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Kholis Amalia Nofianti<sup>1</sup> / Juni Ekowati<sup>2</sup>

# *o*-Hydroxycinnamic derivatives as prospective anti-platelet candidates: *in silico* pharmacokinetic screening and evaluation of their binding sites on COX-1 and P2Y<sub>12</sub> receptors

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## Abstract:

**Background:** The high prevalence of thrombotic abnormalities has become a major concern in the health sector. This is triggered by uncontrolled platelet aggregation, which causes complications and death. The problem becomes more complicated because of the undesirable side effects of the drugs currently in use, some of which have reportedly become resistant. This study aims to evaluate the potency of *o*-hydroxycinnamic acid derivatives (OCA1a–22a) and their pharmacokinetic properties and toxicity for them to be developed as new antiplatelet candidates.

**Methods:** *In silico* analysis of pharmacokinetics was carried out using pKCSM. Molecular docking of the compounds OCA 1a–22a was performed using the Molegro Virtual Docker. *In silico* evaluation of the potency of biological activity was done by measuring the bonding energy of each tested compound to the target receptor i.e. COX-1 and P2Y<sub>12</sub>, as the Moldock score (MDS).

**Results:** pKCSM analyses showed that more than 90% of OCA 1a–22a are absorbed through the intestine and distributed in plasma. Most tested compounds are not hepatotoxic, and none is mutagenic. An evaluation of the COX-1 receptor showed that OCA 2a–22a have lower binding energy compared to aspirin, which is the COX-1 inhibitor used today. So, it can be predicted that OCA 2–22a have stronger activity. Interactions with P2Y<sub>12</sub> show lower MDS than aspirin, but slightly higher than ibuprofen, which is the standard ligand.

**Conclusions:** ADMET (absorption, distribution, metabolism, excretion, and toxicity) profile prediction shows that OCA 1a–22a have the potential to be developed as oral preparations. OCA 1a–22a have strong potential to interact with COX-1 and P2Y<sub>12</sub> receptors, so they are prospective anti-platelet candidates.

**Keywords:** anti-platelet, COX-1 inhibitor, Molegro Virtual Docker, P2Y<sub>12</sub> inhibitor, pKCSM

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## Introduction

Research data have shown that thrombotic disorders are a major health problem [1], [2]. This is because hematological imbalance will cause the formation of pathological thrombi in veins, arteries, and cardiac chambers, leading to complications and death [3], [4].

To date, anti-platelet agents such as aspirin and P2Y<sub>12</sub> inhibitors are still the main choice for the management of vaso-occlusive diseases [5], [6]. Unfortunately, during the last decades, the clinical utility of these drugs have become limited because of some undesirable side effects such as thrombocytopenia, neutropenia, thrombotic thrombocytopenic purpura, and aplastic anemia [7], [8]. Furthermore, in the last decades, these platelet-aggregating agents are reported to have become resistant [9], [10], [11]. Therefore, continuing research to discover new prospective anti-platelet agents is inevitable.

Platelets are one of the most important components in hemostasis, which have  $\delta$ -granules or dense bodies that contain platelet-activating factors such as adenosine diphosphate (ADP) [12]. The outside of the platelet is coated with receptors [13] including P2Y<sub>12</sub> [14]. During injury, platelets are activated, and secrete ADP from the dense granule. ADP then binds to P2Y<sub>12</sub> receptor, inhibits adenylate cyclase, and results in the amplification of

Juni Ekowati is the corresponding author.

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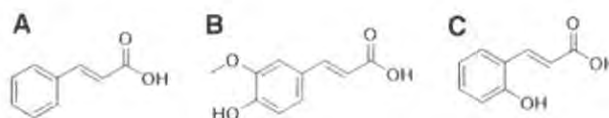


stable platelet aggregation [11], [15], [16], [17]. Therefore, in this study, the P2Y<sub>12</sub> receptor is one of the targets in designing anti-platelet compounds.

Another considerable protein in platelet aggregation is cyclooxygenase-1 (COX-1) [18]. This enzyme is expressed by most tissues and controls basal prostaglandin levels [18]. Ligands that attenuate prostaglandin biosynthesis will reduce the pro-inflammatory response, including platelet aggregation [19], [20]. Once platelets are activated, the phospholipid membrane releases free arachidonic acid, which then is metabolized to prostaglandin (PG) G<sub>2</sub> by the prostaglandin H synthase-1 enzyme, also referred as COX-1. PGG<sub>2</sub> is later converted to PGH<sub>2</sub> and thromboxane A<sub>2</sub> (TxA<sub>2</sub>) [21]. TxA<sub>2</sub> then binds TP receptors to activate the protein Gq and leads to a change in platelet shape, degranulation, and aggregation [22].

Both TxA<sub>2</sub> and P2Y<sub>12</sub> pathways have considerable pro-aggregatory effect on platelets. The use of COX-1 inhibitors, for example, will only negate the TxA<sub>2</sub> pathway but does not affect the P2Y<sub>12</sub> pathway [23]. For that reason, our research group intends to develop drug compounds that are able to inhibit both COX-1 and P2Y<sub>12</sub>.

The interest to develop cinnamic acid (Figure 1) derivatives as anti-platelet agents stemmed from the extensive research on the anti-inflammatory effect of *Kaempferia galangal* and its cinnamic content [24], [25], [26]. Our research group also found that a derivative of ferulic acid (Figure 1), namely 3-methoxy-2-hydroxycinnamic acid, showed the ability to bind P2Y<sub>12</sub> receptor in a molecular docking study [27]. In line with this, the methyl ester derivative of ferulic acid was proven to prolong the bleeding time and clot formation through *in vivo* tests conducted on mice [28]. Some derivatives of *p*-hydroxycinnamic acid also showed anti-platelet activity in mice in an animal model [29].



**Figure 1:** Chemical structure of (A) cinnamic acid, (B) ferulic acid, (C) *o*-hydroxycinnamic acid. A is the chemical structure of cinnamic acid which has aromatic groups, carboxylic acids and alkenes. B is the chemical structure of ferulic acid, a derivative of cinnamic acid with hydroxy and methoxy substituents in the benzene nucleus, which has interactions with P2Y<sub>12</sub> receptors [28]. C is the chemical structure of *o*-hydroxycinnamic acid, which is investigated in this research.

This study aims to examine the bonding of 22 derivatives of *o*-hydroxycinnamic acid (Figure 1) to both COX-1 and P2Y<sub>12</sub> receptors, by utilizing the Molegro Virtual Docker (MVD), to determine their prospective use as new anti-platelet candidates. This software will calculate the bond energy between each ligand and the target receptor, displayed as the MolDock score (MDS). Among all available methods, MVD was chosen because it has the highest accuracy [30], [31]. Furthermore, given the importance of the pharmacokinetic aspects in drug development [32], this study also aims to predict the physicochemical properties, pharmacokinetic profiles, and toxicity of these compounds by using the pKCSM web tool.

## Materials and methods

### Computer and software

We used an Intel(R) Core(TM) i7-4710MQ processor with CPU@2.50 GHz and RAM 8GB, with the software pKCSM and swissADME online tool. ChemDraw v. 15.0 of Perkin Elmer<sup>®</sup> was used along with MVD v. 5.5.

### ADMET analysis

The structures of all *o*-hydroxycinnamic acid derivatives were translated into SMILES structures using the swissADME web tool. After that, each structure of the SMILES was analyzed using the pKCSM web tool. Among the physicochemical parameters calculated in this study were the nature of lipophilicity including water solubility and log P, molecular weight, torque, and the ability of molecules to donate and receive hydrogen. The absorption parameters included intestinal and skin absorption as well as Caco-2 permeability. Volume of distribution, excretion, and toxicity parameters were analyzed in one run analysis.



## Molecular docking

### Receptors

Both receptors were obtained from the Protein Data Bank (<http://www.rcsb.org>). For P2Y<sub>12</sub> receptors, the selected protein with the code PDB 4PXZ is P2Y<sub>12</sub> with 6AD\_1201[A], (5-(6-amino-2-(methylthio)-9H-purine-9-yl)-3,4-dihydroxytetrahydro-furan-2-yl)-methyl diphosphate ligand complex [27]. COX-1 was downloaded from the Protein Data Bank (<http://www.rcsb.org/-pdb>) PDB ID:1EQG. Co-crystal of the reference ligand for the receptor was IBP\_701[A] [33].

### Method validation

To validate the docking process, reference ligands, namely 6AD\_1201[A] for P2Y<sub>12</sub> and IBP\_701[A] for COX-1, were re-docked to the appropriate binding site. The results were considered valid if the root-mean-square value (RMSD) was <2.0 Å [27].

### Ligand preparation

Twenty-two *o*-hydroxycinnamic acid (OCA) derivatives, aspirin, and ibuprofen were drawn using Chem Draw professional 15.0. The three-dimensional structures were obtained by copying the structure to Chem3D v. 15.0. The preferred conformation was based on the minimum energy calculated by MMFF94. These results were then stored in the form of Sybil mol2.

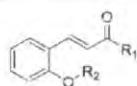
### Docking study

Docking studies were conducted on the crystal structure of the enzyme COX-1 (PDB ID 1CQE) and P2Y<sub>12</sub> receptor (PDB ID 4PXZ) with 2.90 Å resolution. The crystal structure of each complex 1CQE-IBP\_701[A] and 4PXZ-6AD\_1201[A] was downloaded to its active site and determined for its binding sites. The 3D molecular structure of the test compounds was imported into the binding site and placed in a cavity according to each native ligand. The docking study was performed in a suitable cavity of the SE algorithm using MolDock with a maximum of 1500 iterations. The result of this molecular docking study was expressed as the MolDock score (MDS), which represented the interaction energy between ligand and receptor. The best docking result must meet the requirements of the lowest energy and the position of the molecule that is in the same bond with the native ligand, observed visually. Enzyme-ligand interaction was observed through hydrogen-bonding, steric (van der Waals), and electrostatic interactions performed to pose with the lowest MDS [29].

## Results

Table 1 shows that the molecular weight of the 22 compounds ranges from 164.16 to 391.474. Log P value, which is a lipophilicity parameter, ranges from 1.4900 to 3.8705. A low bond rotation is calculated for OCA-1a, which is 2, while the highest one is for OCA-5a. The compounds with the least number of hydrogen donors are OCA-1a and OCA-15a, which is as small as 2, whereas the highest is OCA-22a, with 5. The most hydrogen-receiving candidate compound is OCA-22a, while OCA-17a does not have a hydrogen donor at all. The lowest water solubility is for OCA-1a and the highest is for OCA-21a.

**Table 1:** Prediction of physicochemical properties of *o*-hydroxycinnamic acid derivatives.
















Code	R1	R2	MW	Log P	Bond rotation	HBA	HBD	PSA	Water solubility
OCA-1a	OH	H	164.16	1.4900	2	2	2	69.587	-1.792
OCA-2a	OH		206.197	1.7097	3	3	1	86.797	-2.624
OCA-3a	OH		220.224	2.0998	4	3	1	93.162	-2.9
OCA-4a	OH		234.251	2.4899	5	3	1	99.527	-3.189
OCA-5a	OH		248.278	2.8800	6	3	1	105.892	-3.488
OCA-6a	OH		268.268	3.0036	4	3	1	115.489	-4.18
OCA-7a	OH		282.295	3.31202	4	3	1	121.854	-4.316
OCA-8a	OH		298.294	3.0122	5	4	1	126.968	-4.384
OCA-9a	OH		302.713	3.657	4	3	1	125.793	-4.715
OCA-10a	OCH <sub>3</sub>	H	178.187	1.5784	2	3	1	76.271	-1.835
OCA-11a	OC <sub>2</sub> H <sub>5</sub>	H	192.214	1.9685	3	3	1	82.636	-2.058
OCA-12a	OC <sub>3</sub> H <sub>7</sub>	H	206.241	2.3586	4	3	1	89.001	-2.426
OCA-13a	OC <sub>4</sub> H <sub>9</sub>	H	220.268	2.7487	5	3	1	95.366	-2.821
OCA-14a	OC <sub>5</sub> H <sub>11</sub>	H	234.295	3.1388	6	3	1	101.731	-3.236
OCA-15a	H	CH <sub>3</sub>	178.187	1.793	3	2	1	76.271	-2.958
OCA-17a	CH <sub>3</sub>	OCH <sub>3</sub>	192.214	1.8814	3	3	0	82.955	-2.863
OCA-18a		CH <sub>3</sub>	312.394	3.2216	4	3	2	134.357	-4.462
OCA-19a		CH <sub>3</sub>	326.421	3.53002	4	3	2	140.722	-4.775
OCA-20a		CH <sub>3</sub>	342.42	3.2302	5	4	2	145.836	-4.275
OCA-21a		CH <sub>3</sub>	346.839	3.8750	4	3	2	144.66	-5.139
OCA-22a		CH <sub>3</sub>	391.474	1.8690	5	5	3	156.458	-4.243

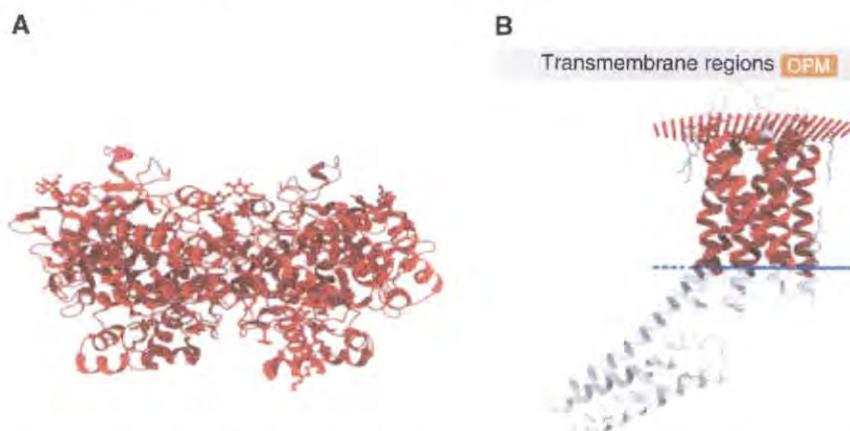
Table 2 shows the ADMET (absorption, distribution, metabolism, excretion, and toxicity) data of the test compounds, from which it can be seen clearly that there are no compounds that fall into the AMES toxicity category.



**Table 2:** ADMET properties of *o*-hydroxycinnamic acid derivatives.

Code	Absorption			Distribution			Metabolism		Excretion Total clearance	Toxicity		LD <sub>50</sub>
	Intestinal absorption	Skin per- meability	Caco-2 perme- ability	VD <sub>ss</sub> (human)	BBB per- meability	CNS per- meability	CYP2D6 substrate	CYP3A4 substrate		AMES toxicity	Hepatotoxicity	
OCA-1a	92.105	-2.499	1.164	-0.553	-0.237	-2.404	No	No	0.794	No	No	2.069
OCA-2a	97.15	-2.664	-0.270	-1.168	-0.135	-2.486	No	No	0.876	No	No	2.657
OCA-3a	97.247	-2.658	1.054	-1.116	-0.182	-2.497	No	No	0.903	No	No	2.675
OCA-4a	96.872	-2.654	0.998	-1.065	-0.230	-2.502	No	No	0.920	No	No	2.683
OCA-5a	96.038	-2.653	0.960	-1.020	-0.258	-2.505	No	No	0.937	No	No	2.687
OCA-6a	94.55	-2.641	1.034	-0.918	-0.300	-2.25	No	Yes	0.849	No	No	2.37
OCA-7a	95.38	-2.577	1.002	-1.581	-0.126	-2.138	No	No	0.794	No	No	2.622
OCA-8a	95.854	-2.471	1.315	-1.694	-0.489	-2.413	No	No	0.769	No	No	2.688
OCA-9a	93.321	-2.639	1.049	-0.857	-0.33	-2.144	No	Yes	-0.087	No	No	2.591
OCA-10a	95.671	-2.701	1.209	-0.105	-0.026	-1.797	No	No	0.807	No	No	1.955
OCA-11a	95.252	-2.771	1.230	-0.033	-0.041	-1.896	No	No	0.836	No	No	2.028
OCA-12a	94.853	-2.848	1.256	0.031	-0.089	-1.841	No	No	0.847	No	No	2.017
OCA-13a	94.233	-2.908	1.279	0.091	-0.104	-1.777	No	No	0.864	No	No	1.991
OCA-14a	93.386	-2.942	1.302	0.145	-0.116	-1.695	No	No	0.882	No	No	1.975
OCA-15a	95.089	-2.283	1.247	-1.231	0.091	-2.085	No	No	0.845	No	No	2.248
OCA-17a	98.951	-2.481	1.046	-0.104	0.049	-2.017	No	No	0.898	No	No	1.995
OCA-18a	89.633	-2.817	1.397	-0.168	0.127	-2.014	No	Yes	-0.138	No	No	2.185
OCA-19a	90.169	-2.858	1.393	-0.087	0.096	-1.947	No	Yes	-0.196	No	Yes	2.262
OCA-20a	92.670	-2.915	1.347	-0.083	0.034	-2.215	No	Yes	-0.096	No	Yes	2.335
OCA-21a	88.711	-2.855	1.420	-0.139	0.083	-1.907	No	Yes	-0.270	No	No	2.33
OCA-22a	73.901	-3.053	0.193	-0.510	-0.838	-2.672	No	Yes	-0.388	No	Yes	1.913

Figure 2 shows A: COX-1 co-crystal (PDB ID: 1EQG) ligand reference: IBP\_701A. Docking study was performed in cavity 4 Vol 61.44. B: P2Y<sub>12</sub> co-crystal (PDB ID: 4PXZ) ligand reference: 6AD-1201. Docking study was conducted in cavity 2 Vol 74.52.



**Figure 2:** (A) COX-1 receptor with PDB ID: 1EQG [33]. (B) P2Y<sub>12</sub> receptor with PDB: ID 4PXZ [27]. A is a co-crystal structure of COX-1 enzymes and B is a co-crystal structure of P2Y<sub>12</sub> receptor with their reference ligand respectively, by which the binding site of the reference ligand and protein will be occupied by the test compounds.

Table A and Table B summarize the results of the docking study of all compounds OCA-1a–22a, aspirin, and ibuprofen against COX-1 enzyme. All binding energies are lower than that of aspirin, except OCA-1a.

**Table A:** Results of the docking of the test ligand (OCA-1a–12a) at the binding site of COX-1 receptor.

Ligand	OCA											
	1a	2a	3a	4a	5a	6a	7a	8a	9a	10a	11a	12a
MDS	-95.893	-115.21	-116.11	-118.75	-119.58	-130.54	-132.37	-138.727	-136.41	-102.26	-109.46	-114.51
kCal/-mol												
H-bond	-3.7307	-2.5	-0.8395	-4.3413	-2.5429	-1.9859	-1.9859	-2.5	-2.5	-2.5348	-2.5	-1.9472
kCal/-mol												
Amino acid residue	199-Ala	199-Ala	199-Ala	199-Ala	199-Ala	-	199-Ala	199-Ala	199-Ala	199-Ala	199-Ala	199-Ala
	202-Ala	200-Phe	202-Ala	202-Ala	202-Ala	202-Ala	202-Ala	202-Ala	202-Ala	202-Ala	202-Ala	202-Ala
	203-Gln	202-Ala	203-Gln	203-Gln	203-Gln	203-Gln	203-Gln	203-Gln	203-Gln	203-Gln	203-Gln	203-Gln
	206-Thr	203-Gln	206-Thr	206-Thr	206-Thr	206-Thr	206-Thr	206-Thr	206-Thr	206-Thr	206-Thr	206-Thr
	207-His	206-Thr	207-His	207-His	207-His	207-His	207-His		207-His	-	-	207-His
	210-Phe	210-Phe	210-Phe	210-Phe	210-Phe	210-Phe	210-Phe	210-Phe	210-Phe	210-Phe	210-Phe	210-Phe
	-	-	-	-	-	-	-	212-Thr	212-Thr	-	-	-
	-	348-Tyr	348-Tyr	348-Tyr	-	-	-	-	-	-	-	-
	382-Asn	-	382-Asn	382-Asn	382-Asn	-	382-Asn	382-Asn	382-Asn	382-Asn	382-Asn	382-Asn
	385-Tyr	385-Tyr	385-Tyr	385-Tyr	385-Tyr	385-Tyr	385-Tyr	385-Tyr	385-Tyr	385-Tyr	385-Tyr	385-Tyr
	386-His	386-His	386-His	386-His	386-His	386-His	386-His	386-His	386-His	386-His	386-His	386-His
	387-Trp	387-Trp	387-Trp	387-Trp	387-Trp	387-Trp	387-Trp	387-Trp	387-Trp	387-Trp	387-Trp	387-Trp
	388-His	388-His	388-His	388-His	390-Leu	388-His	388-His	388-His	388-His	388-His	388-His	388-His



390- Leu	390- Leu	390- Leu	390- Leu	391- Met	390- Leu	390- Leu	390- Leu	390- Leu	390- Leu	-	-	-
-	391- Met	391- Met	-	-	391- Met	391- Met	391- Met	-	-	-	-	391- Met

**Table B:** Results of the docking of the test ligand (OCA-13a–22a, ibuprofen, and aspirin) at the binding site of COX-1 receptor.

Ligand	OCA										Ibuprofen	Aspirin
	13a	14a	15a	17a	18a	19a	20a	21a	22a			
MDS kCal/ mol	-118.773	-121.945	-99.5915	-110.611	-137.417	-136.754	-137.127	-144.911	-117.789	-93.9403	-113.392	
H- bond kCal/ mol	-2.5	-2.21449	-0.371838	-0.161469	-1.08633	-5	-3.2979	-0.806575	-2.07898	-2.95147	-2.5	
	-	-	-	-	-	-	-	-	-	113- Met	-	
	-	-	-	-	-	-	-	116- Val	-	116- Val	-	
	-	-	-	-	-	-	-	117- Leu	-	117- Leu	-	
	-	-	-	-	-	-	-	120- Arg	-	-	-	
	-	-	-	-	-	-	-	-	-	129- Arg	-	
	-	-	-	-	-	-	-	-	148- Tyr	-	-	
	-	-	-	-	-	-	-	-	198- Phe	-	-	
Amino acid residue	199- Ala	199- Ala	199- Ala	199- Ala	199- Ala	199- Ala	199- Ala	-	199- Ala	-	199- Ala	
	-	-	-	-	-	-	-	-	200- Phe	-	-	
	202- Ala	202- Ala	202- Ala	202- Ala	202- Ala	-	202- Ala	-	202- Ala	-	202- Ala	
	-	203- Gln	-	203- Gln	203- Gln	203- Gln	203- Gln	-	203- Gln	-	203- Gln	
	206- Thr	206- Thr	206- Thr	206- Thr	206- Thr	206- Thr	206- Thr	-	206- Thr	-	206- Thr	
	207- His	-	207- His	207- His	207- His	207- His	-	-	207- His	-	207- His	
	210- Phe	210- Phe	210- Phe	210- Phe	210- Phe	210- Phe	210- Phe	-	210- Phe	-	210- Phe	
	-	-	211- Lys	-	-	-	211- Lys	-	211- Lys	-	-	
	212- Thr	212- Thr	-	-	-	212- Thr	212- Thr	-	212- Thr	-	-	
	-	-	-	-	-	-	-	-	-	345-Ile	-	
	-	-	-	-	348- Tyr	348- Tyr	-	348- Tyr	-	-	-	
	-	-	-	-	-	-	-	349- Val	-	349- Val	-	
	-	-	-	-	-	-	-	352- Leu	-	352- Leu	-	
	-	-	-	-	-	-	-	353- Ser	-	353- Ser	-	
	-	-	-	-	-	-	-	355- Tyr	-	355- Tyr	-	
	-	-	-	-	-	-	-	359- Leu	-	359- Leu	-	

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-	-	-	-	-	381- Phe	-	381- Phe	381- Phe	381- Phe	-	-
382- Asn	-	382- Asn	-	382- Asn	382- Asn	382- Asn	-	382- Asn	-	-	-
-	-	-	-	-	383- Gln	-	-	-	-	-	385- Tyr
-	-	-	-	-	-	-	384- Leu	-	384- Leu	-	386- His
385- Tyr	385- Tyr	385- Tyr	385- Tyr	385- Tyr	385- Tyr	385- Tyr	385- Tyr	385- Tyr	385- Tyr	385- Tyr	387- Trp
386- His	386- His	386- His	386- His	386- His	386- His	386- His	-	386- His	-	-	388- His
387- Trp	387- Trp	387- Trp	387- Trp	387- Trp	387- Trp	387- Trp	387- Trp	387- Trp	387- Trp	387- Trp	390- Leu
388- His	388- His	388- His	388- His	388- His	388- His	388- His	-	388- His	-	-	391- Met
390- Leu	390- Leu	-	390- Leu	390- Leu	390- Leu	-	390- Leu	-	390- Leu	-	-
-	-	391- Met	391- Met	391- Met	391- Met	-	-	391- Met	-	-	-
-	-	-	-	-	444-Ile	-	-	444-Ile	-	-	-
-	-	-	-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	518- Phe	-	518- Phe	-	-
-	-	-	-	-	-	-	522- Met	-	-	-	-
-	-	-	-	-	-	-	523-Ile	-	523-Ile	-	-
-	-	-	-	-	-	-	526- Gly	-	526- Gly	-	-
-	-	-	-	-	-	-	527- Ala	-	527- Ala	-	-
-	-	-	-	-	-	-	530- Ser	-	530- Ser	-	-
-	-	-	-	-	-	-	531- Leu	-	531- Leu	-	-
-	-	-	-	-	-	-	-	-	552- Met	-	-
-	-	-	-	-	-	-	-	-	552- Met	-	-

Table C and Table D show the results of docking studies on P2Y<sub>12</sub> receptors. OCA-1A-22A are lower than aspirin but higher than ibuprofen.

**Table C:** Results of the docking of the test ligand (OCA-1a-12a) at the binding site of P2Y<sub>12</sub> receptor.

Ligand	OCA											
	1a	2a	3a	4a	5a	6a	7a	8a	9a	10a	11a	12a
MDS kCal/- mol	-88.092	-109.277	-114.255	-115.816	-121.981	-138.376	-141.739	-134.862	-143.635	-90.055	-99.3538	-101.611
H- bond kCal/- mol	-5	-4.45498	-3.85612	-3.001340		-4.13639	-4.49929	-3.10572	-2.65512	-4.22953	-5.84453	-2.5
Amino acid residue	-	-	-	-	97- Cys	97- Cys	-	-	97- Cys	-	-	-
	-	-	-	101- Ser	101- Ser	101- Ser	101- Ser	101- Ser	-	-	-	-
	102- Val	102- Val	-	102- Val	102- Val	-	102- Val	102- Val	102- Val	102- Val	102- Val	102- Val
	105- Tyr	105- Tyr	105- Tyr	105- Tyr	105- Tyr	105- Tyr	-	105- Tyr	105- Tyr	105- Tyr	105- Tyr	105- Tyr
	106- Phe	106- Phe	106- Phe	106- Phe	106- Phe	-	106- Phe	106- Phe	106- Phe	-	106- Phe	106- Phe

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109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	152-Met	109-Tyr	109-Tyr	109-Tyr
152-Met	152-Met	152-Met	152-Met	152-Met	-	-	-	-	-	-	-	152-Met
155-Leu	155-Leu	-	-	155-Leu	155-Leu	155-Leu	155-Leu	155-Leu	155-Leu	155-Leu	155-Leu	155-Leu
156-Ser	156-Ser	156-Ser	156-Ser	156-Ser	156-Ser	159-Asn	159-Asn	159-Asn	159-Asn	156-Ser	156-Ser	156-Ser
159-Asn	159-Asn	159-Asn	159-Asn	159-Asn	-	-	-	-	-	159-Asn	159-Asn	159-Asn
-	-	-	-	175-Cys	175-Cys	175-Cys	175-Cys	175-Cys	175-Cys	-	-	-
-	-	179-Lys	-	179-Lys	179-Lys	-	-	-	179-Lys	-	179-Lys	-
-	-	-	186-Trp	-	-	-	-	-	-	-	-	-
-	-	187-His	187-His	187-His	187-His	187-His	187-His	187-His	187-His	187-His	187-His	-
190-Val	190-Val	-	190-Val	190-Val	190-Val	190-Val	190-Val	190-Val	-	190-Val	190-Val	190-Val
191-Asn	191-Asn	191-Asn	191-Asn	191-Asn	191-Asn	191-Asn	191-Asn	191-Asn	191-Asn	191-Asn	191-Asn	191-Asn
194-Cys	194-Cys	-	194-Cys	194-Cys	194-Cys	194-Cys	194-Cys	194-Cys	194-Cys	194-Cys	194-Cys	194-Cys
-	-	-	-	-	-	-	-	-	-	-	-	195-Gln
252-Phe	252-Phe	252-Phe	252-Phe	252-Phe	252-Phe	252-Phe	252-Phe	252-Phe	252-Phe	-	-	252-Phe
-	-	-	-	-	-	-	-	-	-	-	-	253-His
256-Arg	256-Arg	256-Arg	256-Arg	256-Arg	256-Arg	256-Arg	256-Arg	256-Arg	256-Arg	256-Arg	256-Arg	256-Arg

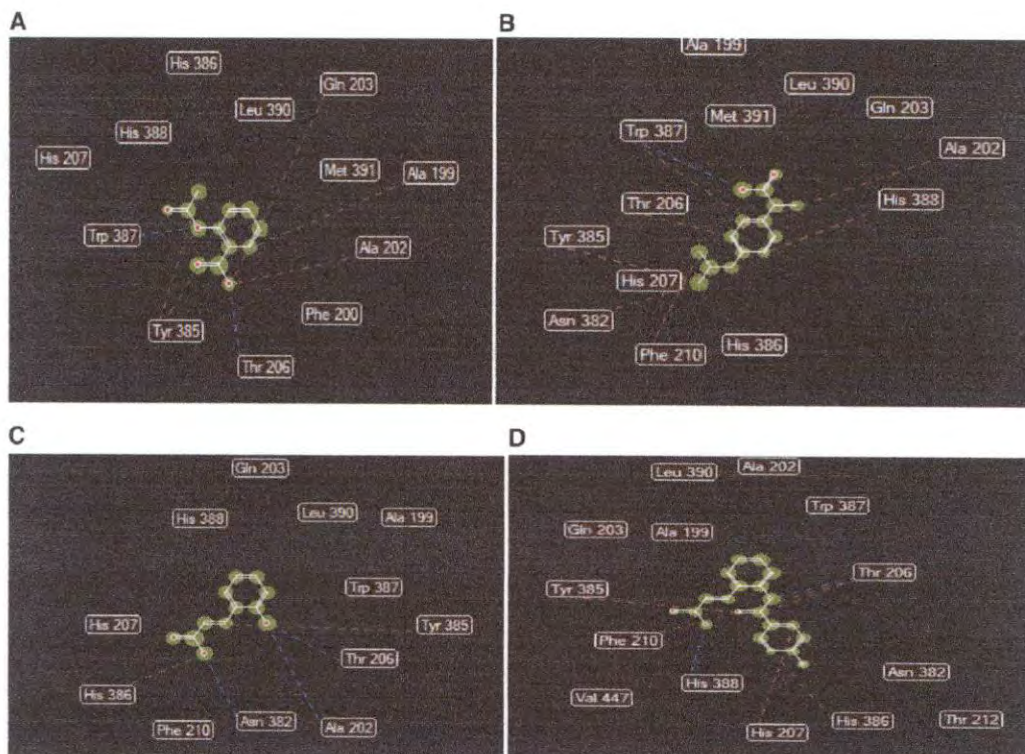
**Table D:** Results of the docking of the test ligand (OCA-13a–22a, ibuprofen, and aspirin) at the binding site of P2Y<sub>12</sub> receptor.

Ligand	OCA										Ibuprofen	Aspirin
	13a	14a	15a	17a	18a	19a	20a	21a	22a			
MDS	-104.067	-107.711	-90.295	-94.6112	-94.9611	-132.141	-138.165	-144.937	-136.335	-147.891	-84.6987	
kCal/-mol												
H bond	-3.34754	-4.83363	-2.83019	-3.18851	-0.59485	-2.20782	-2.11142	-2.39911	-3.21049	-3.14894	-2.5	
kCal/-mol												
Amino acid residue	-	-	-	-	-	-	93-Arg	-	-	-	-	-
	-	-	-	-	-	-	-	-	-	96-Val	-	-
	-	-	-	-	-	97-Cys	97-Cys	97-Cys	97-Cys	-	97-Cys	-
101-Ser	101-Ser	-	-	-	-	-	-	101-Ser	101-Ser	101-Ser	101-Ser	101-Ser
102-Val	102-Val	102-Val	102-Val	102-Val	102-Val	102-Val	102-Val	102-Val	102-Val	102-Val	-	-
105-Tyr	105-Tyr	-	105-Tyr	105-Tyr	105-Tyr	105-Tyr	105-Tyr	105-Tyr	105-Tyr	105-Tyr	105-Tyr	105-Tyr
106-Phe	106-Phe	106-Phe	106-Phe	106-Phe	106-Phe	106-Phe	106-Phe	106-Phe	106-Phe	106-Phe	106-Phe	106-Phe
109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr	109-Tyr
152-Met	152-Met	-	152-Met	-	152-Met	-	-	152-Met	152-Met	-	-	152-Met
-	-	-	-	-	-	-	-	-	-	153-Phe	-	-

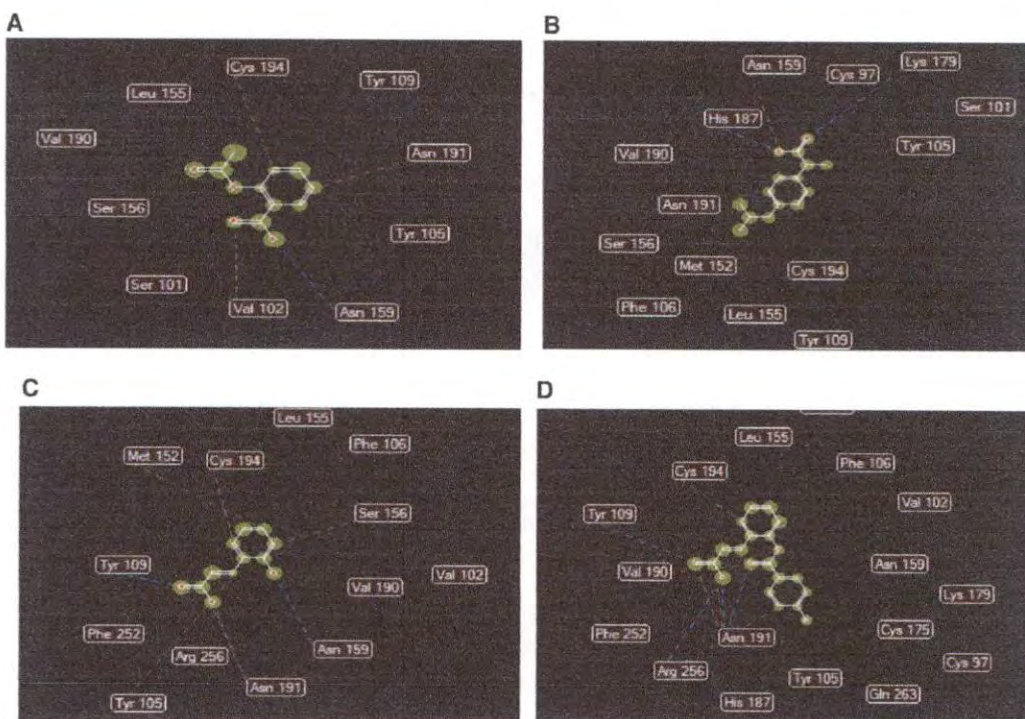
155- Leu	-	-	155- Leu	155- Leu	155- Leu	155- Leu	155- Leu	155- Leu	155- Leu	155- Leu
156- Ser	156- Ser	156- Ser	156- Ser	156- Ser	156- Ser	159- Asn	156- Ser	156- Ser	156- Ser	156- Ser
159- Asn	159- Asn	159- Asn	159- Asn	159- Asn	159- Asn	-	159- Asn	159- Asn	159- Asn	159- Asn
-	-	-	-	-	163- Thr	-	-	-	-	-
175- Cys	-	-	-	-	-	-	175- Cys	-	175- Cys	-
-	-	-	-	-	-	-	176- Ser	-	-	-
179- Lys	179- Lys	-	-	-	179- Lys	179- Lys	179- Lys	179- Lys	179- Lys	179- Lys
187- His	-	187- His	-	-	187- His	187- His	187- His	187- His	187- His	187- His
190- Val	190- Val	190- Val	190- Val	-	190- Val	190- Val	190- Val	190- Val	190- Val	190- Val
191- Asn	191- Asn	191- Asn	191- Asn	191- Asn	191- Asn	191- Asn	191- Asn	191- Asn	191- Asn	191- Asn
194- Cys	194- Cys	194- Cys	194- Cys	194- Cys	194- Cys	-	194- Cys	-	194- Cys	194- Cys
-	-	-	-	195- Gln	-	-	-	-	-	-
-	-	252- Phe	252- Phe	252- Phe	-	-	-	-	-	-
-	-	-	-	253- His	-	-	-	-	-	-
256- Arg	256- Arg	256- Arg	256- Arg	256- Arg	256- Arg	256- Arg	256- Arg	256- Arg	256- Arg	-
-	-	-	-	-	-	-	259- Tyr	263- Gln	259- Tyr	-
-	-	-	-	-	263- Gln	263- Gln	263- Gln	-	263- Gln	-
-	-	-	-	-	-	-	-	277- Phe	-	-
-	-	-	-	-	280- Lys	280- Lys	280- Lys	280- Lys	280- Lys	-
-	-	-	-	-	-	-	-	-	281- Glu	-

Figure 3 shows the interaction between ligands and amino acids at COX-1 receptors. It can be observed that aspirin (A) and OCA-1a (C) have similar amino acid residues. The addition of aromatic constituents to OCA-9a (D) adds to the amino acid bond. In contrast to interactions with COX-1, in Figure 4, the P2Y<sub>12</sub> receptor amino acid residues that interact with *o*-hydroxycinnamic derivatives differ from those of aspirin.





**Figure 3:** Map of the interaction between *o*-hydroxycinnamic acid derivatives and COX-1 receptor: (A) aspirin, (B) ibuprofen, (C) OCA-1a, (D) OCA-9a. Examples of interactions between functional groups of the test compounds with amino acid residues of the COX-1 enzyme, the blue line shows the hydrogen bonding interaction, and the red line shows the hydrophobic interaction.



**Figure 4:** Map of interaction between *o*-hydroxycinnamic acid derivatives and COX-1 receptor: (A) aspirin, (B) ibuprofen, (C) OCA-1a, (D) OCA-9a. Examples of interactions between functional groups of the test compounds with amino acid residues of the P2Y<sub>12</sub> receptor, the blue line shows the hydrogen bonding interaction, and the red line shows the hydrophobic interaction.



## Discussion

The failure of a drug candidate in clinical trial is commonly due to its poor ADMET profile [34], [35]. The success and efficacy of a drug compound are determined by its pharmacokinetic properties. Anti-platelets for the prevention of coronary heart disease recurrence are generally given orally [36] for the comfort and convenience of patients [37]. Consequently, the design of the drug compound must be such that it is well absorbed in the digestive tract.

Based on an in-depth evaluation of the molecular properties with the results of Phase II clinical trials, Lipinski et al. formulated five physical and chemical characteristics of drugs that can predict the absorption and permeability of drug candidates, known as the Lipinski rule of 5. Excluding the possibility of whether a drug compound can bind peptides in the intestinal membrane depends on the following criteria: molecular weight less than 500, log P not greater than 5, number of hydrogen bond donors (HBD) less than 5, and number of hydrogen bond acceptors (HBA) more than 10 [38], [39].

The results in Table 1 show that all compounds OCA1–22 meet the Lipinski rule. OCA-22 has the largest MW, HBA, and HBD, but they are still below 500, 10, and 5, respectively. Navia and Chaturvedi found that the molecular size of a drug is inversely proportional to its absorption ability [40]. Molecules with excessive HBD impair phospholipid membranes [41], while those with HBAs exceeding 10 will hinder absorption [37].

Table 2 shows the ADMET data of all the tested compounds. The compounds OCA1a–22a have good intestinal absorption, which is in line with the physicochemical properties of the tested compounds that meet the Lipinski rule. All this indicates that all the test compounds are suitable for oral administration. A compound is considered to have a high Caco-2 permeability if it has  $P_{app} > 8 \times 10^6$  cm/s. In the case of the pkCSM predictive model, high Caco-2 permeability translates into predicted log  $P_{app}$  values  $> 0.90$  cm/s [42].

Table 2 shows that only OCA-2a and OCA 22-a have Caco-2 permeability values below 0.9, which means that the majority of tested compounds have very high permeability [44]. However, some experts believe that Caco-2 permeability applies only to drugs that are absorbed through passive diffusion. For drugs with active transport, it might give different results [44].

The skin permeability value was calculated from the logarithmic penetrating ability of 211 molecules to human skin *in vitro*. The result is considered low if log  $K_p$  exceeds  $-2.5$  [43]. In Table 2, most of the test compounds have values lower than  $-2.5$ , which shows that these compounds have the potential to be developed as transdermal drugs.

The volume of distribution ( $V_d$ ) illustrates how much blood plasma is needed so that drug compounds have the same levels. The higher the  $V_d$  value, the more the volume of the compound in the tissue. In pkCSM,  $V_d$  is considered low if log L/kg is below  $-0.15$ . Table 2 shows that most of the test compounds have values below  $-0.15$ . This means that there is less drug in the tissues and more in the blood, which is what is expected for drug compounds that target platelets [42].

Toxicity data show that most of the test compounds do not cause hepatotoxicity. AMES toxicity predicts whether the test compound is carcinogenic, and our results indicate that none of the test compounds is predicted to cause genetic mutations [42]. LD50 estimates the threshold for chemicals to cause toxicity in humans. The result is considered low if it is less than or equal to 0.477 [43]. Table 2 shows that the LD50 values of all the test compounds are above 0.477, meaning that the values are high, so they are safe for use in humans.

Consistent with the good pharmacokinetic properties, the interaction of the test compounds with COX-1 and P2Y<sub>12</sub> receptors also gives promising results. MVD optimizes the pose of each ligand structure using an algorithm [45]. This software can also identify the binding sites, called cavity or active sites, which are pockets where the ligands are predicted to bind to the receptors. P2Y<sub>12</sub> and COX-1 receptors in this study were found to be in cavity 4 and cavity 2, respectively. The cavities were chosen because the native ligands were inside.

All ligands OCA1a–22a and the standard ligands ibuprofen and aspirin which were prepared were docked on the selected cavity. The MVD program uses a score to estimate the binding energy in a ligand-protein complex. To improve docking accuracy, an MDS is given, which can identify the most promising docking solution from the docking algorithm [31], [45]. The results of the *in silico* tests are in the form of bond energy values or MDS. MDS is a differential evolution algorithm in the Molegro Virtual Docker program. MDS or  $E_{score}$  is the sum of  $E_{inter}$  (the ligand-receptor interaction energy) and  $E_{intra}$  (the ligand internal energy) [46], [47]. The energy needed by ligands to bind to receptors is called the bonding energy. The smaller the energy, the more stable the bonds, so it can be estimated that the activity will be stronger [27].

Table A shows that the MDS of the test compounds are lower than that of aspirin, both on the COX-1 receptor and P2Y<sub>12</sub>. The MDS difference between OCA-1a and aspirin on COX-1 is 18 kCal/mol, whereas in P2Y<sub>12</sub> the receptor it is 5 kCal/mol. Among them, the compounds OCA-6a, 7a, 8a, and 9a, 18a, 19a, 20a, and 21 show promising results because the MDS is very low in both receptors.

Based on the data in Table A and Table B, it is seen that the interaction of the test compounds, i.e. *o*-hydroxycinnamic acid derivatives, against COX-1 is with the amino acids 199-Ala, 202-Ala, 203-Gln, 206-Thr,



207-His, 210-Phe, 382-Asn, 385-Tyr, 386-His, 387-Trp, 388-His, and 390-Leu. This is similar to aspirin except that there is an additional 391-Met. Likewise, the interaction with P2Y<sub>12</sub> involves 101-Ser, 102-Val, 105-Tyr, 109-Tyr, 155-Leu, 156-Ser, 159-Asn, 190-Val, 191-Asn, and 194-Cys, the same as for aspirin. The tested compounds also have additional interactions with 106-Phe and 256-Arg.

## Conclusions

pKCSM analysis showed that all compounds OCA-1a–22a have good absorption profiles and can be used as oral preparations. Their distribution and toxicity are also good enough for them to be developed as anti-platelet agents. Docking analysis showed that the interaction of amino acids that bind to Cox-1 and P2Y<sub>12</sub> receptors is not much different from that of aspirin. However, MDS for derivatives with aromatic substituents in OCA-6a, 7a, 8a, 9a, OCA-18a, 19a, 20a, and 21a have very low interaction energy compared to aspirin and ibuprofen, both on COX-1 and P2Y<sub>12</sub>. Therefore, it can be predicted that these seven compounds have strong potential to inhibit both receptors.

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**Author contributions:** All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Competing interests:** Authors state no conflict of interest.

## References

- [1] Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis* 2016;41:3–14.
- [2] Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. *Circ Res* 2016;118:1340–47.
- [3] MSD manual professional version. Available at: <https://www.msdmanuals.com/professional/hematology-and-oncology/thrombotic-disorders/overview-of-thrombotic-disorders>. Accessed: 31 Oct 2019.
- [4] Gomar FS, Quilis CP, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. *Ann Transl Med* 2016;4:256–68.
- [5] Mackman N, Spronk HM, Stouffer GA, Cate H. Dual anticoagulant and antiplatelet therapy for coronary artery disease and peripheral artery disease patients. *Arterioscler Thromb Vasc Biol* 2018;38:726–32.
- [6] Koski R, Kennedy B. Comparative review of oral P2Y<sub>12</sub> inhibitors. *P T* 2018;43:352–7.
- [7] Youssef KM, Abou-zeid LA, Haress NG, Al-Omar MA, Abdel-Gader AM, Al-Tuwaijri AS, et al. Synthesis, antiplatelet aggregation activity, and molecular modeling study of novel substituted-piperazine analogues. *Med Chem Res* 2011;20:898–911.
- [8] Floyd CN, Ferro A. Antiplatelet drug resistance: molecular insights and clinical implications. *Prostaglandins Other Lipid Mediat* 2015;120:21–7.
- [9] Angiolillo DJ. International expert consensus on switching platelet P2Y<sub>12</sub> receptor-inhibiting therapies. *Circulation* 2017;136:1955–75.
- [10] Hankey GJ, Eikelboom JW. Aspirin resistance. *Lancet* 2006;367:606–17.
- [11] Armstrong PC, Truss NJ, Ali FY, Dhanji AA, Vojnovic I, Zain ZN, et al. Aspirin and the in vitro linear relationship between thromboxane A<sub>2</sub>-mediated platelet aggregation and platelet production of thromboxane A<sub>2</sub>. *J Thromb Haemost* 2008;6:1933–43.
- [12] Trabold K, Makhoul S, Gambaryan S, van Ryn J, Walter U, Jurk K. The direct thrombin inhibitors dabigatran and lepirudin inhibit GPIIb/α-mediated platelet aggregation. *Thromb Haemost* 2019;119:619–26.
- [13] Saad J, Schoenberger L. Physiology, platelet activation [updated 2019 May 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2019 Jan. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK482478/>. Accessed 23 Oct 2019.
- [14] Caldwell AT, Watkins EB. Recent advances in the development of P2Y<sub>12</sub> receptor antagonists as anti platelet agents. *Ann Rep Med Chem* 2014;49:87–99.
- [15] Broos K, Feys HB, De Meyer SF, Vanhoorelbeke K, Deckmyn H. Platelets at work in primary hemostasis. *Blood Rev* 2011;25:155–67.
- [16] Cattaneo M. New P2Y<sub>12</sub> inhibitors. *Circulation* 2010;121:171–9.
- [17] Cattaneo M. P2Y<sub>12</sub> receptors: structure and function. *J Thromb Haemost* 2015;13:510–6.
- [18] Ornelas A, Zacharias-Millward N, Menter DG, Davis JS, Lichtenberger L, Hawke D, et al. Beyond COX-1: the effects of aspirin on platelet biology and potential mechanisms of chemoprevention. *Cancer Metastasis Rev* 2017;36:289–303.
- [19] Schafer A, Bauersachs J. Endothelial dysfunction, impaired endogenous platelet inhibition and platelet activation in diabetes and atherosclerosis. *Curr Vasc Pharmacol* 2008;6:52–60.
- [20] Ruggeri ZM. Platelet adhesion under flow. *Microcirculation* 2009;16:58–63.
- [21] Kalantzi KI, Tsoumani ME, Goudevenos IA, Tselepis AD. Pharmacodynamic properties of antiplatelet agents. *Expert Rev Clin Pharmacol* 2012;5:319–36.
- [22] Rucker D, Dharmoon AS. Physiology, thromboxane A<sub>2</sub> [updated 2019 Mar 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2019 Jan. Accessed on 31 October 2019. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK539817/>.

- [23] Warner TD, Nylander S, Whatling C. Anti-platelet therapy: cyclooxygenase inhibition and the use of aspirin with particular regard to dual anti-platelet therapy. *Br J Clin Pharmacol* 2011;72:619–33.
- [24] Ridditid W, Sae-Wong C, Reanmongkol W, Wongnawa M. Antinociceptive activity of the methanolic extract of *Kaempferia galanga* Linn. in experimental animals. *J Ethnopharmacol* 2008;118:225–30.
- [25] Jagadish PC, Latha KP, Mudgal J, Nampurath CK. Extraction, characterization and evaluation of *Kaempferia galanga* L. (Zingiberaceae) rhizome extracts against acute and chronic inflammation in rats. *J Ethnopharmacol* 2016;194:434–9.
- [26] Umar MI, Asmawi MZ, Sadikun A, Atangwho IJ, Yam MF, Altaf R, et al. Bioactivity-guided isolation of ethyl-p-ethoxycinnamate, an anti-inflammatory constituent, from *Kaempferia galanga* L. extracts. *Molecules* 2012;17:8720–34.
- [27] Ekowati J, Diyah NW, Nofianti KA, Hamid IS, Siswandono S. Molecular docking of ferulic acid derivatives on P2Y<sub>12</sub> receptor and their ADMET prediction. *J Math Fund Sci* 2018;50:203–19.
- [28] Ekowati J, Pratama RP, Nofianti KA, Diyah NW. The temperature effect on ultrasonic-assisted of synthesis methyl ferulate and its antiplatelet assay. *ALCHEMY J Penelitian Kim* 2019;15:272–86.
- [29] Ghabbour H, El-Bendary E, El-Ashmawy M, El-Kerdawy M. Synthesis, Docking Study and  $\beta$ -Adrenoceptor Activity of Some New Oxime Ether Derivatives. *Molecules*. 2014;19(3):3417–3435. DOI: 10.3390/molecules19033417.
- [30] Kusumaningrum S, Budiarto E, Kosela S, Sumaryono W, Juniarti F. The molecular docking of 1,4-naphthoquinone derivatives as inhibitors of Polo-like kinase 1 using Molegro Virtual Docker. *J Appl Pharm Sci* 2014;4:047–53.
- [31] Thomsen R, Christensen MH. Moldock: a new technique for high-accuracy molecular docking. *J Med Chem* 2006;49:3315–21.
- [32] Toomula N, Sathish KD, Kumar A, Phaneendra M. Role of pharmacokinetic studies in drug discovery. *J Bioequivalence Bioavailab* 2011;3:263–7.
- [33] Selinsky BS, Gupta K, Sharkey CT, Loll PJ. Structural analysis of NSAID binding by prostaglandin H<sub>2</sub> synthase: time-dependent and time-independent inhibitors elicit identical enzyme conformations. *Biochemistry* 2001;40:5172–80.
- [34] Megala B, Shoba K. Lung cancer : a better rational drug designing, docking and predicting the efficacy of drugs. *Int J Novel Trends Pharm Sci* 2012;2:98–105.
- [35] Leszczynski J, editor. Handbook of computational chemistry, 2nd ed. Switzerland: Springer International Publishing, 2017:2265.
- [36] Nishiyama A, Niihara O, Mohri H, Tsumura M. Timing of anti-platelet effect after oral aspirin administration in patients with sympathetic excitement. *Circ J* 2003;67:697–700.
- [37] Kestenbaum MG, Vilches AO, Messersmith S, Connor SR, Fine PC, Murphy B, et al. Alternative routes to oral opioid administration in palliative care: a review and clinical summary. *Pain Med* 2014;15:1129–53.
- [38] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* 2001;46:3–26.
- [39] Lipinski CA. Rule of five in 2015 and beyond: target and ligand structural limitations, ligand chemistry structure and drug discovery project decisions. *Adv Drug Deliv Rev* 2016;101:34–41.
- [40] Navia MA, Chaturvedi PR. Design principles for orally bioavailable drugs. *Drug Dev Today* 1996;1:179–89.
- [41] Abraham MH, Chadha SH, Whiting GS, Mitchell RC. Hydrogen bonding. 32. An analysis of water octanol and water-alkane partitioning and the delta log P parameter of Seiler. *J Pharm Sci* 1994;83:1085–100.
- [42] Pires DE, Blundell TL, Ascher DB. pkCSM: predicting small-molecule pharmacokinetic properties using graph-based signatures. *J Med Chem* 2015;58:4066–72.
- [43] Sun H, Chow EC, Liu S, Du Y, Pang KS. The Caco-2 cell monolayer: usefulness and limitations. *Expert Opin Drug Metab Toxicol* 2008;4:395–411.
- [44] Rabascio C, Bertolini F. Blood-based biomarkers for the optimization of anti-angiogenic therapies. *Cancers* 2010;2:1027–39.
- [45] Ferreira LG, dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. *Molecules* 2015;20:13384–421.
- [46] Zhang J, Zhang K, Gao ZC, Paoletta S, Zhang D, Han GW, et al. Agonist-bound structure of the human P2Y<sub>12</sub> receptor. *Nature* 2014;508:119–22.





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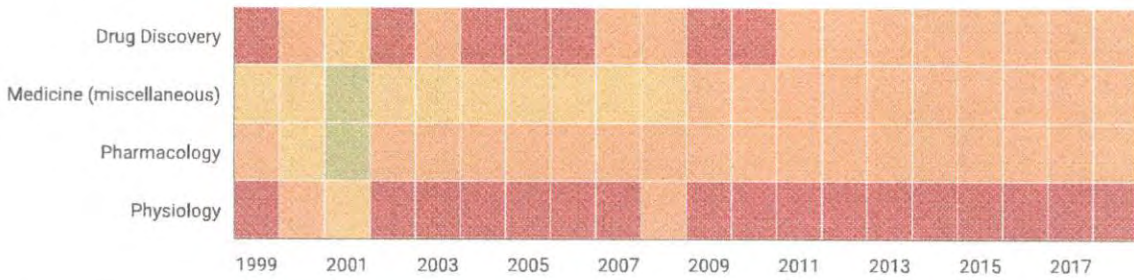
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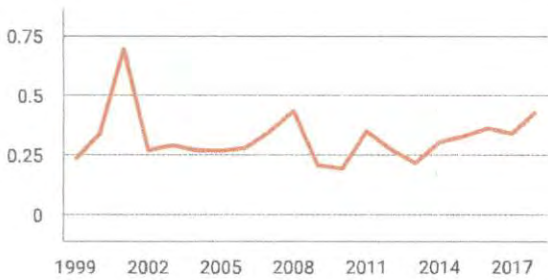
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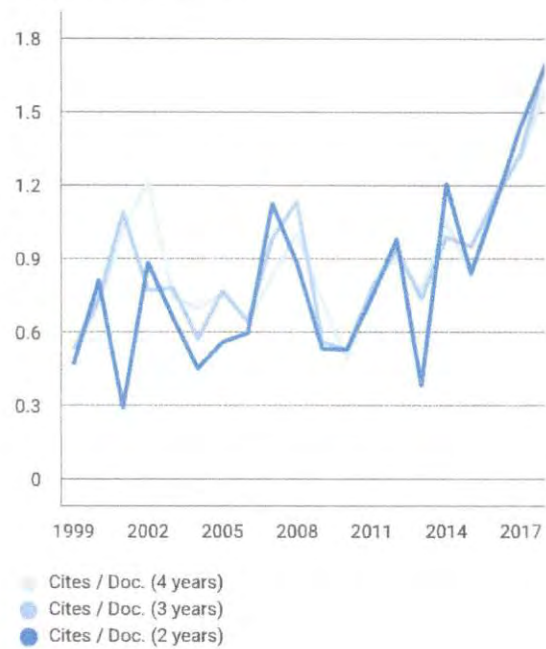
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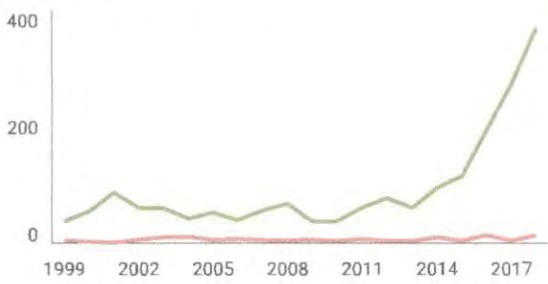
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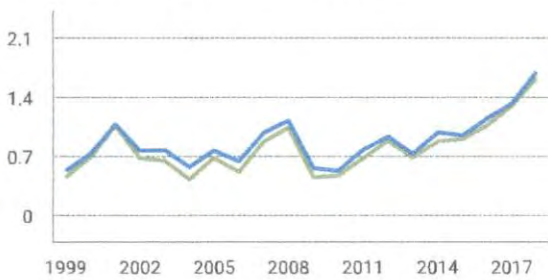
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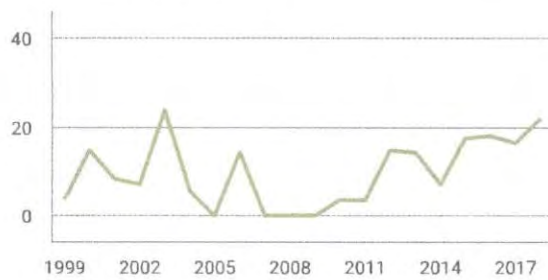
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Dear Prof. Micha Horowitz

Editor-in-chief of Journal of basic and clinical physiology and pharmacology

We wish to submit a new manuscript entitled ***o*-Hydroxycinnamic Derivatives as Prospective Anti-platelet: in silico Pharmacokinetic Screening and Evaluation of their binding site on COX-1 and P2Y<sub>12</sub> receptor** for consideration by the **journal of basic and clinical physiology and pharmacology**.

We confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication elsewhere.

In this paper, we report on pharmacokinetic characteristics and toxicity of *o*-hydroxycinnamic acid derivatives and their ability to bind to COX-1 and P2Y<sub>12</sub> receptors. This is significant because These compounds have the potential to be developed as new anti-platelet candidates. Moreover, we design compounds that can inhibit both the COX-1 and P2Y<sub>12</sub> pathways. The paper should be of interest to readers in the areas of pharmacology and drug discovery.

So far we observe that thrombotic disorder is a concerning problem for public health, which is the cause of death of one third of people aged 35 years and over, in western countries. In developing countries, it is estimated that the amount is not less than that. Apart from drug side effects, new problems arise when many clinical studies have begun to report the resistance of long-term use of aspirin and clopidogrel (the currently used anti-platelet).

From here, we assess the need for scientists in the field of pharmacology and drug discoveries to strive for new anti-platelet compounds, with better potential and smaller side effects. Using the Structure-Guided drug design approach, we evaluated the interaction of 21 *o*-hydroxycinnamic acid derivatives with COX-1 and P2Y<sub>12</sub> receptors. The energy stability of the complex interactions of the ligand-enzyme was calculated using the Molegro virtual docker and presented as a Moldock score. In addition, we also analyze the pharmacokinetic and toxicity properties based on the molecule using the pKCSM web tool. We believe the results of this study will provide useful information for researchers in the field of pharmacology and drug discovery to select prospective antiplatelet compounds that have high biological activity, good pharmacokinetic properties and are not toxic.

Please address all correspondence concerning this manuscript to me at [juni-e@ff.unair.ac.id](mailto:juni-e@ff.unair.ac.id).

Thank you for your consideration of this manuscript.

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Royalties	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
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Payment for development of educational presentations	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
Stock/stock options	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
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	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
Travel/accommodations /meeting expenses unrelated to activities listed	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
Other	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment
	<input type="checkbox"/>	Please enter initials	<input type="checkbox"/>	<input type="checkbox"/>	Please enter Entity	Please enter comment



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\* This means money that your institution received for your efforts. \*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

## SECTION 4

### OTHER RELATIONSHIPS

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- No other relationships/conditions/circumstances that present a potential conflict of interest
- Yes, the following relationships/conditions/circumstances are present (explain below):

Please enter the explanation here

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### SOURCES

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## Fwd: JBCPP.2019.0327 - DecisionAccept

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From: kholis amalia nofianti (kholis-a-n@ff.unair.ac.id)

To: j\_ekowati@yahoo.com

Date: Saturday, November 9, 2019, 12:03 PM GMT+7

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Bersama ini saya kirimkan hasil dari reiewer 1 . Bismillah semoga lancar semua

----- Forwarded message -----

Dari: **Journal of Basic and Clinical Physiology and Pharmacology** <[onbehalf@manuscriptcentral.com](mailto:onbehalf@manuscriptcentral.com)>

Date: Sab, 9 Nov 2019 10:59

Subject: JBCPP.2019.0327 - DecisionAccept

To: <[kholis-a-n@ff.unair.ac.id](mailto:kholis-a-n@ff.unair.ac.id)>

08-Nov-2019

Dear Ms. Nofianti:

I would like to thank you for submitting your manuscript entitled "*o*--Hydroxycinnamic Derivatives as Prospective Anti-platelet: in silico Pharmacokinetic Screening and Evaluation of their binding site on COX-1 and P2Y12 receptor" to Journal of Basic and Clinical Physiology and Pharmacology (JBCPP). Your manuscript has been reviewed, and it is a pleasure to accept it for publication in JBCPP. The comments of the reviewer(s) are included at the bottom of this letter.

The JBCPP production office will contact you for proofreading in the near future. Your article will be published ahead of print as soon as possible, and assigned to an online issue at a later time.

Thank you for your fine contribution. On behalf of the Editors of Journal of Basic and Clinical Physiology and Pharmacology we look forward to your continued contributions to the Journal.

Kind regards

Dr. Chrismawan Ardianto

Guest Editor, Journal of Basic and Clinical Physiology and Pharmacology

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author

The author has described very good data and finding for the new candidate for antiplatelet medicine. The data and the method are very convincing. Discussion has explored all the possibilities needed to build the reader's perspective. The improvement may be done on the result and discussion section. The author may choose to put an explanation of the findings in the result section to increase the readability of the table. The discussion should be done by discussing the finding comprehensively instead of explaining the findings one by one based on the table.

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**WG: Check your Proof: jbcpp-2019-0327**

1 message

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**Appelt, Katharina** <Katharina.Appelt@degruyter.com>  
To: "juni-e@ff.unair.ac.id" <juni-e@ff.unair.ac.id>

Mon, Dec 2, 2019 at 3:26 PM

30 November 2019

Dear Juni Ekowati,

Your article's galley proof is now available:

jbcpp-2019-0327: o-Hydroxycinnamic derivatives as prospective anti-platelet candidates: in silico pharmacokinetic screening and evaluation of their binding sites on COX-1 and P2Y12 receptors

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Wed, Feb 12, 2020 at 7:22 PM

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To: juni-e@ff.unair.ac.id



*Deutsche Version unten*

Dear author,

You have recently published the following article

<https://doi.org/10.1515/jbcpp-2019-0327> in the journal **Journal of Basic and Clinical Physiology and Pharmacology**.

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Kind regards,



Dr. Esther Heckendorf

Manager Insights & Analysis  
De Gruyter

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*Deutsche Version*

Sehr geehrte Autorin, sehr geehrter Autor,

Sie haben kürzlich die folgende Publikation <https://doi.org/10.1515/jbcpp-2019-0327> in der Zeitschrift **Journal of Basic and Clinical Physiology and Pharmacology** veröffentlicht. Wir haben nun noch eine Bitte an Sie: De Gruyter widmet sich momentan intensiv dem Thema, seiner Autorenschaft die bestmöglichen Erfahrungen bei der Veröffentlichung eines Artikels zu bieten.

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GEHEN

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Mit freundlichen Grüßen

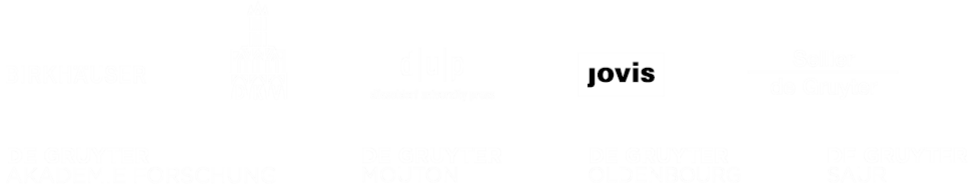


Dr. Esther Heckendorf

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Mon, Feb 17, 2020 at 7:06 PM



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Kind regards,

Maria Hryniewicz  
Senior Marketing Manager, Open Access, De Gruyter

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Mon, Mar 2, 2020 at 7:12 PM



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Kind regards,

Maria Hryniewicz  
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