***In-silico* ANALYSIS OF 1,3-BIS (*p*-HYDROXYPHENYL)UREA AS ANTI-INFLAMMATORY THROUGH INHIBITION OF COX-1 AND TNF- α**

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ABSTRACT

A new compound of 1,3-bis(*p*-hydroxyphenyl) urea was designed and predicted to have fewer hepatotoxic side effects and as analgetic. Synthesis of 1,3-bis(*p*-hydroxyphenyl) urea could be carried out by reaction between *p*-aminophenol and urea. This study evaluated the mechanism of 1,3-bis(*p*-hydroxyphenyl) urea in inhibition of COX-1 and TNF- α with molecular docking. Docking was performed on the receptor file COX-1 (PDB ID: 1CQE) and TNF- α (PDB ID: 2AZ5) using AutoDock Vina PyRx 9.5 program and visualized by Ligplot 2.1 and PyMol 2.3.1. Two and three-dimension conformation models of compounds were generated by the MarvinSketch program. The docking score of ligand control, 1,3-bis(*p*-hydroxyphenyl) urea, diclofenac and dexamethasone towards 1CQE and 2AZ5 were -8.4; -10.6; -7.4 Kcal/mol and -9.2; -9.6; 7.1 Kcal/mol respectively. 1,3-bis(*p*-hydroxyphenyl) urea interacted with more amount of amino acid residues if compare with dexamethasone, diclofenac and ligand control.

Keywords: 1,3-bis(*p*-hydroxyphenyl) urea, Anti-inflammatory, COX-1, TNF- α , *In-silico*

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INTRODUCTION

Inflammation plays an important role in various diseases. Inflammation is an immunological defense mechanism elicited in response to microbial infections, mechanical injuries, allergens, burns, and another noxious stimulus.^{1,2} Inflammation is a complex process and involves inflammatory cells. Inflammation serves to destroy, reduce, or localize both agents that damage or damaged tissue. Inflammation can be triggered by various factors such as physical, chemical, or biological agents. The "molecular inflammatory" distinguishing molecular changes caused by inflammation itself.^{3,4} Tumor necrosis factor- α (TNF- α) is one of the cytokine that play important role in chronic and acute inflammations through triggers prostaglandins (PG) production, stimulating fever induction, and release the acute inflammation phase proteins such as C-reactive protein (CRP), gene expression of chemokines and cytokines and activating of endothelial cell, contributing in vascular changes for increasing blood flow on the site of the wound. TNF- α has another biological activity such as: integrate both innate and adaptive immunities. The cyclooxygenase (COX) enzymes catalyze the bis-oxygenation of free arachidonic acid to PGH₂ (the committed step in PG formation). COX-1 is thought to produce PGs which important in homeostasis and role in the inflammation process.⁵⁻⁷

A new compound of 1,3-bis(*p*-hydroxyphenyl) urea was designed and predicted to have less hepatotoxic activity. Synthesis of 1,3-bis(*p*-hydroxyphenyl) urea could be carried out by reaction between *p*-aminophenol and urea in acidic conditions. The synthetic reaction was given in Fig.-1. 1,3 bis(*p*-hydroxyphenyl)urea is *para*-aminophenol analogs that were more potent than paracetamol.^{8,9} This aimed of this study to assess the activity of 1,3-bis(*p*-hydroxyphenyl) urea in inhibition COX-1 and TNF- α expression with *In-silico* method.

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Fig.-1: Synthesis Reaction of 1,3-bis(*p*-hydroxyphenyl) urea

EXPERIMENTAL

Material and Methods

Aspire Vivobook operated by Windows 7 Home Basic, Intel® Core™ i5 (3.4 GHz), 64-bit, hard disc drive 320 GB and RAM 4 GB DDR3 L were used to run the molecular docking process. *In-silico* docking using Autodock Vina PyRx 9.5 program and visualized by Ligplot 2.1 and PyMol 2.3.1. The model of three dimensions of enzyme structure used in this research was cyclooxygenase-1 (COX-1) and tumor necrosis factor- α (TNF- α) binding pocket with the Protein Data Bank (PDB) code 1CQE and 2AZ5 which were obtained through from <http://www.rcsb.org/pdb>. The Marvin sketch program generates the three-dimension conformation models of control, 1,3-bis-(*p*-hydroxyphenyl)urea, diclofenac and dexamethasone.¹⁰

RESULTS AND DISCUSSION

In-silico Analysis

In-silico docking control, 1,3-bis-(*p*-hydroxyphenyl)urea, diclofenac and dexamethasone into the 1CQE and 2AZ5 binding pocket result in the docking score were showed in Table-1 and 2. Figure-1 is showing the results of visualization of control, 1,3-bis-(*p*-hydroxyphenyl)urea, diclofenac and dexamethasone to COX-1 and TNF- α using PyMol 2.3.1. and Figure 2 and 3 were showed interaction between control, 1,3-bis-(*p*-hydroxyphenyl)urea, diclofenac and dexamethasone towards amino acid residues of COX-1 and TNF- α using Ligplot 2.1.

Table-1: Binding Affinity of Ligand Standard and Compounds towards COX-1 (1CQE)

No.	Ligand	Binding Affinity (Kcal/mol)
1	Control	-8.4
2	1,3-bis-(<i>p</i> -hydroxyphenyl)urea	-10.6
3	Diclofenac	-7.4
4	Dexamethasone	-8.8

Table-2: Binding Affinity of Ligand Standard and Compounds towards TNF- α (2AZ5)

No.	Ligand	Binding Affinity (Kcal/mol)
1	Control	-9.2
2	1,3-bis-(<i>p</i> -hydroxyphenyl)urea	-9.6
3	Diclofenac	-7.1
4	Dexamethasone	-8.2

The docking score represents the binding affinity of the ligand to the target protein. The docking of COX-1 and TNF- α target with compounds using docking procedure revealed that all the computationally predicted lowest energy complexes of COX-1 and TNF- α are stabilized by intermolecular hydrogen bonds and stacking interactions. Docking score of 1,3-bis-(*p*-hydroxyphenyl)urea was lower than Diclofenac and Dexamethasone as anti-inflammatory drugs. The results were obtained at *In-silico* screening have shown that it represents the best step (way) to get an accurate result in a short time and saving manner.^{8,11-13}

Fig.-1: Three Dimension Binding of Compounds with the Protein Target

Fig.-2: Interaction of Compounds with Amino Acids of Protein Target (1CQE)

Fig.-3: Interaction of Compounds with Amino Acids of Protein Target (2AZ5)

Table-3: Interaction Ligands and Protein (1CQE) through Amino Acids and the Bond Type

Control	1,3-bis-(p-hydroxyphenyl)urea	Dexamethasone	Diclofenac	Bond Type
Asp135	Ser154	-	Asp135	Hydrophobic
Ser154	Ser143	Ser143	Ser154	Hydrophobic
Pro156	Val145	Val145	Pro156	Hydrophobic
Cys36	Trp139	-	Cys36	Hydrophobic
Gln461	Asp229	-	-	Hydrophobic
Pro153	Asp236	-	Pro153	Hydrophobic
Tyr39	Leu224	Leu224	-	Hydrophobic
Gly45	Gly225	Gly225	-	Hydrophobic
Ile46	Asn375	-	Ile46	Hydrophobic
-	Phe142	-	-	Hydrophobic
-	His226	His226	-	Hydrophobic
-	Asn375	-	-	Hydrophobic
-	Phe142	-	-	Hydrophobic
-	Arg374	Arg374	-	Hydrophobic
-	Val145	-	-	Hydrogen
Cys47	Arg374	Arg374	Cys47	Hydrogen
Cys41	Gly225	-	-	Hydrogen
-	-	Arg376	-	Hydrophobic
-	-	Asn375	-	Hydrogen

-	-		Val48	Hydrophobic
-	-		Arg49	Hydrogen

Table-4: Interaction Ligands and Protein (2AZ5) through Amino Acids and the Bond Type

Control	1,3-bis-(p-hydroxyphenyl)urea	Dexamethasone	Diclofenac	Bond Type
Ser60	Ser60	Ser60	Ser60	Hydrophobic
Tyr59	Tyr59	Tyr59	Tyr59	Hydrophobic
Leu120	Leu120	Leu120	-	Hydrophobic
Gly121	Gly121	Gly121	Gly121	Hydrophobic
Leu57	Leu57	-	-	Hydrophobic
Tyr151	Tyr151	-	-	Hydrophobic
Tyr119	Tyr119	Tyr119	Tyr119	Hydrophobic
Gln61	Gln61	Gln61	Gln61	Hydrophobic
Leu55	Leu55	-	-	Hydrophobic
-	Leu157	-	-	Hydrophobic
-	Ile58	-	-	Hydrophobic
-	Gly122	-	-	Hydrophobic
-	-	Tyr151	-	Hydrophobic
-	-	-	Tyr152	Hydrogen

CONCLUSION

Based on the research, it can be concluded that 1,3-bis-(p-hydroxyphenyl)urea has higher activity on binding to COX-1 (1CQE) and TNF- α (2AZ5) than control, dexamethasone and diclofenac. This compound is the potential to develop as an anti-inflammatory agent.

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