

# Design, Synthesis, In Silico Study and Anti-Inflammatory Evaluation of New Ketoprofen Thiourea Derivatives

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**Abstract** The In the current study, six new derivatives of ketoprofen thiourea were designed and synthesized In order to enhance COX-2 enzyme selectivity. The chemical structures of these derivatives were confirmed by spectral analysis. The anti-inflammatory activities of these derivatives was investigated insilico and in vivo. The results revealed that compound B4 were the most active . The new derivatives also showed drug-likeness and gastric absorption as predicted by computational methods. These results above indicated that the synthesized compounds deserve additional investigation as potential selective COX-2 inhibitors.



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**Keywords:** anti-inflammatory activity; ketoprofen; COX-2; paw edema; thiourea.

## 1. INTRODUCTION

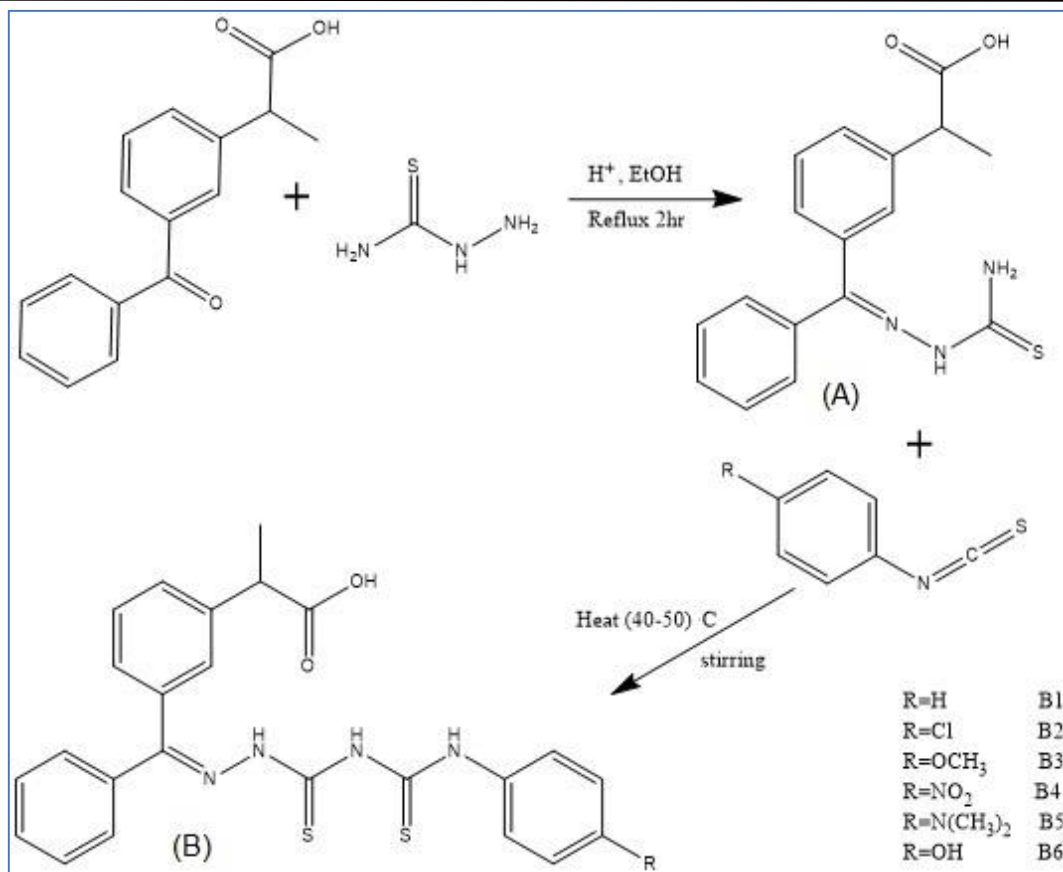
Non-steroidal anti-inflammatory medications (NSAIDs) are extensively utilized pharmaceuticals globally<sup>(1)</sup> due to its possession of anti-inflammatory, antipyretic, and analgesic characteristics<sup>(2)</sup>. The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX)<sup>(3)</sup>. Which is responsible for biosynthesis of prostaglandins, prostaglandins play a key role in the generation of the inflammatory response<sup>(4)</sup>.

Ketoprofen is classified as a non-steroidal anti-inflammatory drug (NSAID) in the propionic acid class. It has antipyretic and analgesic properties. It functions by suppressing the body's synthesis of prostaglandin. <sup>(5)</sup>. Ketoprofen is a non-selective COX inhibitor. It suppresses the activity of human COX-1 as well as COX-2 enzymes. The non-selective nature of ketoprofen led to the most common side effect which is gastric ulceration <sup>(6)</sup>. This side effect can be reduced by increase selectivity of drug to COX-2 enzyme. To increase the COX-2 enzyme suppressive effect of ketoprofen, A variety of ketoprofen compounds were synthesized, via the addition of extra functional groups to the ketoprofen molecule.<sup>(7)</sup>. Medicinal chemists utilize many approaches to improve the selectivity, efficacy and undesirable properties of a certain drug's lead structure for COX-2 enzyme specific targeted. The newly synthesized compounds demonstrate enhanced efficacy

as anti-inflammatory drugs and greater binding affinity for the COX-2 enzyme, attributed to their larger molecular size in comparison to the original ketoprofen substance. It is worth mentioning that the COX-2 binding site has a side pocket near its base, which results in the site being larger than COX-1 by twenty percent.<sup>(8)</sup>, Consequently, the COX-2 active site possesses the capacity to accommodate larger structures compared to the COX-1 active site.<sup>(9)</sup>.

## 2. MATERIALS AND METHODS

The research investigation utilized reagents and solvents sourced from commercial vendors, mainly Fluka Company (Germany), and Sigma-Aldrich and BDH in England. The supply of ketoprofen was provided by HI-Media, India. The calculation of the melting point was done by using the capillary method by a Stuart SMP-10 electrical melting point instrument from the United Kingdom. The chemical compounds were identified using a Fourier Transform Infrared (FT-IR) spectrum and recorded on a Shimadzu iraffinity-1s FT-IR spectrophotometer as potassium bromide (KBr) discs. NMR is determined using an NMR instrument. The instrument model is the Bruker 300 MHz-Avanc III. Typical procedure for the synthesis is summarized in scheme 1:



Scheme 1: synthesis of compounds (B1-B6)

**Synthesis of Ketoprofen thiosemicarbazone intermediate, (A):**

The ketoprofen-thiosemicarbazide reaction was performed by mixing ketoprofen as (0.253g, 0.001mole) and thiosemicarbazide (0.093g, 0.001mole) in 20 mL of methanol, alongside by concentrated hydrochloric acid single drop. The resulting mixture was thereafter subjected to a water bath reflux for a period of two hours. After the mixture was cooled, it produced a white microcrystalline substance. This substance was then filtered, washed with ether, and dried using a vacuum.<sup>(10)</sup>

**The standard protocol for the production of (Z)-2-(3-(phenyl (2-((phenylcarbamothioyl) carbamothioyl) hydrazineylidene) methyl) phenyl) propanoic acid, (B1-B6):**

To a solution of compound A (0.5g, 0.00364 mol) in 25 ml of absolute ethanol, different substituted phenyl isothiocyanate (0.00364 mol) was added. The reaction mixture was stirred at 40-50 °C for 4 h, then kept stirring overnight. Half of the solvent was removed using rotary evaporator, and the residue was poured into ice. The precipitate was filtered, and washed with cold ethanol to give a product, which is recrystallized from 70% ethanol to yield the corresponding final target compounds (B1-B6)<sup>(11)</sup>.

**(Z)-2-(3-((2-carbamthioyl hydrazino) (phenyl) methyl ) phenyl) propanoic acid (A):**

crystals that are off-white (73% yield); m.p 161-163 °C; FTIR (KBr)  $\nu$  (cm<sup>-1</sup>): 3412 (NH<sub>2</sub>), 3150 (NH), 3300-2400 (OH), 1715 (C=O), 1580 (C=N), 924 (C=S); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300 MHz):  $\delta$  1.8 (d, 3H, CH<sub>3</sub>),  $\delta$  3.45 (q, 1H, CH),  $\delta$  7.25 (m, 9H, Ar-H),  $\delta$  8.46 (d, 2H, NH<sub>2</sub>),  $\delta$  8.58 (s, 1H, NH),  $\delta$  12.37 (br. s, 1H, OH); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 75.6 MHz):  $\delta$  17.45 (1C, CH<sub>3</sub>),  $\delta$  43.33 (1C, CH),  $\delta$  122.39-138.67 (Aromatic C),  $\delta$  176.35 (1C, C=N),  $\delta$  178.53 (1C, C=O),  $\delta$  179.35 (1C, C=S).

**(Z)-2-(3-(phenyl (2-((phenylcarbamothioyl) carbamothioyl) hydrazineylidene) methyl) phenyl) propanoic acid (B1):**

Yellow crystals (81% yield); m.p 169-171 °C; FTIR (KBr)  $\nu$  (cm<sup>-1</sup>): 3253 (NH), 3212 (NH), 3157 (NH), 3210-2400 (OH), 1712 (C=O), 1579 (C=N), 913 (C=S); <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 300 MHz):  $\delta$  1.92 (d, 3H, CH<sub>3</sub>),  $\delta$  3.45 (q, 1H, CH),  $\delta$  7.25 (m, 5H, Ar-H),  $\delta$  7.85 (m, 5H, Ar-H),  $\delta$  8.05 (m, 4H, Ar-H),  $\delta$  8.40 (d, 1H, NH-Ar),  $\delta$  8.59 (s, 1H, NH-C=N),  $\delta$  12.17 (broad. s, 1H, OH)  $\delta$  12.94 (s, 1H, NH-C=S); <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 75.6 MHz):  $\delta$  15.45 (1C, CH<sub>3</sub>),  $\delta$  41.93 (1C, CH),  $\delta$  125.3-141.6 (Aromatic C),  $\delta$  175.16 (1C, C=N),  $\delta$  176.59 (1C, C=O),  $\delta$  179.41 (1C, C=S).

**(Z)-2-(3-((2-(((4-chlorophenyl) carbamothioyl) carbamothioyl) hydrazineylidene) (phenyl) methyl phenyl) propanoic acid (B2):**

Brown powder (70% yield); m.p 173-175 °C; FTIR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3255 (NH), 3159 (NH), 3151 (NH), 3200-2400 (OH), 1710 (C=O), 1586 (C=N), 927 (C=S), 813 (C-Cl);  $^1\text{H-NMR}$  (DMSO- $d_6$ , 300 MHz):  $\delta$  1.92 (d, 3H,  $\text{CH}_3$ ),  $\delta$  3.45 (q, 1H, CH),  $\delta$  7.25 (m, 5H, Ar-H),  $\delta$  7.85 (m, 5H, Ar-H),  $\delta$  8.05 (m, 4H, Ar-H),  $\delta$  8.42 (d, 1H, NH-Ar),  $\delta$  9.59 (s, 1H, NH-C=N),  $\delta$  12.19 (broad. s, 1H, O-H),  $\delta$  12.91 (s, 1H, NH-C=S);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ , 75.6 MHz):  $\delta$  14.75 (1C,  $\text{CH}_3$ ),  $\delta$  43.88 (1C, CH),  $\delta$  124.8-143.9 (Aromatic C),  $\delta$  175.19 (1C, C=N),  $\delta$  176.43 (1C, C=O),  $\delta$  179.22 (1C, C=S).

**(Z)-2-(3-((2-(((4-methoxyphenyl) carbamothioyl) carbamothioyl) hydrazineylidene) (phenyl) methyl phenyl) propanoic-acid (B3):**

chalky substance (57% yield); m.p 187-190 °C; FTIR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3212 (N-H), 3153 (NH), 3069 (NH), 3200-2400 (OH), 1738 (C=O), 1589 (C=N), 1233 (C-O), 927 (C=S);  $^1\text{H-NMR}$  (DMSO- $d_6$ , 300 MHz):  $\delta$  1.97 (d, 3H,  $\text{CH}_3$ ),  $\delta$  3.36 (q, 1H, CH), 3.87 (s, 3H, O- $\text{CH}_3$ ),  $\delta$  7.25 (m, 5H, Ar-H),  $\delta$  7.85 (m, 5H, Ar-H),  $\delta$  8.05 (m, 4H, Ar-H),  $\delta$  8.45 (d, 1H, NH-Ar),  $\delta$  8.54 (s, 1H, NH-C=N),  $\delta$  12.22 (broad. s, 1H, OH),  $\delta$  12.94 (s, 1H, NH-C=S);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ , 76.6 MHz):  $\delta$  12.32 (1C,  $\text{CH}_3$ ),  $\delta$  41.22 (1C, CH),  $\delta$  55.31 (1C, O- $\text{CH}_3$ ),  $\delta$  121.1-144.7 (Aromatic C),  $\delta$  175.47 (1C, C=N),  $\delta$  176.43 (1C, C=O),  $\delta$  179.11 (1C, C=S).

**(Z)-2-(3-((2-(((4-nitrophenyl) carbamothioyl) carbamothioyl) hydrazineylidene) (phenyl) methyl phenyl) propanoic acid (B4):**

Orange powder (55% yield); m.p 161-163 °C; FTIR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3393 (NH), 3258 (NH), 3155 (NH), 3200-2400 (OH), 1731 (C=O), 1589 (C=N), 1480 (N-O), 927 (C=S);  $^1\text{H-NMR}$  (DMSO- $d_6$ , 300 MHz):  $\delta$  1.93 (d, 3H,  $\text{CH}_3$ ),  $\delta$  3.31 (q, 1H, CH),  $\delta$  7.25 (m, 5H, Ar-H),  $\delta$  7.85 (m, 5H, Ar-H),  $\delta$  8.05 (m, 4H, Ar-H),  $\delta$  8.45 (d, 1H, NH-Ar),  $\delta$  8.66 (s, 1H, HN-C=N),  $\delta$  12.24 (broad. s, 1H, OH),  $\delta$  13.21 (s, 1H, HN-C=S);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ , 75.6 MHz):  $\delta$  17.75 (1C,  $\text{CH}_3$ ),  $\delta$  42.34 (1C, CH),  $\delta$  121.8-145.9 (Aromatic C),  $\delta$  175.28 (1C, C=N),  $\delta$  176.43 (1C, C=O),  $\delta$  179.53 (1C, C=S).

**(Z)-2-(3-((2-(((4-(dimethylamino) phenyl) carbamothioyl) carbamothioyl) hydrazineylidene) (phenyl) methyl phenyl) propanoic-acid (B5):**

Brown powder (67% yield); m.p 146-148 °C; FTIR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3322 (N-H), 3243 (NH), 3159 (NH), 3200-2400 (OH), 1722 (C=O), 1584 (C=N), 920 (C=S);  $^1\text{H-NMR}$  (DMSO- $d_6$ , 300 MHz):  $\delta$  1.93 (d, 3H,  $\text{CH}_3$ ),  $\delta$  2.71 (s, 6H,  $\text{CH}_3$ ),  $\delta$  3.37 (q, 1H, CH),  $\delta$  7.31 (m, 5H, Ar-H),  $\delta$  7.85 (m, 5H, Ar-H),  $\delta$  8.22 (m, 4H, Ar-H),  $\delta$  8.45 (d, 1H, NH-Ar),  $\delta$  8.51 (s, 1H, NH-

C=N),  $\delta$  12.32 (broad. s, 1H, O-H),  $\delta$  12.85 (s, 1H, NH-C=S);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ , 75.6 MHz):  $\delta$  15.98 (1C,  $\text{CH}_3$ ),  $\delta$  40.65 (2C, N- $\text{CH}_3$ ),  $\delta$  42.31 (1C, CH),  $\delta$  125.8-145.1 (Aromatic C),  $\delta$  175.54 (1C, C=N),  $\delta$  176.12 (1C, C=O),  $\delta$  179.43 (1C, C=S).

**(Z)-2-(3-((2-(((4-hydroxyphenyl) carbamothioyl) carbamothioyl) hydrazineylidene) (phenyl) methyl phenyl) propanoic acid (B6):**

Pale yellow crystals (82% yield); m.p 177-179 °C; FTIR (KBr)  $\nu$  ( $\text{cm}^{-1}$ ): 3229 (NH), 3216 (NH), 3144 (NH), 3200-2400 (OH), 1721 (C=O), 1567 (C=N), 922 (C=S);  $^1\text{H-NMR}$  (DMSO- $d_6$ , 300 MHz):  $\delta$  1.90 (d, 3H,  $\text{CH}_3$ ),  $\delta$  3.33 (q, 1H, CH),  $\delta$  7.28 (m, 5H, Ar-H),  $\delta$  7.82 (m, 5H, Ar-H),  $\delta$  8.05 (m, 4H, Ar-H),  $\delta$  8.45 (d, 1H, NH-Ar),  $\delta$  8.72 (s, 1H, NH-C=N),  $\delta$  10.21 (broad. s, 1H, Ar-OH),  $\delta$  12.49 (broad. s, 1H, OH),  $\delta$  12.93 (s, 1H, NH-C=S);  $^{13}\text{C-NMR}$  (DMSO- $d_6$ , 75.6 MHz):  $\delta$  16.12 (1C,  $\text{CH}_3$ ),  $\delta$  42.35 (1C, CH),  $\delta$  127.8-143.1 (Aromatic C),  $\delta$  175.14 (1C, C=N),  $\delta$  176.65 (1C, C=O),  $\delta$  179.47 (1C, C=S).

### 3. INSILICO STUDY

#### 3.1-Prediction of biological target:

PASS (Prediction of Activity Spectra for Substances) is a software evaluating the biological potential of an organic drug-like molecule. PASS provides simultaneous predictions of many types of biological activity based on the structure of organic compounds<sup>(12)</sup>.

#### 3.2- Docking study

**a- Gold software:** GOLD is a software programme that uses algorithm of a genetic to precisely position flexible ligands within the binding sites protein.<sup>(10)</sup> GOLD was extensively validated and shown exceptional accuracy in posture predictions and outstanding performance in virtual screening for docking findings<sup>(13)</sup>. The objective is to identify the energy associated with the binding and the selectivity of the recently synthesized compounds to the COX-2 enzyme (PDB code: 4m11).

The (B1-B6) synthesized compound's molecular interactions and the targeted protein active binding sites were studied using the GOLD Suite programme through docking experiments. The synthesized compounds were graded based on their PLP fitness, which determines their ability to inhibit COX-2 by interacting with the active sites during complex formation<sup>(14)</sup>.

**b- Schrodinger Maestro:** The process began by constructing the 3D structures and modifying the chosen compounds to make them suitable for docking studies. This was done using the build panel feature in Maestro - Schrodinger 12.1. The crystallized human cyclooxygenase enzymes COX-2 (PDBID:4M11) complexes with meloxicam were obtained from the Protein Data Bank. The PDB complex structures were chemically and structurally optimized using the Protein



Preparation Wizard integrated into the Maestro programme<sup>(15)</sup>. The protein preparation process involves adding hydrogen atoms to the receptor structures, eliminating water molecules that are more than 5 Å away from the hit group, and determining bonding orders and charges. Subsequently, the protein structures that had been constructed were subjected to reduction using the OPLS\_2005 force field, employing a root mean square deviation (RMSD) value of 0.30. Active site docking studies can be defined as the process of investigating the interaction between a ligand and the active site of a protein<sup>(16)</sup>. The Maestro Receptor Grid Generation programme was utilized to generate the receptor grids, and the default values were maintained. Finally, the ligands and receptor grids that were constructed were transferred to the Glide module, which is included into the Maestro - Schrodinger molecular modelling software. The extra-precision Glide docking mode was then used to conduct molecular docking studies. The Maestro software was utilized to forecast the precise location and alignment of the synthesized molecules when they are attached to a protein receptor or enzyme. Meloxicam served as the benchmark for comparison<sup>(17)</sup>.

### 3.3- ADME Studies

The ADME studies (absorption, distribution, metabolism, and excretion) results for our synthesized compounds were demonstrated by the Swiss ADME server. These results were used to identify the more potent and safer drug candidate(s) and exclude any examined compounds that may be unsuccessful in later phases of drug development due to unfavorable results of ADME.<sup>(18)</sup>

All the synthesized chemicals were subjected to ADME assessment. The rule of Lipinski pertains to the pharmaceuticals oral administration, which should meet the following criteria: having no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, a Log P value of no more than 5, and a molecular weight of no more than 500<sup>(13)</sup>.

In addition, the calculation of the polar surface area's topological (TPSA) was performed, as it is a crucial parameter connected with the bioavailability of medications. Consequently, compounds that passively absorb within a TPSA greater than 140 Å<sup>2</sup> are regarded as having reduced oral bioavailability<sup>(10)</sup>.

### In-vivo anti-inflammatory evaluation:

Albino rats of either sex weighing (150 ± 10 g) were divided into seven groups (each group consisting of six rats) as follows: Group A: served as control; and treated with the vehicle (propylene glycol 50% v/v). Group B: treated with ketoprofen

as reference substance suspended in propylene glycol 50% (v/v). Group C-H: treated with the tested compounds (B1-B6) in doses (Suspended in propylene glycol 50% v/v). The anti-inflammatory activity of the tested compounds was studied using the egg-white induced edema model<sup>(19)</sup>. Acute inflammation was produced by a subcutaneous injection of undiluted egg-white (0.05 mL) into the plantar side of the left hind paw of the rats; 30 min after intraperitoneal (i.p) administration of the drugs or their vehicle. The paw thickness was measured by vernier at seven time intervals (0, 30, 60, 120, 180, 240, and 300 min) after drug administration<sup>(20)</sup>.

Data are expressed in milliliter paw thickness as the mean ± SEM (The standard error of the mean), Time zero is the time of the tested compounds intraperitoneal injection and propylene glycol, Time thirty is the injection time of the egg white (induction of paw edema).

## 4. RESULTS AND DISCUSSION

### 4.1. Chemistry

The initial stage of chemical production entails the nucleophilic assault of NH<sub>2</sub> from thiosemicarbazide in the carbon atom in the ketoprofen carbonyl group, leading to creation of a schiff base bond (C=N) intermediate (A)<sup>(21)</sup>.

The second step involve the reaction of this intermediate (A) with different substituted isothiocyanates which are useful and widely used building blocks in the synthesis of compounds that have academic, pharmaceutical and industrial interest. The high electrophilicity associated with the carbon atom of the isothiocyanate and their extended π electron system make them unique precursors of a large variety of target molecules<sup>(22)</sup>.

This electrophilic carbon atom can readily react with nucleophiles such as terminal amino group of (A) to form thiourea. Thiourea represents well-established privileged structures in medicinal and synthetic chemistry<sup>(23)</sup>. These structural motifs constitute a common framework of a variety of drugs and bioactive compounds endowed with a broad range of therapeutic and pharmacological properties such as anti-viral, anti-convulsant, anti-inflammatory, anti-microbial and anti-tumor effects<sup>(24)</sup>.

### 4.2. Insilico Study

The insilico study gives a good indication for the anti-inflammatory activity, as predicted by PASS webserver for prediction of biological targets. The result concerning anti-inflammatory activity of synthesized compounds (B1-B6) are listed in table 1:



**Table 1:** results of anti-inflammatory prediction by PASS website (Pa: probability of active, PI: probability of inactive)

Compound	Probability of active (Pa)	Probability of inactive (Pi)
B1	0.645	0.024
B2	0.616	0.028
B3	0.604	0.031
B4	0.555	0.042
B5	0.565	0.039
B6	0.63	0.026

The docking analysis utilizing GOLD software revealed that the fitness of docking PLP values in all investigated drugs on COX-2 ranged from 65 to 84, as reported in table (2). The docking investigation revealed that Arg120, Tyr385, Ser530, and Met522, which are mentioned in table 2 of this enzyme, participate in interactions through hydrogen bonding as well as short contacts. GOLD reports the distances of the hydrogen bonds and brief contacts between our synthesised chemicals and a specific protein atom, with all bond lengths being less than 3Å. Short-range contacts refer to various types of interaction forces, such as van der Waals, steric, electrostatic,

dipole-dipole, pi-pi stacking and other forces<sup>(25)</sup>. All of the synthesized compounds exhibit excellent docking results with COX-2, effectively fitting into the COX-2 active site. Compound B6 exhibited the highest docked PLP fitness score of 84.55. It formed two hydrogen bond contacts with Tyr385 and Ser530, and had a brief contact with Leu352, Tyr355, and Leu93. Hydrophobic contacts with low biological activity can be enhanced by increasing their number. This is because the increased hydrophobic connections will surpass the importance of H-bonding contacts, which are crucial for attaching to the active site of molecule<sup>(26)</sup>.

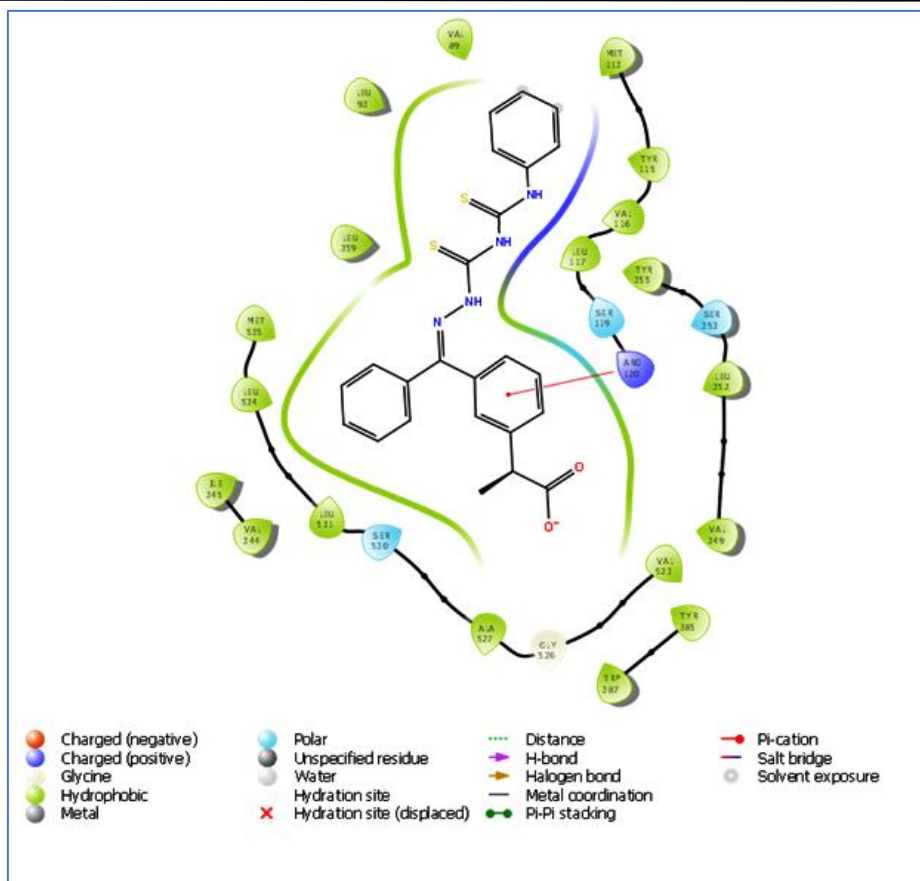
**Table 2:** The binding energies of synthesised compounds (B1-B6) and ketoprofen were determined through docking with the COX-2 enzyme (PDB code 4m11)

Compound	The binding energy of COX-2 as measured by PLP (protein-ligand binding) fitness.	Amino acid involved in H-bonding	Amino acid involved in hydrophobic interaction
B1	79.2	Arg 120, Ser 530	Arg 120, Val 349
B2	78.17	Tyr 385, Ser 530	Leu 352, Tyr 355
B3	66.52	Ser 530	Phe 512, Val 349
B4	82.13	Met 522	Tyr 385
B5	81.66	Tyr 385, Ser 530	Tyr 355
B6	84.51	Tyr 385, Ser 530	Leu 352, Tyr 355, Leu 93
Ketoprofen	68.49	Tyr 355, Met 522	Gly 526

While the docking results obtained by Schrodinger Maestro software also give a good indication for selectivity and activity. The dock result are listed in (table: 3) while figure 1 illustrate the binding of compound B1 in the active site of enzyme

**Table 3:** Docking scores of the docked compounds on the active site of COX-2 enzyme (pdb: 4m11)

Ligand	Docking Scoring
B1	-6.38
B2	-5.99
B4	-4.56
B3	3.76
B6	-3.752
B5	-3.098
(Meloxicam)	-5.74



*Scheme 2: Compound B1 in the active site of COX-2 enzyme*

The ADME analysis revealed that all synthesized compounds, with the exception of compound B1, exhibited a total polar surface area (TPSA) below 140, falling within the range of 106 to 115. Additionally, the bioavailability results indicated a value of 0.55, suggesting that all compounds (B2-B6) are capable of entering the systemic circulation.

Compounds B1, B3, B4, and B6 satisfied the Lipinski rule. Furthermore, all compounds met the criteria for topological description and exhibited molecular drug-likeness structural keys such as Log P and Log S.

The result score of GIT absorption quantifies the extent of chemical intestinal absorption following oral delivery. The absorption could be optimal if the outcome was elevated. As seen in the result, the gastrointestinal absorption of the synthesized chemicals was generally high, with the exception of B4 and B6.

Ultimately, it is anticipated that none of the synthesized chemicals will be expelled by the P-glycoprotein. Table 4 is a list of some ADME settings.

*Table 4: some predicted pharmacokinetic parameters, drug likeness ranking and synthetic accessibility for synthesized compounds (B1-B6)*

Comp.	TPSA	M.Wt	solubility	GI absorb	BBB	P-gp substrate	Lipinski #violations	Synthetic Accessibility
B1	105.81	403.5	Poorly soluble	High	No	No	0	3.82
B2	105.81	437.94	Poorly soluble	High	No	No	1	3.8
B3	115.04	433.52	Poorly soluble	High	No	No	0	3.86
B4	151.63	448.49	Poorly soluble	Low	No	No	0	3.97
B5	109.05	446.56	Poorly soluble	High	No	No	0	4.11
B6	126.04	419.5	Poorly soluble	Low	No	No	0	3.8

### 4.3. In Vivo Anti-Inflammatory Activity

The results of the synthesized compounds (B1-B6) are listed in (table 5) which show clearly superior ability in decreasing paw edema than that of reference drug ketoprofen.

**Table 5:** The impact of chemicals B1-B6, ketotifen, and propylene glycol on the development of paw edema produced by egg white in rats.

compounds	Duration (minutes) versus Paw Thickness. Measured in millimetres (mm).						
	0	30	60	120	180	240	300
control	5±0.0552.	5±0.015.8	5±0.0596.	6±0.0736.	3±0.0416.	5±0.0186.	3±0.0915.
ketoprofen	3±0.0562.	7±0.0835.	4±0.0706.	4±0.0576.	3±0.035.8	4±0.0784.	05±0.943.
B1	4±0.092.4	6±0.0455.	5±0.0336.	2±0.0745.	5 ±0.064.9	3±0.014.2	7±0.083.6
B2	4±0.052.4	4±0.0715.	5±0.0646.	4±0.016.1	5±0.0355.	5±0.0684.	5±0.0783.
B3	2.53±0.04	5.42±0.04	6.47±0.03	5.86±0.05	4.67±0.07	4.06±0.07	3.32±0.04
B4	2.51±0.03	5.89±0.04	6.22±0.05	5.79±0.03	4.91±0.06	4.22±0.04	3.37±0.03
B5	2.53±0.05	5.81±0.03	6.67±0.04	5.59±0.04	4.97±0.04	4.12±0.05	2.93±0.04
B6	2.57±0.05	5.84±0.06	6.71±0.03	6.02±0.05	5.81±0.05	4.13±0.05	2.86±0.05

## 5. CONCLUSIONS

The anti-inflammatory activity of ketoprofen thiourea derivatives (B1-B6) was evaluated, indicating that the addition of a thiourea group to ketoprofen increased its anti-inflammatory properties. The ADME investigation revealed that the majority of compounds satisfied the Lipinski rule, and all of the synthesised compounds were absorbed by the gastrointestinal tract (GIT). The investigation conducted by Docking demonstrated a high level of agreement with in vivo research. The preliminary study on anti-inflammatory efficacy indicated that chemicals B5 and B6 have a greater anti-inflammatory effect compared to the other compounds.

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## AUTHORS CONTRIBUTIONS

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## CONFLICT OF INTERESTS

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