemistry and pharmacology.

Benzoimidazole is a bicyclic compound consisting of the fusion of benzene ring with imidazole ring which ultimately gives a privileged structure. This moiety has many pharmacological properties. Till now the most common benzoimidazole moiety is *N*-ribosyl- dimethylbenzimidazole found in nature and it serves as the axial ligand for cobalt in vitamin B12[6].

The 4-thiazolidinone derivatives are versatile and found in a number of clinically used drugs. They have found many uses as antibacterial [7], anti-tubercular [8], anti-inflammatory [9] and as antiviral agents, especially as anti-HIV agents [10] Therefore, groups of 4-thiazolidinone pharmacophore derivatives incorporated in 2-methyl benzoimidazole were designed, synthesized and evaluated as anti-inflammatory agents with expected inhibitory selectivity towards COX-2 enzyme.

## Materials and Methods

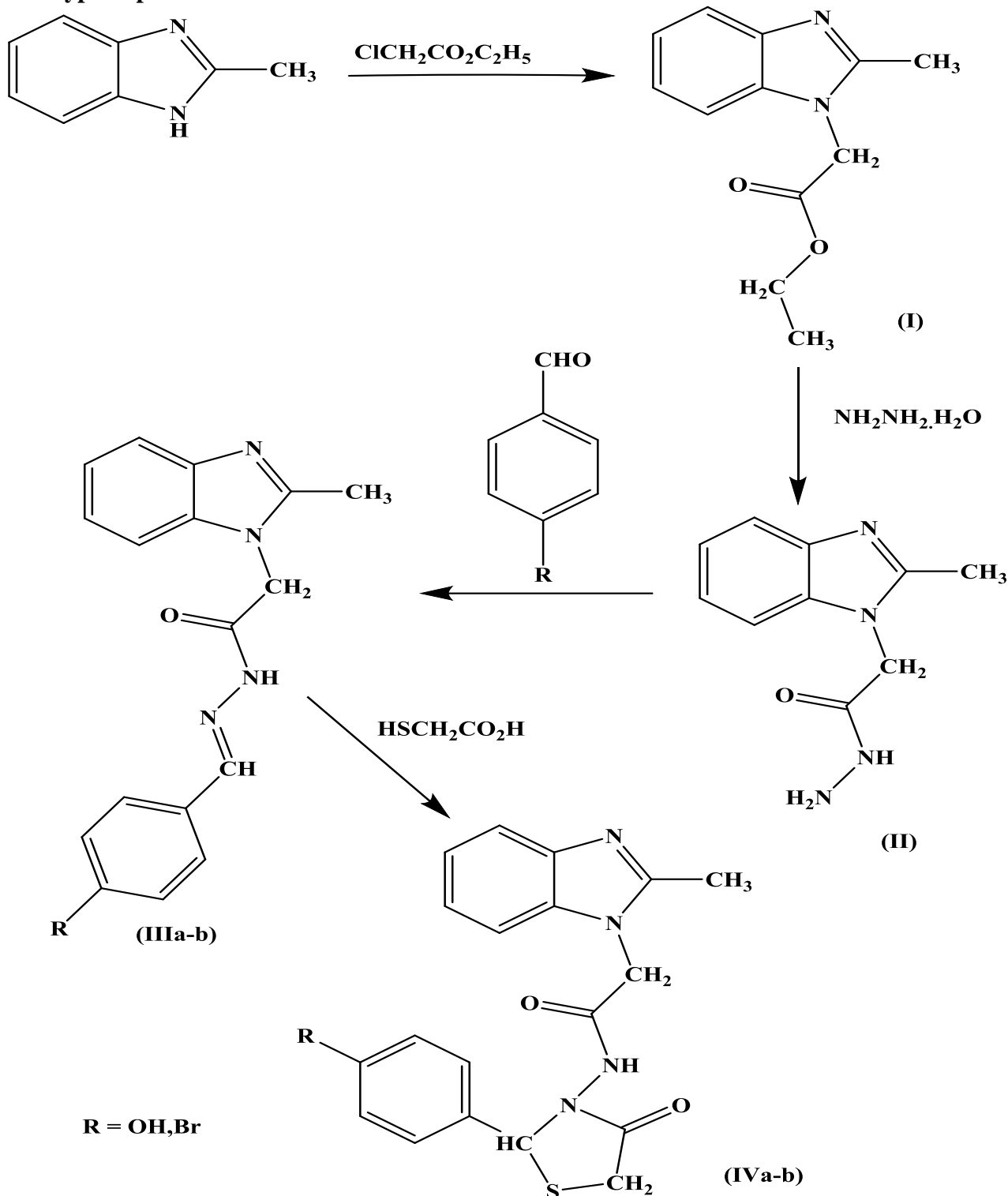
### General

All reagents and anhydrous solvents were of analar type and generally used as received from the commercial suppliers [Merck, Germany, ALPHA CHEMIKA, India, Sigma-Aldrich, Germany and BDH, England]. 2-methyl benzoimidazole was supplied by the Merck Company, China. Melting points were determined by capillary method on Electric melting point apparatus Stuart [England]. The identification of compounds was done using a FT-IR, <sup>1</sup>H-NMR data and physical properties. Infrared spectra were recorded as KBr disc by using FT-IR spectrophotometer, in Baghdad University, college of education for pure sciences Ibn-Al Haitham, central service laboratory. The <sup>1</sup>H-NMR spectra were performed at The

University of Iran, Faculty of Science, and the department of chemistry

The synthesis of final compounds [IVa-b] was achieved following procedures illustrated in scheme 1.

**The typical procedure for the reactions**



**Scheme (1): Synthesis of intermediates and final compounds**

**General procedure for the synthesis ethyl 2-(2-methyl-1H-benzo[d]imidazol-**

**1-yl) acetate [I]:** To a suspension of 2-methyl benzoimidazole [0.01 mol, 1.32 g],

anhydrous potassium carbonate [0.015 mol, 2 g] in dry acetone, ethyl chloroacetate [0.01 mol, 1.2 ml] was added dropwise. Then the reaction mixture was stirred at room temperature for 12 h. The inorganic solid disposed of by filtration and the resultant collected liquid has been evaporated under reduced pressure and recrystallized from 1:1 benzene: diethyl ether [11].

**General procedure for the synthesis of benzoimidazole acetyl hydrazide, 2-(2-methyl-1H-benzo[d]imidazol-1-yl)**

**acetohydrazide [II]:** Hydrazine hydrate [99.5%] [0.02 mol, 1ml] was added to compound [I] [0.01 mol, 2.18g] in ethanol [15 mL]. This mixture refluxed for three hours. Then the reaction mixture was cooled, the solid obtained was filtered and recrystallized from ethanol [12].

**General procedure for the synthesis of 2-methyl benzoimidazole acetyl**

**hydrazide [IIIa-b]:** Compound (II) (0.001 mole, 0.2 g) and appropriate aromatic aldehydes [0.0011 mol] in 25mL of absolute ethanol were mixed. The mixture was heated under reflux on a water bath for [4hrs.], after [15 min.] of the refluxing period [2-3] drops of glacial acetic acid were added. The excess of the solvent was reduced under reduced pressure and pour the residue into ice-cooled water to obtain the product. The product was filtered, washed with cold water, dried & recrystallized from ethanol [13].

**General procedure for the synthesis of thiazolidin-4-one derivatives [IVa-b]:**

A mixture of thioglycolic acid (0.0145 mol, 1mL) and either compound [IIIa-b] [0.001 mol] was heated at [60°C] until the reaction was complete about [3hrs.]. 5mL of ethyl acetate was added to the mixture. The organic layer was washed with a saturated solution of sodium bicarbonate [3x20mL] and water [1x10mL], and dried with anhydrous sodium sulfate, and

concentrated to give an oil using rotary evaporator. The oil was triturated with ether to give the final compounds [14].

**Ethyl 2-(2-methyl-1H-benzo[d]imidazol-1-yl) acetate**

**C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> [II],** Yellowish crystals (94% yield); m.p. 104-105°C; FT-IR: 3055 cm<sup>-1</sup> (C-H aromatic), 1734 cm<sup>-1</sup> (C=O of ester) and 1111 cm<sup>-1</sup> (C-O). <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ, ppm) 1.24 (3H,t,CH<sub>3</sub>), 2.56(3H,s,CH<sub>3</sub>), 4.82(2H,q, CH<sub>2</sub>), 5.23(2H,s,CH<sub>2</sub>) and 7.17-7.60 (4H, m,Ar-H).

**methyl-1H-benzo[d]imidazol-1-yl)**

**acetohydrazide C<sub>10</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub> [III],**

White powder (72% yield); m.p. 226–228°C; FT-IR: 3305-3211 cm<sup>-1</sup> (NH<sub>2</sub>), 3151cm<sup>-1</sup> (N-H) and 1660cm<sup>-1</sup>(C=O of amide). <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ, ppm) 2.48(3H,s,CH<sub>3</sub>), 4.34(2H,s,NH<sub>2</sub>), 4.8 (2H, s,CH<sub>2</sub>), 7.07-7.52(4H,m,Ar-H) and 9.52 (1H ,s,NH)

**(Z)-N'-(4-hydroxybenzylidene)-2-(2-methyl-1H-benzo[d]imidazol-1-**

**yl)acetohydrazide C<sub>18</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub> [IIIa],**

White fluffy powder (71% yield); m.p. 288-290°C; FT-IR: 3440 cm<sup>-1</sup> (OH) 3291 cm<sup>-1</sup> (N-H) and 1687cm<sup>-1</sup>(C=O of amide) .<sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ, ppm) 2.49 (3H,s,CH<sub>3</sub>) ,5.4 (2H,s,CH<sub>2</sub>), 6.79-7.61(8H,m,Ar-H), 8.03 (1H,s,CH), and 11.73(1H,s,NH).

**(Z)-N'-(4-bromobenzylidene)-2-(2-methyl-1H-benzo[d]imidazol-1-yl)acetohydrazide**

**C<sub>17</sub>H<sub>15</sub>BrN<sub>4</sub>O [IIIb],**

White fluffy powder (74% yield); m.p. 267-268°C; FT-IR: 3435 cm<sup>-1</sup> (NH), 1682 cm<sup>-1</sup> (C=O of amide) and 739 cm<sup>-1</sup> (C-Br). <sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ, ppm) 2.45 (3H,s,CH<sub>3</sub>), 5.4 (2H,s,CH<sub>2</sub>), 8.04 (1H,s,CH), 7.11-7.75 (8H,m,Ar-H) , 8.04 (1H,s,CH) and 11.86 (1H,s,NH).

**(S)-N-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-(2-methyl-1H-benzo[d]imidazol-1-yl)acetamide**

**C<sub>20</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>S [IVa],** Off white powder

(61% yield); m.p. 182-183°C; FT-IR: 3417  $\text{cm}^{-1}$  (NH), 1720  $\text{cm}^{-1}$  (C=O of thiazolidinone ring), 1658  $\text{cm}^{-1}$  (C=O of amide) and 1161  $\text{cm}^{-1}$  (C-OH).  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm) 2.47 (3H,s,CH<sub>3</sub>), 3.69-3.85 (2H,d of d, CH<sub>2</sub>), 4.98 (2H,s,CH<sub>2</sub>), 5.69(1H,s,CH), 6.79-7.63 (8H,m, Ar-H) and 11.60 (1H,s,NH).

**(S)-N-(2-(4-bromophenyl)-4-oxothiazolidin-3-yl)-2-(2-methyl-1H-benzo[d]imidazol-1-yl)acetamide**

$\text{C}_{19}\text{H}_{17}\text{BrN}_4\text{O}_2\text{S}$  [IVb], Off white powder (63% yield); m.p. 268-269°C; FT-IR: 3440  $\text{cm}^{-1}$  (NH), 1714  $\text{cm}^{-1}$  (C=O of thiazolidinone ring), 1678  $\text{cm}^{-1}$  (C=O of amide) and 737  $\text{cm}^{-1}$  (C-Br).  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ,  $\delta$ , ppm) 2.36 (3H,s,CH<sub>3</sub>), 3.71-3.92 (2H,d of d, CH<sub>2</sub>), 4.87 (2H,s,CH<sub>2</sub>), 5.78 (1H,s,CH), 7.11-7.62 (8H,m, Ar-H) and 10.72 (1H,s,NH).

**Preliminary pharmacological studies**

**Anti-inflammatory evaluation study**

In vivo anti-inflammatory effects of the chemically synthesized compounds [IVa-b] were assessed by using egg-white induced paw edema model. Their assessment for their anti-inflammatory activity based on the reduction of paw thickness.

**Table [1] final compounds with their molecular weight and dose**

Compounds	Molecular weight	Dose mg/ kg
Ibuprofen	206.29	10
IVa	382.44	18.9
IVb	445.34	18.3

**C. Experimental design**

The anti-inflammatory activity of the tested compounds [IVa-b] was done by using the egg-white induced edema method. The thickness of rat's paw was measured by vernier at seven-time intervals (0, 30, 60, 120, 180, 240, and 300 min) after taking the drug. Subcutaneous injection of [0.05 ml] of undiluted egg-

**Methods**

**A. Animals:**

Albino rats of either sex weighing [170  $\pm$  10 gm] were housed in the animal house of the College of Pharmacy, Mustansiriyah University under same circumstances. Animals were fed commercial chaw and had free access to water ad libitum. Animals were transferred to the laboratory, and were divided into four groups one hours before the experiment [each group consisting of 6 rats] as follows:

**Group A:** six rats served as control and treated with the vehicle (propylene glycol 50% v/v).

**Group B:** six rats treated with ibuprofen as a reference substance in a dose of 10 mg/kg [5].

**Group C-D:** six rats per each group treated with the tested compounds [IVa-b] respectively in the dose that determined below. Propylene glycol was used as a vehicle.

**B. Calculations for dose determination**

Molecular weight (M.Wt.) of ibuprofen = 206.29 g/mol.

$10 \text{ mg / kg} / 206.29 = \text{Dose} / \text{M.Wt. of the tested compound}$

white into the plantar side of the left-hand paw of the rats was induced acute inflammation; 30 min after intraperitoneal [i.p.] administration of the drugs or their vehicle [16].

**Statistical analysis**

The data were expressed as the mean  $\pm$  SEM. The results were analyzed for statistical significance using student *t*-test [Two Sample Assuming Equal Variances] to compare mean values. While

comparisons between different groups were made using ANOVA: two factors without repetition. The probability value [P] was considered to be less than 0.05 significant.

### Results and discussion

The anti-inflammatory activity of the tested compounds has been done in comparison with their vehicle [control group] and ibuprofen. The tested compounds and the reference drug produced a significant reduction of paw

edema with respect to the effect of propylene glycol 50% v/v [control group]. All tested compounds significantly limited the inflammation in paw edema, the onset of compounds started at time 120 min and show higher anti-inflammatory activity than ibuprofen [10mg/kg, i.p.]. However, the duration of action of all tested compounds continued till the end of the experiment with statistically significant [ $P < 0.05$ ] reduction in paw edema thickness as shown in table [2] and figure [1].

Non-identical superscripts (a, b & c) among different examined agents were considered

	Compound s	Time (min)						
		0	30	60	120	180	240	300
Paw Thickness (mm) / n=6	Control	2.33 ±0.05	5.58 ±0.02	6.55 ±0.05	6.92 ±0.02	6.70 ±0.02	6.26 ±0.03	5.20 ±0.04
	Ibuprofen	2.31 ±0.02	5.51 ±0.02	6.49 ±0.03	5.89 ±0.02 <sup>*a</sup>	5.12 ±0.06 <sup>*a</sup>	4.20 ±0.05 <sup>*a</sup>	2.90 ±0.02 <sup>*a</sup>
	IVa	2.25 ±0.04	5.44 ±0.05	6.33 ±0.03	5.52 ±0.04 <sup>*b</sup>	3.94 ±0.03 <sup>*b</sup>	3.50 ±0.05 <sup>*b</sup>	2.34 ±0.04 <sup>*b</sup>
	IVb	2.28 ±0.02	5.48 ±0.03	6.37 ±0.05	5.75 ±0.04 <sup>*a</sup>	4.52 ±0.02 <sup>*c</sup>	3.83 ±0.02 <sup>*c</sup>	2.44 ±0.02 <sup>*b</sup>

significantly different ( $P < 0.05$ ); \*significantly different compared to control agent ( $P < 0.05$ ). Numbers are stated in mm paw width as mean ± SEM. n= number of rats. Time (0) is the time of i.p. injection of ibuprofen, examined agents and control agent. Time (30) is the time of egg white injection.

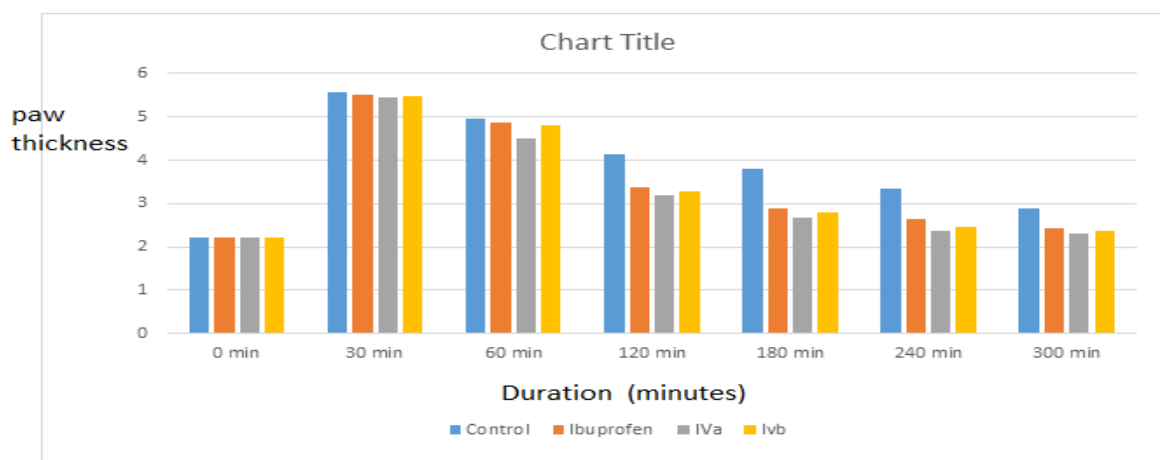


Figure [1]: Effect of propylene glycol, ibuprofen, compounds [IVa-b] on egg white provoked paw edema in rats.



**Comparative analysis:**

The comparison explains that at 0-30 min. there are no differences among all groups. Compound IVa showed significantly higher activity than standard from time [120 to 300 min.] and higher than compound IVb from time [120 to 240 min.]. Compounds IVa and IVb showed significantly higher activities than standard from time [180 to 300 min.].

**Insilico analysis and molecular docking study:**

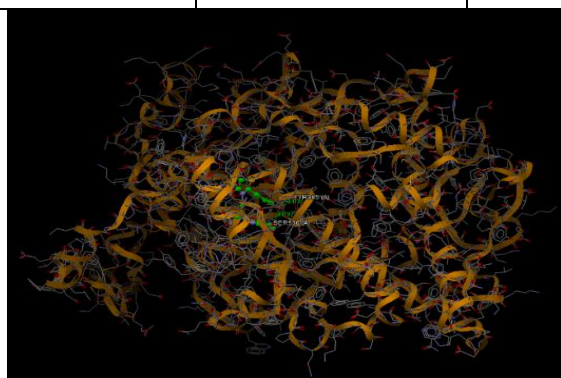
The aim of this study was to analyze the inhibitory action of the newly synthesized compounds to COX-2 isoenzymes by computational docking studies. The crystallographic structures of molecular target COX-2 and COX-1 isoenzymes

were obtained from the protein data bank [PDB] database. Ibuprofen and diclofenac are classical NSAID were taken as the standards for comparative analysis. Computational docking analysis was performed using GOLD.

The PLP fitness indicated that the COX-2 protein was successfully blocked with the newly synthesized compounds as shown in table (3). The docking of COX-2 target with the newly synthesized compounds using docking procedure revealed that all the computationally predicted lowest energy complexes of COX-2 are stabilized by intermolecular hydrogen bonds while COX-1 does not have any intermolecular hydrogen bonds with synthesized compounds.

**Table [3] PLP fitness value and H bonding of final compounds**

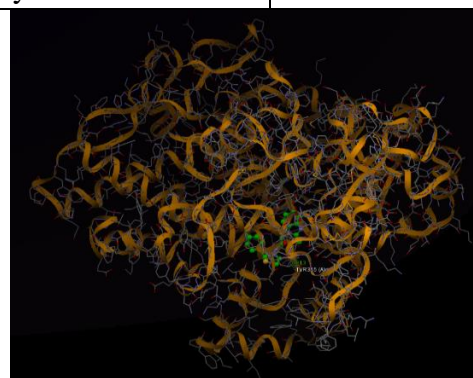
Compounds	COX-2 Binding Energy [PLP Fitness]	Amino Acids Included in H-bonding	COX-1 Binding Energy [PLP Fitness]
Ibuprofen	66.10	Arg120 & Tyr355	60.3
Diclofenac	71.8	Ser530 & Tyr385	60.1
IVa	81.2	Ser530 & Tyr385	54.4
IVb	71.2	Tyr 355	44



**Figure [2] Docking result of compound IVa**

Docking results showed that the newly synthesized compounds can enter the substrate-binding region of the active site and the compound IVa had shown the highest PLP fitness for COX-2. Finally, the results demonstrated clearly that there is a good correlation between in vivo and in silico study.

**5. ADME studies**



**Figure [3] Docking result of compound IVb**

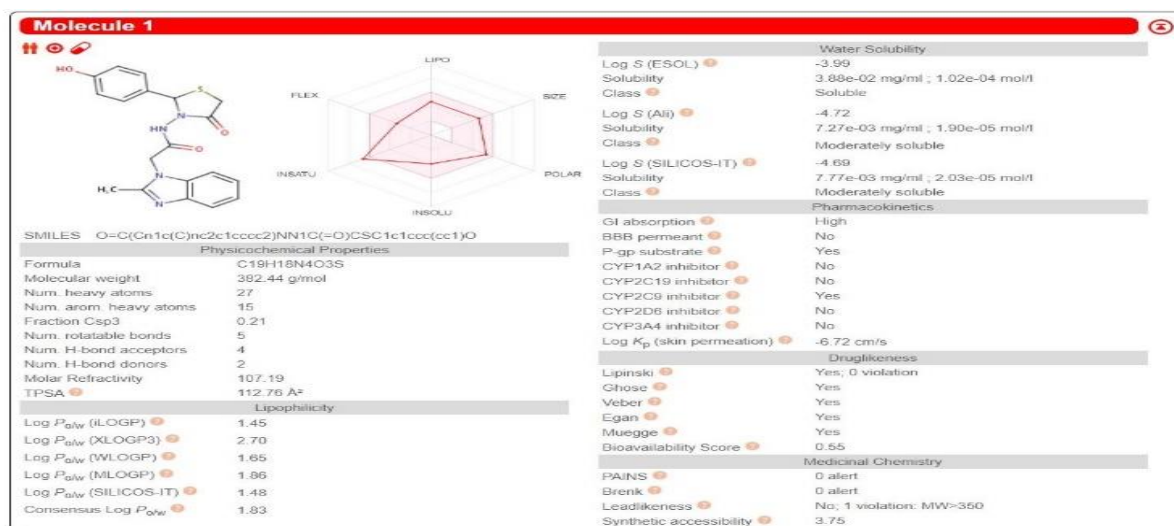
The ADME properties profile of our synthesized compounds were studied by Swiss ADME server to predict the safer and potential drug candidate(s) to filter out the compounds which are most likely to fail in the subsequent stages of drug development due to unfavorable ADME properties (17). We assessed all synthesized compounds ADME

method. Also, we calculated the topological polar surface area (TPSA), since it is another critical property that has been linked to the drug bioavailability. Thus, passively absorbed molecules with a TPSA > 140 Å<sup>2</sup> are thought to have low oral bioavailability (19). Our results showed that all synthesized compounds have TPSA below 140, which is in the range of (78.70-138.35) and the bioavailability for all ligands was 0.55 which mean that all ligands reach the systemic

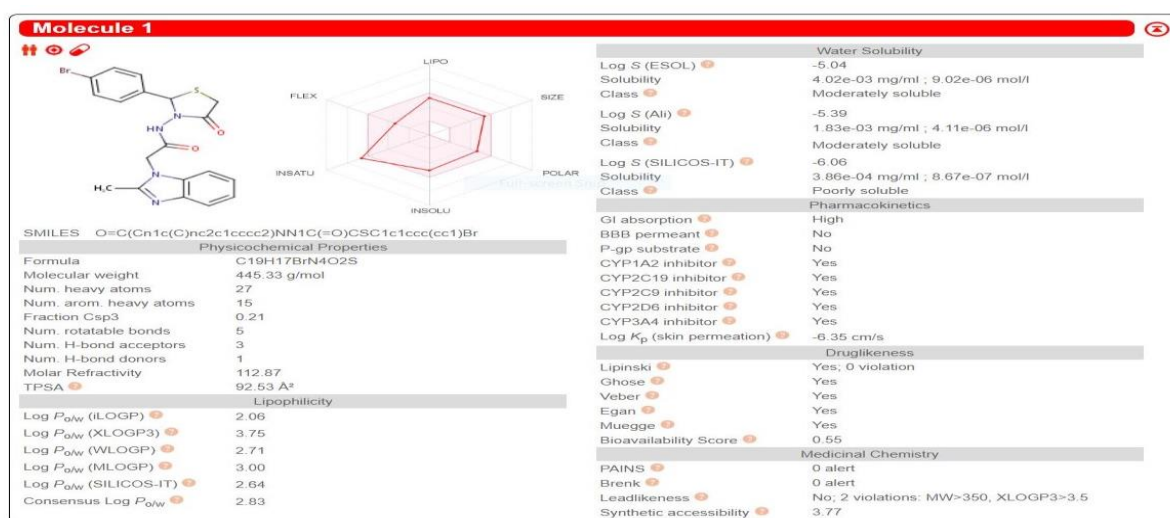
circulation. All compounds fulfilled Lipinski rule. Also, it also fulfilled the topological descriptors and finger-prints of molecular drug-likeness structure keys as LogP and LogS. The GI absorption score is a measure of the extent of absorption of a molecule from the intestine following oral administration. The absorption could be excellent if the result were high. In this study, the GI absorption of all compounds was high predicting them to be well absorbed from the intestine.

**Table [4] the ADME properties for final compounds**

compound	M.Wt	H-bond acceptors	H-bond donors	MR	TPSA	GI Abs.	BBB permeant	Lipinski violations
IVa	382.44	4	2	107.19	112.76	high	No	0
IVb	445.33	3	1	112.87	92.53	high	No	0



**Figure [4]: ADME study of compound [IVa].**



**Figure [5]: ADME study of compound [IVb].**



## Conclusion

The synthesis of the designed compounds has been successfully achieved. Characterization and identification of the synthesized compounds were confirmed by determination of FT-IR, <sup>1</sup>H NMR data and physical properties. The anti-inflammatory assessment of the final products indicates that the incorporation of 4-thiazolidinone pharmacophore into 2-methyl benzimidazole improved its anti-inflammatory action. The ADME studies showed that all compounds fulfilled the Lipinski rule, and all synthesized compounds absorbed from GIT. Docking studies showed a perfect agreement with *in vivo* study. The preliminary study of anti-inflammatory activity showed that all compounds have significantly more anti-inflammatory outcome than ibuprofen.

## Acknowledgments

The authors are greatly thankful for management and principal, Department of Pharmaceutical Chemistry College of Pharmacy /Mustansiriyah University for their help and support.

## References

- 1- Srivastava SP, Verma NK, Kumar S, Mishra A. In vitro testing of Ficus dalhousiae Miq root extract on Wistar albino rat for its anti-inflammatory activity. Asian Journal of Plant Science and Research.2016;6(1):41-4.
- 2- Vogel H.G, Goethe J.H. "Drug Discover and Evaluation." Pharmacological Assays (2nd ed). Berlin Heidelberg: Springer-Verlag; 2002.
- 3- Rayapaneni C, Dhulipallasowmya, Malarkodi V. Review of Inflammation and Its Medicinal Plants. International Journal of frontiers and Technology. 2014; 2 (3):75-85.
- 4- Gunaydin, C., & Bilge, S. S. Effects of Nonsteroidal Anti-Inflammatory Drugs at the Molecular Level. The Eurasian journal of medicine, 2018; 50(2), 116–121.
- 5- Lancet. Lanas, A., & Chan, F. K. L.: Peptic ulcer disease. The Lancet. 2017; 390(10094), 613–624.
- 6- Walia, R, Md. Hedaitullah, Naaz, SF, Iqbal, K and Lamba,HS.: Benzimidazole Derivatives: An overview. International Journal of Research in Pharmacy and Chemistry 2011; 1(3): 565-574.
- 7- Gupta, A., Singh, R., Sonar, P. K., & Saraf, S. K. Novel 4-Thiazolidinone Derivatives as Anti-Infective Agents: Synthesis, Characterization, and Antimicrobial Evaluation. Biochemistry research international, 2016, 8086762.
- 8- Zhou, C.F.; Chen, J.; Liu, P.G.; et al.: Design, synthesis and biological evaluation of thiazolidinone derivatives as potential EGFR and HER-2 kinase inhibitors. Bioorg. Med. Chem.2010; 18(1):314-9.
- 9- Chandra, T.; Garg, N. and Kumar, A.: Synthesis of Sulpha Drug Quinazolin - 4-one Derivatives and Their Evaluation for Anti-inflammatory Activity. World Journal of Chemistry.2009; 4 (2): 210-218.
- 10- Rawal, R.K.; Tripathi, R.; Kulkarni, S.; et al.: 2-(2,6-Dihalo-phenyl)-3-heteroaryl-2-ylmethyl-1, 3-thiazolidin-4-ones: Anti-HIV agents. Chem Biol. Drug Des.2008; 72(2):147 –54.
- 11- Salahuddin, et al., Synthesis, characterization and antimicrobial activity of 1,3,4-oxadiazole bearing 1H-benzimidazole derivatives. Arabian Journal of Chemistry (2012).
- 12- El-Faham A, Al Marhoon Z, Abdel-Megeed A, Siddiqui M. An efficient and mild method for the synthesis and hydrazinolysis of N-glyoxylamino acid esters. Journal of Chemistry. Volume 2013, Article ID 901745, 6 pages.

- 13- Telvekar VN, Bairwa VK, Satardekar K, Bellubi A. Novel 2-(2-(4-aryloxybenzylidene)hydrazinyl) benzothiazole derivatives as anti-tubercular agents. *Bioorg Med Chem Lett* 2012; 22(1):649-652.
- 14- Neuenfeldt PD, Drawanz BB, Siqueira GM, Gomes CR, Wardell SM, Flores AF, et al. Efficient solvent-free synthesis of thiazolidin-4-ones from phenylhydrazine and 2, 4-dinitrophenylhydrazine. *Tetrahedron Lett* 2010; 51(23):3106-3108.
- 15- Chidambaran Suthakaran and Gopalakrishnan Senthil, Evaluation of Analgesic and AntiInflammatory Activity of Ibuprofen and Pregabalin in Animal Models. *Journal of Clinical and Diagnostic Research*. 2018; 12(9): FC05-FC08
- 16- Naser, N.H.; Mahdi, M.F and Omar, T.N.A.: Synthesis and Preliminary Pharmacological Evaluation of New Analogues of Diclofenac as Potential Anti-inflammatory Agents. *Iraqi J Pharm Sci*.2011; 20 (1).
- 17- Daina, Antoine et al. "SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules." *Scientific reports* vol. 7 42717. 2017.