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MORALITY BEFORE KNOWLEDGE

In silico development and evaluation of pyruvic acid derivatives as potential analgesic and anti-inflammatory agents

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ABSTRACT

Background: Drug development is a process aimed at creating new drugs with enhanced biological activity through various approaches. One such approach is the rational design of new compound candidates using computer-based or in silico modeling technologies, such as molecular docking. Pyruvic acid is known to possess various pharmacological activities, including antioxidant and anti-inflammatory effects. Derivatives of pyruvic acid have the potential to be developed as candidate analgesic and anti-inflammatory drugs. This study explores the in silico development and evaluation of pyruvic acid derivatives as potential analgesic and anti-inflammatory drug candidates. **Methods**: Drug-likeness was evaluated using Lipinski's Rule of Five via pkCSM, while pharmacokinetic and toxicity profiles were predicted using the same platform. Molecular docking was performed on the cyclooxygenase-2 (COX-2) enzyme (PDB ID: 5IKR) using Molegro Virtual Docker 6.0. **Findings:** All test compounds met drug-likeness criteria. Compounds H6, H8, H9, H11, H17, and H18 exhibited superior binding affinities compared to paracetamol. Several compounds, including H8 and H10, demonstrated lower predicted toxicity compared to paracetamol. All test compound exhibits favorable pharmacokinetics properties based on the pkCSM preditive model. **Conclusion**: From this results, compound H6 and H8 emerged as the most promising candidate, exhibiting optimal characteristics across all evaluated parameters. These findings support further development of H6 and H8 as potential analgesic and anti-inflammatory agent targeting COX-2 Inhibition. **Novelty/Originality of this article:** This study developed and evaluated pyruvic acid derivative compounds as novel analgesic and anti-inflammatory agents based on in silico studies.

KEYWORDS: analgesic; anti-inflammatory; development; in silico; pyruvic acid.

1. Introduction

Drug development is the process of creating new drugs with enhanced biological activity, based on several considerations including the stage of disease progression and severity, as well as the effectiveness of the therapy (Barrett et al., 2022). One advancement in the modern drug design approach is computer-aided drug design or in silico modeling technology (Doytchinova, 2022). In silico drug development is the process of designing, discovering, and optimizing biologically active compounds using computer technology, which includes ligand docking to proteins, optimization, and prediction of molecular potency and characteristics (Chackalamannil et al., 2017). One example of drug compound development using this method is the in silico testing of paracetamol derivatives using molecular docking as analgesics (Widiandani et al., 2013).

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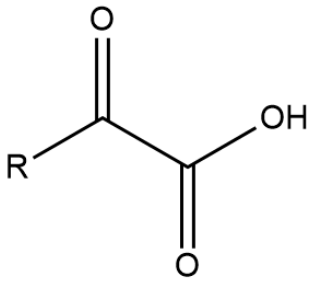
Pyruvate (CH_3COCOO^-), the anion of pyruvic acid or 2-oxopropanoic acid, is a compound that plays an important role in mediating cellular metabolic processes. Pyruvate is the end product of glycolysis, derived from additional sources in the cell cytoplasm, and is transported to the mitochondria as a primary substrate in the citric acid cycle (Gray et al., 2014). Pyruvate has the ability to capture reactive oxygen species. This is supported by research showing that the use of exogenous pyruvate provides benefits in initiating antioxidant and anti-inflammatory activity both in vitro and in vivo (Koprivica et al., 2022). Additionally, exogenous pyruvate, as an alkalizer, can increase cellular tolerance to hypoxia and anoxia by maintaining the glycolysis pathway and reactivating pyruvate dehydrogenase activity to enhance oxidative metabolism (Zhou, 2022). However, pyruvate has the drawback of spontaneously undergoing condensation and cyclization reactions in aqueous solution, resulting in the formation of 2-hydroxy-2-methyl-4-ketoglutarate, a potentially toxic compound that can inhibit the tricarboxylic acid cycle and disrupt energy metabolism homeostasis (Lu et al., 2021). Therefore, the development of pyruvic acid compounds is necessary to minimize this toxicity potential and enhance the compound's activity.

Efforts to modify the molecular structure of pyruvic acid derivatives as analgesic and anti-inflammatory agents have been carried out to some extent. Lee et al. (2017) conducted in vivo testing of the anti-inflammatory and anti-excitotoxic activities of pyruvic acid derivatives, diethyl oxopropanamide, which showed that the compound possesses anti-inflammatory activity through the suppression of NF-κB, inhibition of microglial activation, neutrophil infiltration, and excitotoxicity in nerves (Lee et al., 2017). In addition, ethyl pyruvate, fatty acid derivatives originating from pyruvic avid, demonstrates antioxidant, anti-inflammatory, anti-apoptotic, anti-fibrotic, and several other pharmacological activities (Yang et al., 2016). This development serves as a reference for the development of pyruvic acid derivatives as analgesic and anti-inflammatory agents in the upcoming research.

This research conducted involved the development of pyruvic acid derivative compounds. The test compounds used in this study consisted of 18 pyruvic acid derivatives with modifications on the alkyl side chain groups, including $-CH_3$, $-OCH_3$, $-C_2H_5$, $-CHCl_2$, $-CH_2$-cyclo-C_3H_5, $-C_6H_5$, i-C_3H_7, $-CH_2SO_2CH_3$, cyclo-C_5H_9, $-CF_3$, $-C_6H_{11}$, $-C(CH_3)_3$, -H, $-CH_2CF_3$, $-CH_2SCH_3$, cyclo-C_4H_7, $-CH_2-C_6H_5$, and $-CH_2CH_2-C_6H_5$. The selection of these substituents was based on the Topliss approach model. The research conducted covered several aspects, namely drug likeness prediction, pharmacokinetic and toxicity prediction, and activity prediction using molecular docking. This study is expected to provide information regarding the development of pyruvic acid derivative compounds as candidate analgesic and anti-inflammatory drugs by inhibiting cyclooxygenase-2 (COX-2) in silico.



Compound Code	Substituent (-R)	Compound Code	Substituent (-R)
H1	$-CH_3$	H10	$-CF_3$
H2	$-OCH_3$	H11	$-C_6H_{11}$
H3	$-C_2H_5$	H12	$-C(CH_3)_3$
H4	$-CHCl_2$	H13	-H
H5	$-CH_2$-siklo-C_3H_5	H14	$-CH_2CF_3$
H6	$-C_6H_5$	H15	$-CH_2SCH_3$
H7	i-C_3H_7	H16	siklo-C_4H_7
H8	$-CH_2SO_2CH_3$	H17	$-CH_2-C_6H_5$
H9	siklo-C_5H_9	H18	$-CH_2CH_2-C_6H_5$

Fig. 1. Structure of pyruvic acid derivative compounds

2. Methods

This study employs a computer-based experimental research design conducted in silico, which includes drug-likeness prediction, prediction of pharmacokinetic properties (absorption, distribution, metabolism, and excretion) and toxicity (rat LD50, hepatotoxicity, and AMES toxicity), as well as the prediction of analgesic and anti-inflammatory activity through molecular docking. The materials used in this study included 2D structures of 18

pyruvic acid derivative compounds and reference compound, paracetamol, as well as the 3D structure of the cyclooxygenase-2 (COX-2) enzyme (PDB ID: 5IKR). The tools used in this study were ChemDraw Professional 17.1, Chem3D 17.1, the pkCSM online tool, Molegro Virtual Docker 6.0, and a DELL Latitude 3410 laptop with a Windows 10 Home 64-bit operating system, an Intel(R) Core(TM) i3-10110U CPU @ 2.10GHz 2.59 GHz processor, and 4.00 GB of RAM.

The independent variables in this study are the minimized 3D structures and SMILES notations of 18 pyruvic acid derivative compounds and paracetamol. The dependent variables in this study are the ligand-receptor interaction energy in the form of the rerank score; the predicted pharmacokinetic properties, including absorption, distribution, metabolism, and excretion parameters; the predicted toxicity properties, including rat LD50, AMES toxicity, and hepatotoxicity parameters; and the drug-likeness prediction results (molecular weight (MW) <500 g/mol; hydrogen bond acceptors (HBA) <10; hydrogen bond donors (HBD) <5; and lipophilicity (LogP <5)). The controlled variables in this study are the structure of the cyclooxygenase-2 (COX-2) enzyme (PDB ID: 5IKR) containing ligand ID8, the laptop specifications, and the software used for in silico testing. The laptop specifications include a DELL Latitude 3410 with a Windows 10 Home 64-bit operating system, an Intel(R) Core(TM) i3-10110U CPU @ 2.10GHz 2.59 GHz processor, and 4.00 GB of RAM. The software used includes ChemDraw Professional 17.1, Chem3D 17.1, the pkCSM online tool, and Molegro Virtual Docker 6.0.

2.1 Research procedure

2.1.1 Ligand and receptor preparation

The 2D structures of the test and reference compounds were drawn using ChemDraw Professional 17.1 software. The 2D structures were optimized using the "clean-up structure" feature. These 2D structures were then converted into 3D structures using Chem3D 17.1 software. Energy minimization of the 3D structures was carried out using the MMFF94 force field in Chem3D 17.1 to obtain the most stable conformations. The most stable 3D structures were saved in both SD file and SMILES formats. The receptor structure was downloaded from the Protein Data Bank (PDB) by visiting the official PDB website (https://www.rcsb.org), entering the PDB code of the cyclooxygenase-2 (COX-2) enzyme, which is 5IKR, into the search bar, and saving the file in .pdb format. The downloaded structure was prepared using the “prepare molecule” feature in Molegro Virtual Docker 6.0

2.1.2 Drug-likeness, pharmacokinetics, toxicity, and activity prediction via molecular docking

Drug-likeness prediction was conducted using the pkCSM online tools. The minimized 3D structures were converted into SMILES format. The SMILES representation of each compound was then input into pkCSM Online. By clicking “ADMET” menu, the drug-likeness prediction of the compounds was displayed. Pharmacokinetics and toxicity prediction was conducted using the pkCSM online tool. The minimized 3D structures were converted into SMILES format. The SMILES of each compound was then input into pkCSM online tools. By clicking “ADMET” menu, the predicted pharmacokinetic and toxicity properties of the respective compounds were displayed

Molecular docking included validation of the docking method, docking of the test and reference compounds, and visualization of the ligand-receptor interactions. Docking method validation was performed through redocking of the native ligand ID8 into the cyclooxygenase-2 (COX-2) enzyme (PDB ID: 5IKR). The validation parameter used was the Root Mean Square Deviation (RMSD), with the criterion of RMSD ≤2 Å. The next step was the molecular docking of the reference and test compounds to the receptor. Visualization of the 2D and 3D ligand-receptor interactions resulting from the molecular docking was carried out using the ligand map feature in Molegro Virtual Docker 6.0.

2.2 Data analysis

The drug-likeness prediction results were evaluated based on Lipinski's Rule of Five (molecular weight (MW) <500 g/mol; hydrogen bond acceptors (HBA) <10; hydrogen bond donors (HBD) <5; and lipophilicity (LogP <5)). Predicted pharmacokinetic and toxicity properties were assessed using the criteria provided in the pkCSM online tool (Pires et al., 2015). Predicted activity results from molecular docking were analyzed descriptively, including the rerank score values of the test and reference compound; the amino acid residues and functional groups involved in ligand-receptor interactions; and the visualization of the docking results.

3. Result and Discussion

3.1 Overview of drug development

Drug discovery and development are carried out continuously in order to produce drugs with higher activity, lower toxicity, and better pharmacokinetic profiles. Drug discovery is defined as the process of creating chemical or biological compounds that have the desired biological effects through appropriate testing, and have the potential to be developed as therapeutic agents (Taylor & Triggie, 2006). Drug development is a process of creating new drugs with increased potential based on several considerations including the level of disease progression and severity, as well as the effectiveness of the therapy or drug given (Barrett et al., 2022). Drug development can be carried out through several approaches, one of which is rational drug design.

The rational drug design approach includes identifying biological targets (macromolecules involved in a disease), ligands that interact with macromolecules, and optimizing the structure until a compound is obtained with affinity, selectivity, non-toxicity, solubility, permeability, and bioavailability, as well as other properties required for a molecule to become a drug (Doytchinova, 2022). Rational drug design approaches include ligand-based and structure-based drug design. One of the developments in the modern drug design approach is computer-aided drug design or in silico-based modeling technology. In silico drug development is the process of designing, discovering, and optimizing biologically active compounds by utilizing computer technology that includes ligand docking to proteins, optimization, prediction of biological activity and molecular characteristics (Chackalamannil et al., 2017). The rational approach to designing new drug compound candidates is divided into two types, namely ligand-based and structure-based approaches (Siswandono, 2016). The ligand-based drug design approach is used if the structure of the active molecule or ligand of the target macromolecule is known. Meanwhile, the structure-based drug design approach is carried out if the structure of the target macromolecule is known.

3.2 Review of analgesic and anti-inflammatory compounds

Analgesic compounds are compounds that can selectively suppress the function of the central nervous system, used to reduce pain without affecting consciousness (Siswandono, 2016). Analgesics work by increasing the threshold value of pain perception (Siswandono, 2016). Based on the mechanism of action at the molecular level, Analgesics are divided into two groups, namely narcotic and non-narcotic analgesics. Narcotic analgesics: Compounds that can selectively suppress the function of the central nervous system, used to reduce pain, moderate or severe, work by binding to the opioid receptor side (Siswandono, 2016). Non-narcotic analgesics: Compounds used to reduce mild to moderate pain, so called mild analgesics, can lower high body temperature (antipyretic), and anti-inflammatory (anti-inflammatory). Non-narcotic analgesics work on the periphery and central nervous system (Siswandono, 2016).

Anti-inflammatory compounds are compounds that can suppress or reduce inflammation through several mechanisms such as inhibition of prostaglandin biosynthesis and release through reversible inhibition of cyclooxygenase enzymes, inhibition of enzymes involved in mucopolysaccharide and glycoprotein biosynthesis, inhibition of phospholipase A2, and several other mechanisms (Siswandono, 2016). An example of a compound that has analgesic and anti-inflammatory activity is paracetamol. Paracetamol is a popular p-aminophenol derivative analgesic-antipyretic compound that is widely used in Indonesia. The mechanism of action as an analgesic is by blocking the generation of peripheral pain stimuli, as an antipyretic by inhibiting the heat regulation center in the hypothalamus, and a weak anti-inflammatory effect in inhibiting prostaglandin synthesis (Siswandono, 2016). The use of paracetamol in large doses and in the long term can cause methemoglobin and liver damage (Siswandono, 2016). The selection of paracetamol as a comparison compound is based on the similarity of the working mechanism in the form of inhibition of the cyclooxygenase-2 (COX-2) enzyme.

3.3 Review of pyruvic acid compounds and their derivatives

Pyruvate (CH_3COCOO-), an anion of pyruvic acid or 2-oxopropanoic acid, is a compound that plays an important role in mediating cell metabolism processes. Pyruvate is the end product of glycolysis, comes from additional sources in the cell cytoplasm, and is transported to the mitochondria as the main ingredient in the citric acid cycle (Gray et al., 2014). Pyruvate has the ability to capture reactive oxygen species. This is supported by research showing that the use of exogenous pyruvate provides benefits in the form of initiating antioxidant and anti-inflammatory activities in vitro and in vivo (Koprivica et al., 2022). In addition, exogenous pyruvate as an alkalizer can increase cell tolerance to hypoxia and anoxia by maintaining the glycolysis pathway and reactivating pyruvate dehydrogenase activity to increase oxidative metabolism (Zhou, 2022). Pyruvate has the disadvantage of spontaneously undergoing condensation and cyclization reactions in aqueous solution to produce 2-hydroxy-2-methyl-4-ketoglutarate compounds which are potentially toxic through inhibition of the tricarboxylic acid cycle and disruption of energy metabolism homeostasis (Lu et al., 2021). Therefore, the development of pyruvic acid compounds needs to be carried out in order to minimize the potential for toxicity and increase the activity of these compounds.

One of the developments of pyruvic acid compounds is ethyl pyruvate. Ethyl pyruvate, ethyl 2-oxy-propionate, is a derivative of pyruvic acid which has a special bifunctional group structure and has been widely used in biomedicine due to its low cost, low toxicity, and relative stability (Lu et al., 2021). Research shows that ethyl pyruvate has anti-oxidative, anti-inflammatory, anti-apoptotic, anti-fibrosis, and several other pharmacological activities (Yang et al., 2016). In addition to these developments, Lee et al. develop and test the anti-inflammatory, anti-excitotoxic, and neuroprotective activities of the bioisosteric compound ethyl pyruvate. This development is a reference for researchers in developing other pyruvic acid derivatives.

3.4 Drug-likeness Prediction

Drug-likeness is a qualitative concept used in drug design to estimate a compound's similarity to known drugs (Veber et al., 2002). Drug-likeness is determined based on the physicochemical properties of compounds developed as candidates for oral drugs (Daina et al., 2017). The drug-likeness prediction results of 18 pyruvic acid derivative compounds and paracetamol are as shown in Table 1.

Table 1. Drug-likeness prediction results

Compound Code	MW (g/mol)	HBA	HBD	LOGP
H1	88.06	2	1	-0.34
H2	104.06	3	1	-0.34

H3	102.08	2	1	-0.75
H4	156.95	2	1	0.05
H5	128.12	2	1	0.44
H6	150.13	2	1	0.44
H7	116.11	2	1	0.95
H8	166.15	4	1	0.29
H9	142.15	2	1	-1.31
H10	142.03	2	1	0.83
H11	156.18	2	1	0.20
H12	130.14	2	1	1.22
H13	74.035	2	1	0.68
H14	156.05	2	1	-0.73
H15	134.15	2	1	0.59
H16	128.12	2	1	0.003
H17	164.16	2	1	0.44
H18	178.18	2	1	1.27
Paracetamol	151.16	2	2	1.35

These results indicate that all 18 pyruvic avid derivatives meet the four parameters of Lipinski's rule of five. Compound H18 showed the highest molecular weight (MW) and LogP values compared to the other derivatives. This is due to the addition of $-CH_2CH_2-C_6H_5$ group increase the steric and lipophilic properties of the compound. Furthermore, compound H8 exhibited the highest number of hydrogen bond acceptors and donors compared to the other derivatives and the reference compound. This suggest that compound has a higher potential to form hydrogen bond with the receptor. Compliance with Lipinski's rule of five is associated with an increased likelihood of the compound being a viable candidate for oral drug use (Lipinski et al., 2001).

3.5 Activity prediction via molecular docking

The activity prediction results include method validation; molecular docking of test and reference compounds against the cyclooxygenase-2 (COX-2) enzyme (PDB ID: 5IKR); and visualization of ligand-receptor interactions. The RMSD value obtained from the method validation process was 1,00269. This value indicates that the molecular docking method used is valid and can be applied to predict the activity of both the test and reference compounds. The visualization of the molecular docking method validation results can be seen in Figure 2.

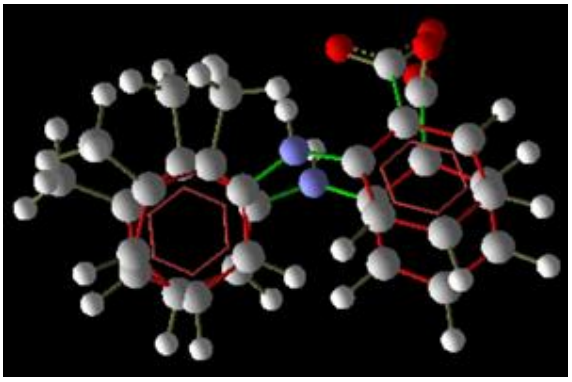


Fig. 2. Overlay of native ligand position before and after the validation process

The molecular docking results include interaction energy values, types of interactions, and the amino acids contributing to the ligand–receptor binding. The interaction energy values used in this study are represented by the rerank score. The rerank score is a linear combination of intermolecular energies (steric, van der Waals, hydrogen bonding, electrostatic) between the ligand and the protein, as well as intramolecular energies

(torsion, sp2–sp2, hydrogen bonding, van der Waals, electrostatic) that have been weighted according to predetermined coefficients (Singh et al., 2015). The types of interactions identified in this study include hydrogen bonding, electrostatic interactions, and steric interactions. The predicted activity results from molecular docking of 18 pyruvic acid derivative compounds and the reference compound, paracetamol, are shown in Table 2.

Table 2. Molecular docking results of test and reference compound against COX-2 (PDB ID:5IKR)

Compound Code	Amino Acids (Hydrogen Bond Interactions)	Amino Acids (Electronic Interactions)	Amino Acids (Steric Interactions)	Rerank Score
H1	Met522	-	-	-41.72
H2	Met522	-	Leu384, Val523	-46.56
H3	Tyr385	-	-	-47.86
H4	Met522	-	-	50.54
H5	Tyr385	-	-	-56.54
H6	Ser530, Tyr385	-	Gly526, Trp387, Val523	-64.23
H7	Tyr385	-	-	-53.53
H8	Met522, Tyr385, Val523	-	-	-62.12
H9	Met522	-	Leu384	-61.86
H10	Met522	-	-	-52.92
H11	Ser530, Tyr385	-	Leu352	-63.31
H12	Met522	-	Leu352	-53.19
H13	Met522	-	-	-40.04
H14	Met522	-	-	-58.73
H15	Met522	-	-	-54.13
H16	Ser530, Tyr385	-	-	-59.68
H17	Ser530, Tyr385	-	-	-67.30
H18	Arg120, Tyr355	-	Leu352	-72.44
Paracetamol	Met522, Ser 530	-	-	-61.02

These results demonstrate that compounds H6, H8, H9, H11, H17, and H18 have lower rerank scores than the reference compound. The lower the rerank score, the more stable the interaction between the ligand and receptor, which suggests a higher predicted activity against COX-2. Visualization of the test compounds and the reference compound within the COX-2 enzyme cavity (PDB ID: 5IKR) is presented in Figure 3.

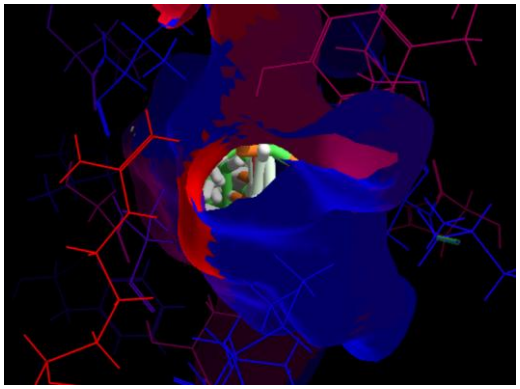


Fig. 3. Visualization of the test and reference compounds within the COX-2 enzyme cavity

Ligand–receptor interaction visualization aims to identify the types of interactions involved in the binding between the test compounds and the reference compound with the receptor. These interactions can be visualized in both 2D and 3D formats. The interaction visualizations of compounds H6, H8, H9, H11, H17, H18, and the reference compound paracetamol with the COX-2 enzyme receptor (PDB ID: 5IKR) are shown in Figures 4 and Figure 5.

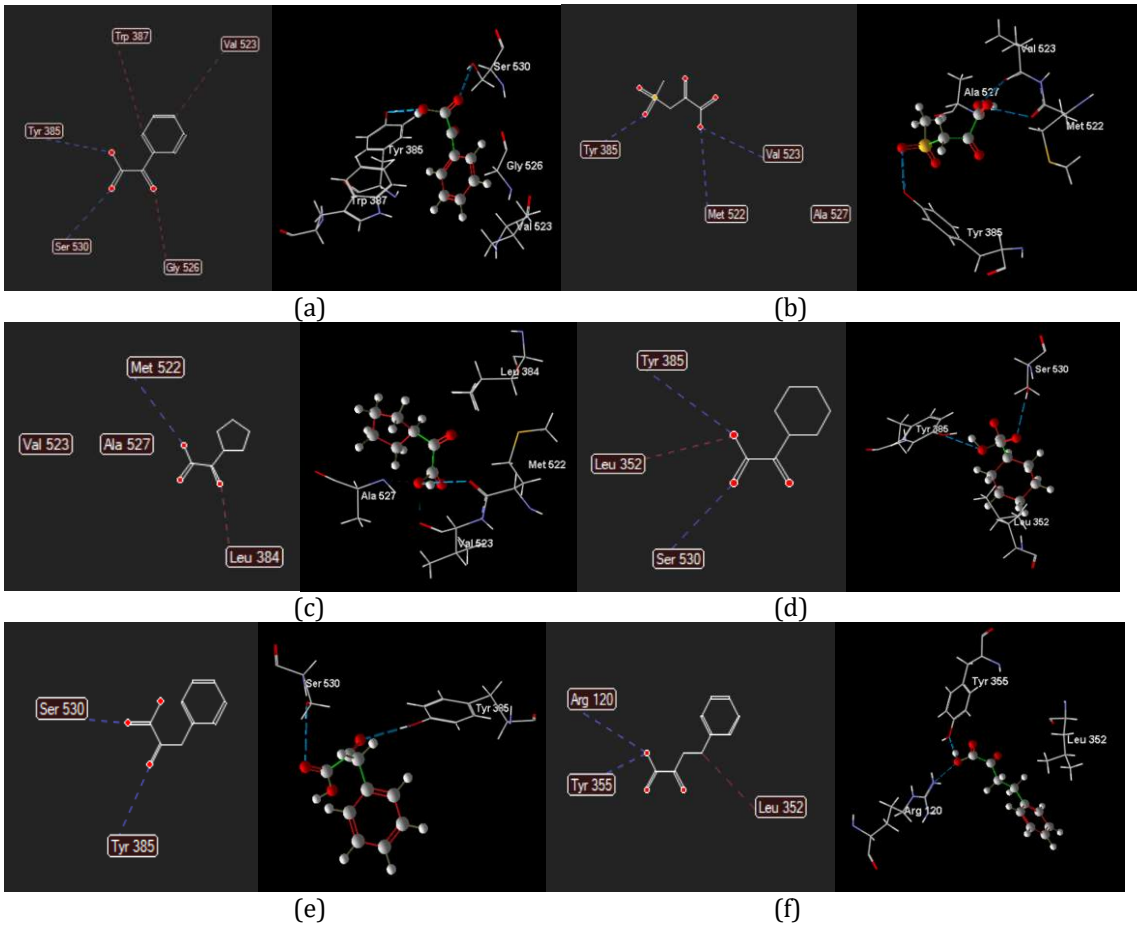


Fig. 4. Interaction of compound (a) H6 with COX-2 enzyme (PDB ID: 5IKR); (b) H8 with COX-2 enzyme (PDB ID: 5IKR); (c) H9 with COX-2 enzyme (PDB ID: 5IKR); (d) H11 with COX-2 enzyme (PDB ID: 5IKR); (e) H17 with COX-2 enzyme (PDB ID: 5IKR); (f) H18 with COX-2 enzyme (PDB ID: 5IKR)

The rational drug design approach includes identifying biological targets (macromolecules involved in a disease), ligands that interact with macromolecules, and optimizing the structure until a compound is obtained with affinity, selectivity, non-toxicity, solubility, permeability, and bioavailability, as well as other properties required for a molecule to become a drug (Doytchinova, 2022). Rational drug design approaches include ligand-based and structure-based drug design. One of the developments in the modern drug design approach is computer-aided drug design or in silico-based modeling technology.

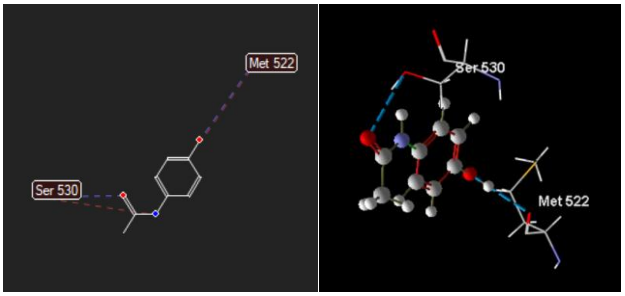


Fig. 5. Interaction of paracetamol with COX-2 enzyme (PDB ID: 5IKR)

In silico drug development is the process of designing, discovering, and optimizing biologically active compounds by utilizing computer technology that includes ligand docking to proteins, optimization, prediction of biological activity and molecular characteristics (Chackalamannil et al., 2017). The rational approach to designing new drug compound candidates is divided into two types, namely ligand-based and structure-based

approaches (Siswandono, 2016). The ligand-based drug design approach is used if the structure of the active molecule or ligand of the target macromolecule is known. Meanwhile, the structure-based drug design approach is carried out if the structure of the target macromolecule is known.

3.6 Toxicity prediction

The toxicity prediction results include several parameters, namely rat LD50, which describes the potential for acute toxicity by representing the concentration of a compound that causes the death of 50% of a group of test animals; AMES toxicity, which indicates the mutagenic potential of a compound; and hepatotoxicity, which reflects the potential of a compound to cause liver toxicity (Pires et al., 2015). The purpose of toxicity prediction is to estimate the safety of a drug candidate compound. The predicted toxicity properties of 18 pyruvic acid derivative compounds and paracetamol are presented in Table 3.

Table 3. Predicted toxicity properties of pyruvic acid derivatives and paracetamol

Compound code	Rat LD_{50}		AMES toxicity	Hepatotoxicity
	mol/kg	mg/kg	(+/-)	(+/-)
H1	1.62	143624	-	-
H2	1.89	197508	-	-
H3	1.91	195297	-	-
H4	2.65	416080	+	-
H5	1.82	233191	-	-
H6	1.76	264835	-	-
H7	1.80	209589	-	-
H8	2.00	332806	-	-
H9	1.77	252892	-	-
H10	2.65	377095	-	-
H11	1.77	276596	-	+
H12	1.79	233346	-	-
H13	2.15	159175	-	-
H14	2.73	426041	+	-
H15	2.12	285618	+	-
H16	1.79	230500	-	-
H17	1.78	292697	-	+
H18	1.84	328220	-	+
Paracetamol	2.18	329540	+	-

The results indicate that compounds H4, H8, H10, and H14 have higher rat LD50 values compared to paracetamol. These four derivative compounds are predicted to have a lower potential to cause acute toxicity than paracetamol. Furthermore, all 18 pyruvic acid derivative compounds fall into the category of non-toxic compounds based on the criteria for acute toxicity classification. The criteria for acute toxicity classification are presented in Table 4.

Table 4. Predicted toxicity properties of pyruvic acid derivatives and paracetamol

Toxicity Level	Oral LD50 (in rats)	Classification
1	≤ 5 mg/kg	Super Toxic
2	5-50 mg/kg	Highly Toxic
3	> 50-500 mg/kg	Toxic
4	> 500-2000 mg/kg	Moderate Toxic
5	> 2000-5000 mg/kg	Mild Toxic
6	> 5000 mg/kg	Non Toxic

Compounds H4, H14, and H15 showed positive (+) results for the AMES toxicity parameter, indicating that these three compounds are predicted to have a high potential for mutagenicity. On the other hand, compounds H11, H17, and H18 showed positive (+) results

for the hepatotoxicity parameter, suggesting that these compounds are predicted to have a high potential to cause liver damage. Testing based on these three parameters aims to ensure the safety of drug candidate compounds, particularly for both acute and chronic use.

3.7 Pharmacokinetic properties prediction

The prediction of pharmacokinetic properties aims to understand how a potential drug compound is absorbed, distributed, metabolized, and excreted in the body. This prediction is carried out to assist in the initial design of dosage, the prediction of potential side effects, and the optimization of therapeutic benefits. The prediction includes several parameters: absorption, distribution, metabolism, and excretion.

3.7.1 Absorption Parameters

Absorption is the transportation of the drug from the site of administration to the general circulation (Currie, 2018). The absorption parameters assessed in this study include human intestinal absorption and Caco-2 permeability. Human intestinal absorption reflects the percentage of a drug absorbed through the intestinal tract (Azman et al., 2022). Caco-2 permeability serves as an in vitro model for predicting drug absorption in the human intestine, utilizing Caco-2 cells, a colon epithelial cancer cell line, that simulates various transcellular transport pathways and metabolic transformations occurring in the intestinal epithelium (Hubatsch et al., 2007). The predicted absorption parameters of 18 pyruvic acid derivatives are presented in Table 5.

Table 5. Predicted absorption parameters of pyruvic acid derivatives

Compound Code	Caco-2 Permeability (log Papp in 10-6 cm/s)	Human Intestinal Absoprtion (% Absorbed)
H1	1.09	93.14
H2	0.62	93.54
H3	1.12	91.75
H4	1.16	99.33
H5	1.14	86.59
H6	1.19	76.14
H7	1.14	88.30
H8	0.91	89.99
H9	1.17	84.88
H10	1.16	100
H11	1.19	83.30
H12	1.17	86.54
H13	1.07	93.04
H14	1.19	100
H15	1.13	95.53
H16	1.14	86.62
H17	1.20	74.49
H18	1.22	73.06
Parcsetamol	1.18	92.15
Criteria	>0.9	>30

The results show that the range of Caco-2 permeability values obtained is 0.624–1.224 log Papp (in 10^{-6} cm/s). According to the pkCSM prediction model, a compound is considered to have a high Caco-2 permeability if it has a log Papp > 0.90 (Pires et al., 2015). Based on these criteria, compound H2 exhibits poor permeability, with a Caco-2 permeability value below 0.90. Compound H18 shows the highest Caco-2 permeability among the derivatives. This may be attributed to the addition of a lipophilic -CH_2CH_2–C_6H_5 group, which increases the compound's overall lipophilicity. Higher lipophilicity often enhances membrane permeability, facilitating a drug's passage through the lipid bilayers of

cell membranes (Mobitz, 2023). Permeability is critical for efficient absorption into the bloodstream and subsequent delivery to the target site (Dahlgren & Lennernas, 2019).

The results show that the range of human intestinal absorption values obtained is 73,068 – 100%. According to the pkCSM prediction model, a compound with an absorbance of less than 30% is considered to be poorly absorbed (Pires et al., 2015). Based on these criteria, 18 pyruvic acid derivatives demonstrated high intestinal absorption, as indicated by a predicted absorption percentage greater than 30%. Compound H10 and H14 exhibited the highest predicted absorption percentages among the pyruvate acid derivatives. This may be attributed to the presence of a $-CF_3$ group in H10 and a $-CH_2CF_3$ group in H14, both of which contain fluorine (F) atoms. The electronegativity, size, electrostatic interactions, and lipophilicity of fluorine are known to significantly influence chemical reactivity, physicochemical properties, and biological activity (Nair et al., 2022). Intestinal drug absorption is a key process for determining oral bioavailability (Augustijns et al., 2014).

3.7.2 Distribution parameters

Distribution refers to movement of the drug from the systemic circulation to tissues (Currie, 2018). The drug needs to be distributed to the site of action in sufficient concentration to generate the therapeutic action (Currie, 2018). The distribution parameters assessed in this study include volume of distribution (VDss) and blood-brain barrier (BBB) permeability. VDss describes the distribution of a compound by representing the equivalent volume in which a given dose would need to be uniformly distributed to achieve the observed plasma concentration (Pires et al., 2015). It reflects the compound's ability to bind to tissues or plasma proteins (Pires et al., 2015). BBB permability indicates the ability of a compound to penetrate the blood-brain barrier, which is essential for assessing its potential to reach the central nervous system (Wu et al., 2023). The predicted distribution parameters of 18 pyruvic acid derivatives are presented in Table 6.

Table 6. Predicted distribution parameters of pyruvic acid derivative

Compound Code	VDss (Human) (log L/kg)	BBB Permeability (log BB)
H1	-0.69	-0.35
H2	-0.86	-0.40
H3	-0.85	-0.35
H4	-092	-0.37
H5	-0.78	-0.30
H6	-1.1	-0.21
H7	-0.93	-0.31
H8	-0.98	-0.67
H9	-0.79	-0.24
H10	-0.92	-0.33
H11	-0.78	-0.19
H12	-0.95	-0.29
H13	-0.70	-0.36
H14	-0.97	-0.33
H15	-0.86	-0.36
H16	-0.79	-0.28
H17	-0.98	-0.18
H18	-0.86	-0.13

The results show that the range of VDss values obtained is -1.1–-0.691 log L/kg. According to the pkCSM prediction model, a compound is considered to have low VDss if log VDss <-0.15 and high VDss if log VDss >0.45 (Pires et al., 2015). Based on these criteria, 18 pyruvic acid derivatives demonstrated low volume of distribution, as indicated by a predicted log VDss lower than -0.15. Compound with low volume of distribution tend to remain in the plasma rather than distribute into tissues (Currie, 2018). Compound H1 exhibited the highest volume of distribution, whereas compound H6 showed the lowest

volume of distribution. The volume of distribution is a critical parameter for calculating the loading dose and play a key role in preventing the drug from reaching toxic concentrations within the body (Currie, 2018).

The results show that the range of BBB permeability values obtained is -0.677–-0/137 log BB. According to the pkCSM prediction model, a compound is considered to readily cross the blood-brain barrier if log BB >0.3 and poorly distributed to the brain if log BB <-1 (Pires et al., 2015). Based on these criteria, 18 pyruvic acid derivatives demonstrated moderate BBB permeability, as indicated by a predicted BBB permeability value -1< log BB <0.3. Compound H18 exhibited the highest BBB permeability, whereas compound H8 showed the lowest BBB permeability. The evaluation of these parameters aims to minimize the potential of drug candidate compounds to cause side effects and toxicity, particularly in the central nervous system, while enhancing the efficacy of drugs that act on the central nervous system (Pires et al., 2015).

3.7.3 Metabolism parameters

Drug metabolism refers to the process by which the chemical structure of a drug is altered, typically by specialized enzyme systems, resulting in the formation of a new compound known as a metabolite (Hedaya, 2024). Drugs can be metabolized by various enzyme systems through different metabolic pathways, which can be classified to phases I and II metabolic reactions (Meyer, 1996). The cytochrome P450 enzymes (CYPs) are a superfamily of metabolizing enzymes responsible for approximately 75% of all drug metabolism in humans (Guengerich, 2003). The ability of a compound to induce or inhibit cytochrome P450 enzymes can significantly impact metabolic pathways and warrants careful evaluation during drug development (Hedaya, 2024). The metabolism parameters assessed in this study include cytochrome P450 inhibitors and CYP2D6/CYP3A4 substrate. Cytochrome P450 inhibitors serve as a parameter to predict whether a molecule falls into the category of inhibitors of cytochrome P450 isoforms (Pires et al., 2015). The cytochrome P450 isoforms evaluated in this study were CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. CYP2D6/CYP3A4 substrate is parameter for assesing wheter a compound is likely to be metabolyzed by cytochrome P450, particularly isoforms 2D6 and 3A4 (Pires et al., 2015). The predicted absorption parameters of 18 pyruvic acid derivatives are shown in Table 7.

Table 7. Predicted metabolism parameters of pyruvic acid derivatives

Compound code	CYP2D6 substrate	CYP3A4 substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
H1	-	-	-	-	-	-	-
H2	-	-	-	-	-	-	-
H3	-	-	-	-	-	-	-
H4	-	-	-	-	-	-	-
H5	-	-	-	-	-	-	-
H6	-	-	-	-	-	-	-
H7	-	-	-	-	-	-	-
H8	-	-	-	-	-	-	-
H9	-	-	-	-	-	-	-
H10	-	-	-	-	-	-	-
H11	-	-	-	-	-	-	-
H12	-	-	-	-	-	-	-
H13	-	-	-	-	-	-	-
H14	-	-	-	-	-	-	-
H15	-	-	-	-	-	-	-
H16	-	-	-	-	-	-	-
H17	-	-	-	-	-	-	-
H18	-	-	-	-	-	-	-

The results show that 18 pyruvic acid derivative compounds have a low potential to inhibit several cytochrome P450 isoform, as indicated by negative (-) values in the assay results. According to the pkCSM prediction model, a compound is considered to be a cytochrome P450 inhibitor of the concentration required to lead to 50% inhibition is less than 10 μM (Pires et al., 2015). A lower inhibitory potential against cytochrome P450 is directly associated with reduced risk of drug-drug interaction (Palleria et al., 2013). Furthermore, the findings suggest that the 18 pyruvic acid derivative compounds exhibit a low metabolic potential via cytochrome P450 isoforms 2D6 and 3A4, as indicated by negative (-) assay values. This low metabolic liability toward CYP2D6 and CYP3A4 suggests favorable pharmacokinetic properties, as these isoforms are responsible for the metabolism of a large proportion of clinically used drugs (Pires et al., 2015). Therefore, the 18 pyruvate-derived compounds may be considered safer candidates for further development, particularly in combination therapy settings.

3.7.4 Excretion parameters

Drugs are eliminated from the body either through excretion in their unchanged form or via metabolic conversion into one or more metabolites, which are subsequently excreted (Hedaya, 2024). The major excretion pathways include renal excretion of drugs in urine, biliary excretion of drugs to the gastrointestinal tract, and lung excretion of volatile drugs during expiration (Hedaya, 2024). Assessment of excretion parameters is essential for understanding the elimination of drugs or other substances from the body and for optimizing dosage regimens and therapeutic strategies (Asiri, 2023). The excretion parameters assessed in this study include renal Organic Cation Transporter 2 (OCT2) substrate and total clearance. OCT2 is a renal uptake transporter that plays an important role in disposition and renal clearance of drugs and endogenous compounds (Pires et al., 2015). Renal OCT2 substrate is a pharmacokinetics parameter serves as an indicator of a compound's potential interaction with OCT2. This parameter is critical in assessing drug clearance and identifying potential contraindications when co-administered with OCT2 inhibitors (Pires et al., 2015). Total clearance is a pharmacokinetics parameter that represent the volume of plasma from which a drug is completely cleared per unit time, reflecting the body's efficiency in eliminating the drug (Derendorf & Schmidt, 2020). This parameter is related to bioavailability and plays a crucial role in determining the dosing rate required to achieve steady-state conditions (Pires et al., 2015). The predicted absorption parameters of 18 pyruvic acid derivatives are shown in Table 8.

Table 8. Predicted excretion parameters of pyruvic acid derivatives

Compound code	Renal OCT2 substrate (+/-)	Total clearance (log ml/min/kg)
H1	-	0.75
H2	-	0.81
H3	-	0.77
H4	-	0.30
H5	-	0.54
H6	-	0.63
H7	-	0.75
H8	-	0.93
H9	-	0.59
H10	-	0.68
H11	-	0.59
H12	-	0.70
H13	-	0.70
H14	-	0.65
H15	-	0.43
H16	-	0.58
H17	-	0.66
H18	-	0.67

The results show that 18 pyruvic acid derivative compounds exhibits a low potential for interaction with renal OCT2, as indicated by negative (-) values in the assay results. According to the pkCSM prediction model, a compound is considered a renal OCT2 substrate based on a model developed using compounds with experimentally validated OCT2-mediated transport (Pires et al., 2015). Identifying whether a compound is an OCT2 substrate is essential for understanding its renal clearance mechanisms, particularly for drugs eliminated primarily through active tubular secretion. Therefore, 18 pyruvic acid derivatives compounds may be considered safe due to their low potential for interaction with OCT2 inhibitors.

The result show that range of total clearance obtained is 0.308–0.937 log ml/min/kg. Compound H8 exhibited the highest clearance, whereas compound H4 showed the lowest clearance. This effect may be attributed to the addition of the -$CHCl_2$ group in compound H4 and the -CH_2-SO_2-CH_3 group in compound H8. The presence of halogen-containing functional groups, such as -$CHCl_2$, can improve metabolic stability by reducing the susceptibility of the molecule to phase I oxidative reactions, potentially reducing clearance rate (Faleye et al., 2024). On the other hand, the presence of polar group, such as -CH_2-SO_2-CH_3, can promote renal excretion and facilitate interactions with transporters involved in drug clearance, potentially enhancing drug clearance (Currie, 2018). These findings highlight the significant role that chemical structure plays in influencing pharmacokinetic behavior, particularly drug clearance. Structural modifications, such as the incorporation of halogenated or polar functional groups, can dramatically alter a compound's metabolic fate and elimination route. Therefore, understanding the relationship between molecular features and pharmacokinetic parameters is essential during the early stages of drug design and optimization.

4. Conclusion

Based on the results of this study, several pyruvate-derived compounds, specifically H6, H8, H9, H11, and H18, demonstrated significant analgesic and anti-inflammatory activity through greater inhibition of the COX-2 enzyme compared to the reference drug, paracetamol. In addition, compounds H8 and H10 exhibited lower predicted toxicity profiles, as indicated by rat LD_{50}, AMES toxicity, and hepatotoxicity parameters, suggesting a better safety margin than paracetamol. The pharmacokinetic properties of the pyruvate derivatives were also favorable, as predicted by the pkCSM model. Among the tested compounds, H6 and H8 emerged as the most promising candidates for further development as COX-2-selective analgesic and anti-inflammatory agents. Future studies are recommended, particularly those involving quantitative structure–activity relationship (QSAR) analysis, synthetic pathway design, and comprehensive in vitro and in vivo evaluations to validate and optimize these findings.

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