Research Article

Chemical Review and Letters
journal homepage: www.chemrevlett.com
ISSN (online): 2645-4947(print) 2676-7279

Molecular Docking, Drug likeness Studies and ADMET prediction of Flavonoids as Platelet-Activating Factor (PAF) Receptor Binding

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ARTICLE INFO

Article history:
Received 19 December 2020
Received in revised form 18 April 2021
Accepted 7 May 2021
Available online 7 May 2021

Keywords:
Flavonoids
Platelet-activating factor (PAF)
Docking study
ADMET

ABSTRACT

Studies and scientific research indicate that the platelet-activating factor (PAF) is a major pro-inflammatory mediator in the initiation and development of cancer. There is also evidence confirming that PAF is an integral part of suppressing the immune system and promoting the appearance of a malignant tumor. For this reason, it is useful to analyze the molecular docking data of eleven flavonoids derivatives isolated from the active leaf extracted from chromolaena odorata with their anti-PAF activity. As a result, it is evident that the natural product of flavonoids may have a positive effect in the development of both therapeutic and preventive agents for platelet activating factor (PAF) antagonist and suggests potential guidelines for the design of PAF inhibitors. Based on the docking score analysis, drug likeness study, and ADMET prediction. We found that six compounds respect all drug-likeness rules and can be used as a potent molecule for inhibition of platelet activating factor (PAF).

1. Introduction

Platelet Activating Factor (PAF) is a phospholipid derived from arachidonic acid whose particularity is to activate the aggregation and degranulation of platelets. PAF is also a potent mediator of inflammation secreted by multiple cells (Figure1). PAF is an acetylated derivative of glycerophosphorylcholine [1]; one of the main effects of which is to cause platelet aggregation. This is how it is named [2].

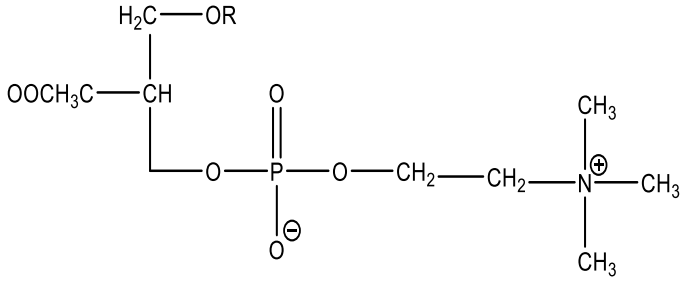

Figure 1. Molecular structure of PAF.

A body of research on the role of PAF in cancer has revealed several interesting findings over the last twenty years. It has confirmed that PAF is an essential mediator for many types of cancer [3].

However, we may conclude that PAF play a major role in reducing cancer that are particularly difficult to treat. For example, melanoma is a skin cancer. It is among the most aggressive forms of cancer because it frequently metastasizes as a result of pro-inflammatory signaling that is mediated by PAF/PAF-R [4,5, 6].

There is a wide range of compounds as PAF inhibitor, whichare divided into two categories: the non-specific inhibitors and the specific PAF inhibitors [7]. Cedrol and kadsurenone (Figure 2) are considered specific PAF inhibitors [8].

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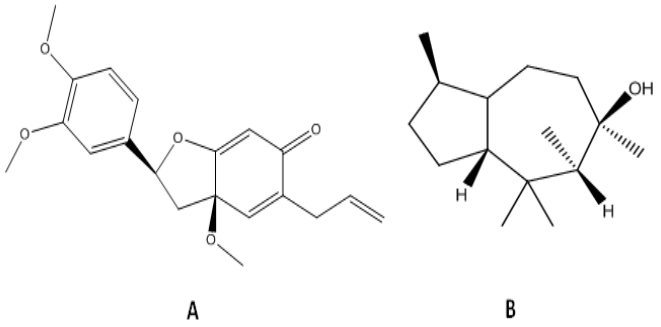


Figure 2: Chemical structure of Cedrol (A) and Kadsurenone (B) with anti-PAF activity.

Cedrol is an alcohol of the well-known PAF antagonists [9, 10].Another potent PAF antagonist is kadsurenone, which is derived from the Chinese herb Piper futokadsurae. Its structure has been used as a model for the development of synthetic PAF antagonists [11].

In silico methods including, molecular docking, absorption_distribution_metabolism_excertion_toxicity (ADMET) and drug likeness studies are key steps employing in drug development and discovery processes. Molecular docking study finds the interactions between the binding molecules; ADMET assessments provide adequate information on properties that influence absorption, distribution, metabolism, excretion and toxicity. However, the concept of drug-likeness was proposed to provide useful guidelines during the early stages of drug discovery to improve the chance of a chemical entering and passing clinical trials[12]. It can be defined as the sum of the molecular physicochemical properties that are characteristic of chemicals known as drugs.

Ligands (usually small molecules) bind to proteins in cavities on their surface. An analysis of docking stimulations data enables us to identify these interactions [13]. Nowadays, the docking process is one of the first steps used in the design of drugs. In this paper, eleven flavonoids derivatives isolated from the active leaf extract of Chromolaena odorata (Table 1) is docked to the PAF receptor. The objective is to improve the understanding of recognition in order to refine the selection of new molecular entities that can become drug candidates, to gain insight if those natural compounds of flavonoids derivatives could be of use as therapeutics in medicine, using Cedrol and Kadsurenone as reference PAF inhibitors for docking.

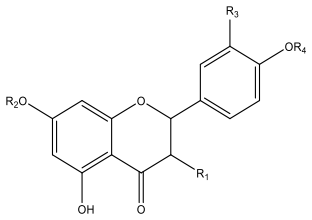
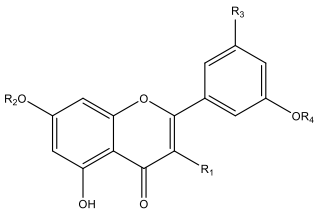
2. Material and Methods

2.1. Data collection

2.1.1. Ligands

In the present study, a series of eleven selected Flavonoids derivatives (Table 1) has been subsequently isolated from the active leaf extract of Chromolaena odorata and evaluated fortheir effects on PAF receptor binding [14]. These molecules could be docked into the substrate-binding pocket of human platelet-activating factor receptor (PDBId: 5ZKP). For the energy minimization of the compounds, we have used the MM2 method [15] with Gasteiger-Hückel atomic partial charges [16].

Table 1. Chemical structures of the studied Flavonoids.

Studied Structures	Com.	R_1	R_2	R_3	R_4
	**X_1**	OH	H	H	CH_3
	X_2	H	CH_3	OH	CH_3
	X_3	H	H	H	CH_3
	X_4	OH	H	OH	CH_3
	X_5	OH	CH_3	OH	H
	**X_6**	H	CH_3	H	CH_3
	X_7	H	H	H	CH_3
	X_8	Glu(6-4) rham	H	OH	H
	X_9	Glu(6-4)rham	H	H	H
	X_{10}	H	H	OH	CH_3
	X_{11}	H	CH_3	OH	H

2.1.2. Receptor

The x-ray crystal structure of the receptor (PDBId: 5ZKP) has been retrieved from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/). Crystallographic properties of the protein are reported in Table 2.

Table 2. Crystallographic properties of protein used in our study.

	Property				
Protein	Classification	Resolution	R-Value Free	Method	Chaine
5ZKP	Protein	2.81 Å	0.259	X-Ray Diffraction	A

2.2. Molecular Docking

In drug design, Molecular docking is frequently used to identify the type of interactions between the ligand and the receptor. First, we have docked the two compounds Cedrol and Kadsurenone as reference inhibitors of PAF, in order to compare obtained score to score from chosen ligands of eleven selected Flavonoids derivatives. General procedures for molecular docking are shown in Figure 3.

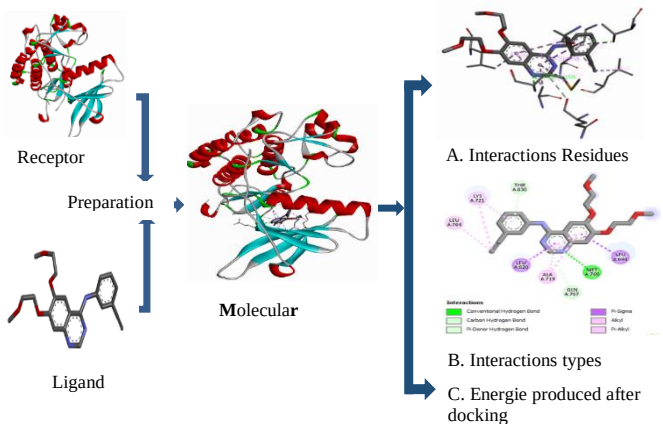


Figure 3: General procedures for molecular docking.

Autodock Vina [17] and Autodock tools 1.5.6 program [18] have been used to simulate the bioactive conformations. The crystallographic structure of the receptor (PDBId: 5ZKP) is imported into "work space" of Discovery Studio 2016 program [19] to obtain the binding site [20].The cubic grid box: x= 33.578, y = -4.452 and z=7.541 at 1 Å have been centered at the active site of the receptor with grid size at 30×30×30 xyz points by using the co-crystallized ligand SR 27417(N1,N1-dimethyl-N2-[(pyridin-3-yl)methyl]-N2-{4-[2,4,6-tri(propan-2-yl)phenyl]-1,3-thiazol-2-yl} ethane-1,2-diamine)as the center for docking. During docking, the complex of human platelet-activating factor receptor with SR 27417 has been imported, the co-crystal ligand SR 27417 has been removed from the binding pocket, and experimental ligands have been placed in the predicted binding site.

2.3. Docking validation protocol

Validation of the results obtained for docking is done by re-docking the co-crystallized ligand into the active site of the receptor (PDB Id: 5ZKP). We have used the same parameters of grid box [21, 22].

2.4. Drug-likeness studies

Molecular properties and drug-likeness parameters have been calculated in silico for all the designed molecules (X1 to X11) using swissadmet web server[23], with the aim of identifying the molecules which satisfy the optimum requirements to exhibit as drug-like molecules based on the following five rules and one score:

Lipinski rule [24], Ghose rule [25], Veber rule [26] , Egan rule [27], Muegge rule [28] and the bioavailability score [29] .

2.5. ADMET prediction

Absorption_Distribution_Metabolism_Excertion_Toxicity (ADMET) has been calculated using pkCSM web server[30]. To improve the quality control of drugs there are several important steps in pharmacokinetic terms. These steps include Absorption of the molecule, distribution in the body, elimination including biotransformation or metabolism, excretion and toxicity have been used to predict ADMET properties [31]. The major role of ADMET study is to determine oral bioavailability, cell permeation, metabolism and elimination (Pharmacokinetic characteristics) of drug molecules.

3. Results and Discussion

3.1. Molecular Docking

Molecular docking is performed to find the most favorable mode of interaction of a ligand within its receptor (therapeutic target) which helps the prediction of molecules in a limited time and especially sometimes without having to synthesize them. Eleven isolated flavonoids derivatives have been evaluated for their affinity (Table 3) with the human platelet-activating factor receptor (PAF) (PDB code: 5ZKP).The molecular docking of these structures to the active site of the PAF allows us to bring out the most potent inhibitors against this enzyme.

Table 3. The results obtained: the best pose conformation ordered by their binding affinities.

Compounds	Affinity (Kcal/mol)	Compounds	Affinity(Kcal/mol)
X_1	-8.4	**X_5**	-8.9
X_2	-8.7	**X_{10}**	-8.9
X_3	-8.7	**X_6**	-10.1
X_8	-8.8	**X_7**	-10.7
X_9	-8.8	**Cedrol**	**-8.1**
X_{11}	-8.8	**Kadsurenone**	**-8.8**
X_4	-8.9		

According to the results obtained from the docking molecular, the compounds X_4, X_5, X_6, X_7, X_8, X_9, X_{10} and X_{11} (X_4-X_{11}) have lower energies of interaction with the human platelet-activating factor receptor than the two references inhibitors Cedrol and Kadsurenone. Therefore, these molecules could be potential inhibitors for the studied receptor. The co-crystallized is re-docked into the active site of the receptor(Figure4).The following interactions are observed: Conventional Hydrogen Bonds interactions with Tyr77 residue, three carbon Hydrogen Bonds interactions with Phe174, His275 and Tyr177, two p-Sigma interactions with Leu279 and His188 residues, Pi-Pi interactions with Trp73, Phe97 and Phe98 residues.

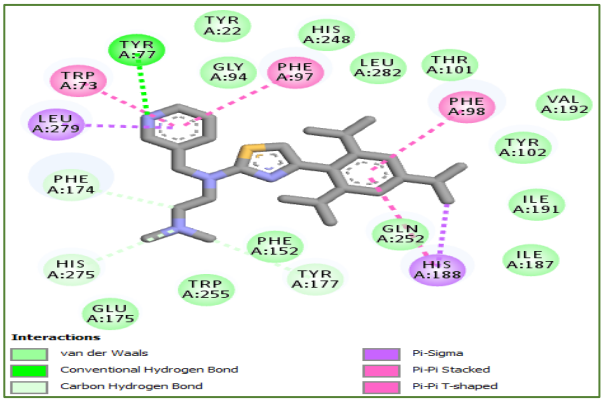


Figure4. Interaction between SR 2724 (co-crystallized ligand) and the receptor (code: 5zkp).

The interaction results between Cedrol and the receptor in Figure 5 show three Pi-Sigma interactions with Trp73, Phe97 and Phe174 residue, alkyl interactions with Phe97 residue.

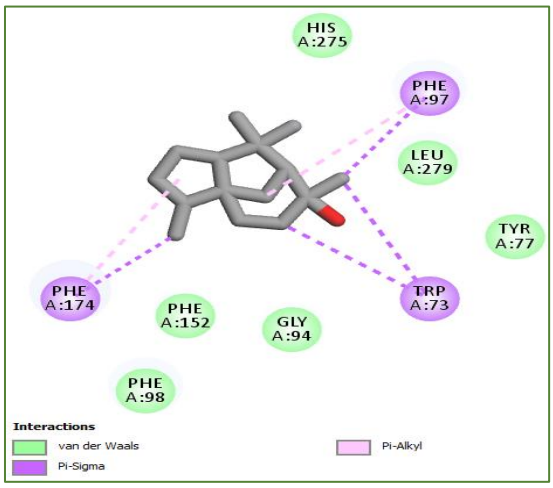


Figure5. Interaction between Cedrol and the receptor (5zkp).

The interaction results of the Kadsurenone as the second reference inhibitor of PAFwith the studied receptor (Figure 6) show the following interactions: two hydrogen bonds interaction with Tyr77 and Tyr102, carbon hydrogen bond formed with Tyr22, two alkyl bonds with His188 and Phe18, Pi-Pi Stacked with Trp73 and Pi-Pi T-Shaped with Phe98. Through the results of the docking obtained by the three compounds Cedrol, kadsurenone and co-crystallized ligand (SR 2724).It is clear that kadsurenone has a pharmacological importance compared toCedrol and co-crystallized ligand (SR 2724).

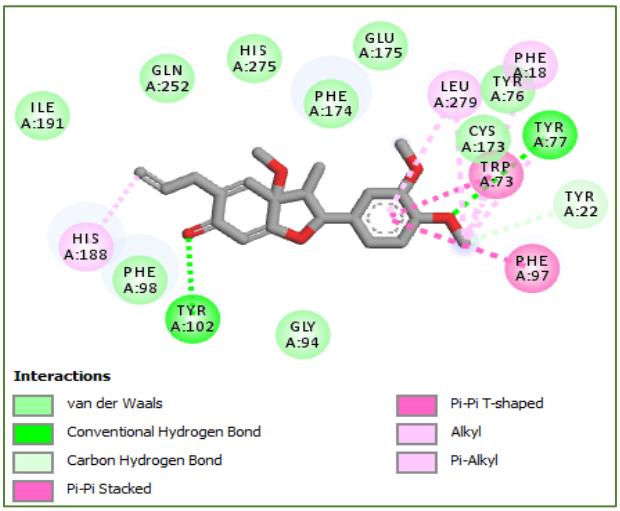
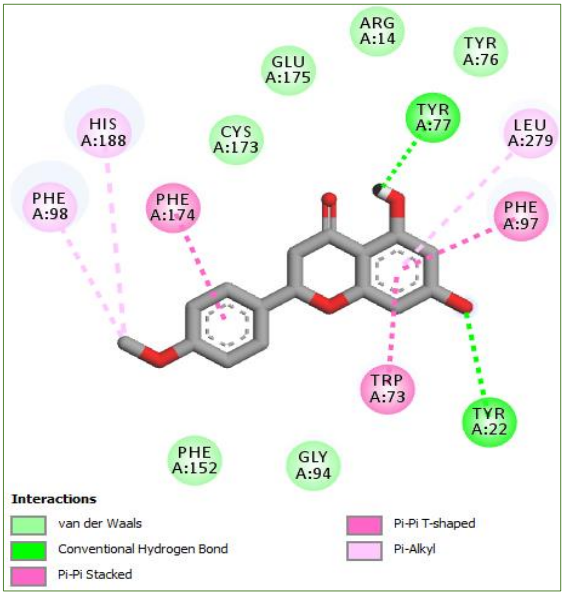
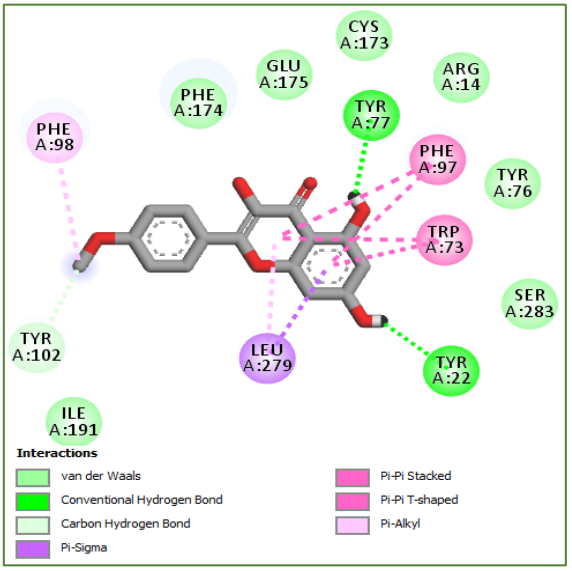


Figure 6. Interactions between kadsurenone and the human platelet-activating factor receptor (5zkp).

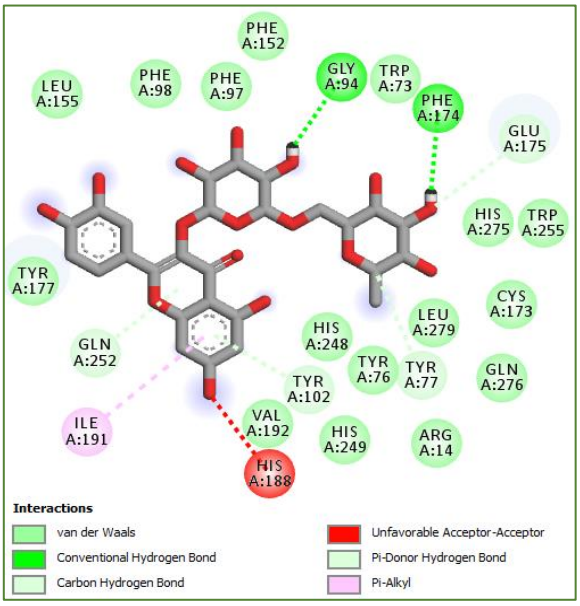
The interaction results of 8 compoundsX_4-X_{11}in the cavity of the receptor (5zkp) (Figure7) show more type and number of interactions (Hydrogen Bond interaction) compared to Cedrol and kadsurenone as reference inhibitors of PAF. Based on the obtained results the compounds (X_4 _X_{11}) could be good inhibitors of PAF compared to Cedrol and kadsurenone.



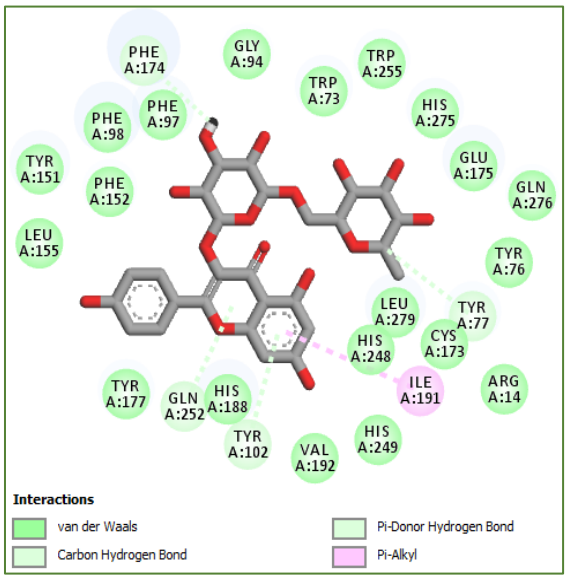
Molecule X_4



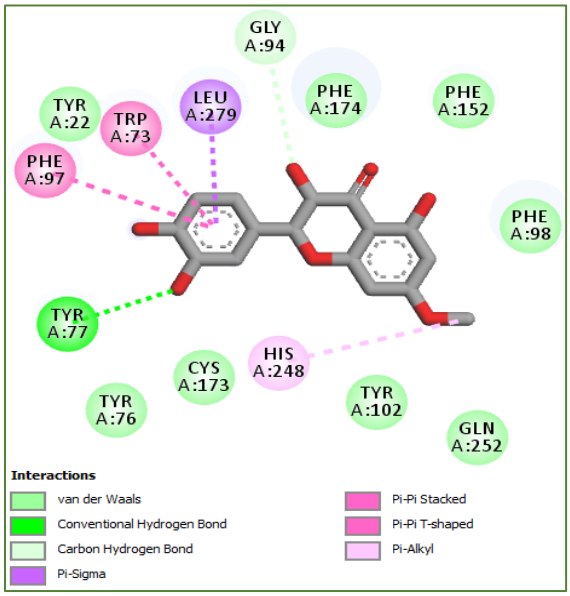
Molecule X_5



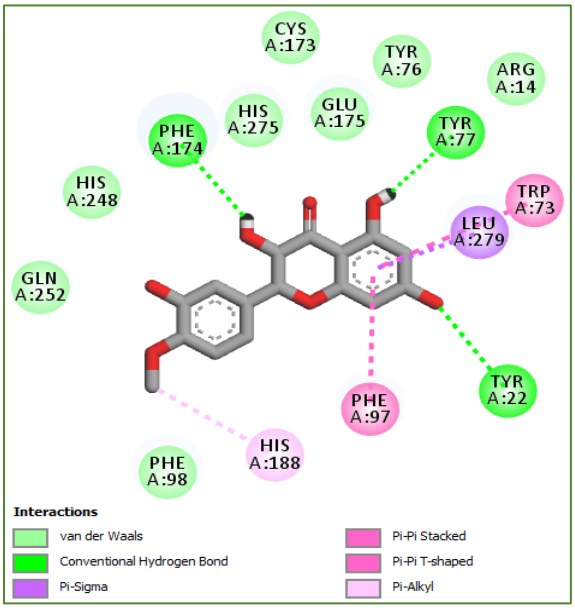
Molecule X_6



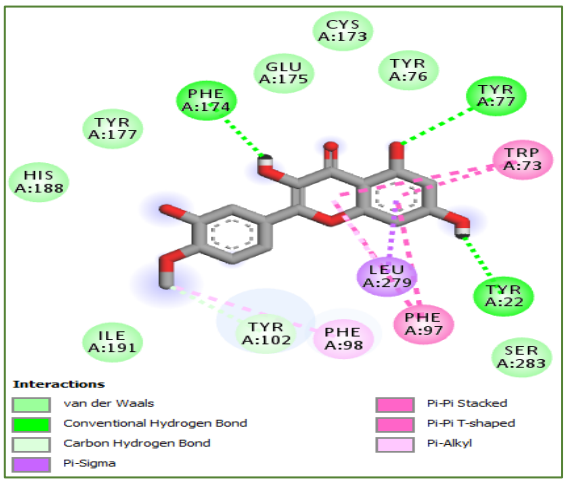
Molecule X_7



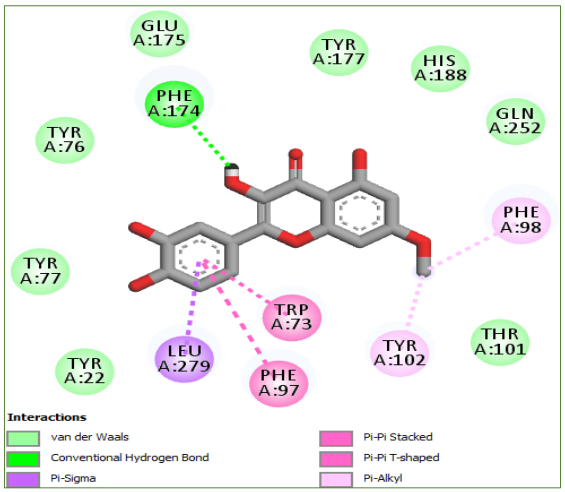
MoleculeX_8



Molecule X_9



Molecule X_{10}



Molecule X_{11}

Figure 7. Types of interactions between PAF-R (PDB code: 5ZKP) and eight selected Flavonoids derivatives.

Visual inspection of the docked poses of sixcompounds X_4, X_5, X_8, X_9, X_{10} and X_{11} clearly indicates similarity between binding modes and interactions of these molecules compared to the co-crystallized ligand (SR2724) with the human platelet-activating factor receptor 5zkp. Both of them form hydrogen bonds with Tyr77 and Tyr22 residual, carbon hydrogen bonds with Tyr 102, while Pi-Sigma bond is formed with Leu279. Moreover, similarities between interactions of the natural flavonoid derivatives (X_4, X_5, X_8, X_9, X_{10} and X11) and reference inhibitor (Cedrol and kadsurenone) confirm that these molecules can be certified as inhibitor of PAF receptor.

3.2. Docking validation protocol

Validation of the docking study is carried out by re-docking the co-crystallized ligand with the protein. Figure 8 shows the superposed conformation between the docked ligand (blue colored) and the co-crystallized ligand (Green colored). Thus, the docking process in this study has been successfully validated.

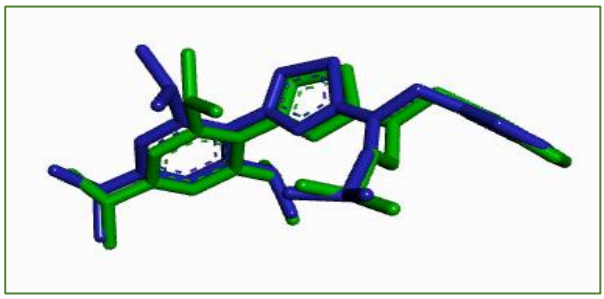


Figure 8. Overlay of default conformation (Green colored) on docked conformation (blue colored) of the co-crystallized ligand validating docking protocol.

3.3. Drug-likeness studies

Results depicted in table 4 reveal that all molecules selected of their good results in docking study (X_4 to X_{11}) possess acceptable drug-like properties, based on Lipinski's rule of five [13, 14]except the two compounds X_6 and X_7. The Lipinski's rule including, log P, number of hydrogen bonds acceptor, number hydrogen bonds donor, a number of rotatable bonds and molecular weight are shown in Table 4.

Table 4. Lipinski's role potential inhibitors and the most potent inhibitor in the dataset.

Compounds	Property						Lipinski violations
	Log P	H-bond Acceptor	H-bond Donor	Rotatable bonds	TPSA	Molecular weight g/mol	
Rule	<5	≤10	<5	<10		≤500	≤1
X_4	2.39	5	2	2	75.99	286.28	0
X_5	2.43	6	3	2	100.13	300.26	0
X_6	2.05	16	10	6	265.52	612.53	3
X_7	1.62	15	9	6	249.20	594.52	3
X_8	1.26	7	4	2	116.45	318.28	0
X_9	2.15	7	4	2	116.45	318.28	0
X_{10}	2.24	7	4	2	120.36	316.26	0
X_{11}	2.23	7	4	2	120.36	316.26	0
Cedrol	2.99	1	1	0	20.23	222.37	0
kadsurenone	3.51	5	0	6	53.99	356.41	0

The value of polar surface area (PSA) for the six compounds X_4, X_5, X_8, X_9, X_{10} and X_{11}indicates good oral bioavailability. The parameters, like a number of rotatable bonds and number of rigid bonds are linked to intestinal absorption results show that all compounds have good absorption except the two compounds X_6 and X_7. Another four drug-likeness rules namely Ghose, Veber, Egan and Muegge are contemporarily satisfied for the compounds that are obeyed Lipinski rule of five. The selected compounds are also evaluated for their synthetic accessibility.

The Synthetic accessibility values for all compounds is about three. Therefore, they are easy to synthetic (Table 5).

3.4. ADMET prediction

The molecules selected by their good results in drug likeness are subject to ADMET prediction. The predicted values of ADME-Tox studies are presented in Table 6. All ADMET values are found within an acceptable range. ADMET properties affect pharmacokinetic (absorption, distribution, metabolism, excretion) and pharmacodynamic (drug efficacy and toxicity) properties of drug substances.

Table 5. Drug likeness prediction of the selected compounds based on Ghose, Muegge, veber and Egan rules, and their synthetic accessibility.

Compounds	Ghose	Muegge	Veber	Egan	Synthetic accessibility
X_4	Yes	Yes	Yes	Yes	3.11
X_5	Yes	Yes	Yes	Yes	3.16
X_8	Yes	Yes	Yes	Yes	3.62
X_9	Yes	Yes	Yes	Yes	3.62
X_{10}	Yes	Yes	Yes	Yes	3.26
X_{11}	Yes	Yes	Yes	Yes	3.30

Table 6. Lipinski's role of potential inhibitors.

Comp.	Absorption		Distribution		Metabolism						Excretion	
	Water solubility	Intestinal absorption (human)	Volume of distribution	Blood-brain barrier permeability	CYP						Total clearance	Toxicity Ames
					2D6	3A4	1A2	2C19	2C9	2D6 3A4		
					Substrate		Inhibition					
	(log mol/l) (% absorbed)	Numeric (log L/Kg)	Numeric (log BB)		Categorical (yes/No)						Nemeric (Log/mol/ min/Kg)	Yes/No
X_4	-3.57	83.390	0.301	-1.222	No	No	Yes	Yes	No	No Yes	0.187	No
X_5	-3.437	84.538	0.316	-1.230	No	No	Yes	Yes	Yes	No No	0.731	No
X_8	-3.305	88.785	0.906	-1.118	No	No	No	No	No	No No	0.233	No
X_9	-3.550	89.788	0.263	-1.159	No	No	No	No	No	No No	0.193	No
X_{10}	-3.644	87.064	0.291	-1.311	No	No	Yes	No	No	No No	0.691	No
X_{11}	-3.470	85.162	0.287	-1.349	No	No	Yes	No	No	No No	0.715	No

The results of ADMET analysis show that all the selected compounds X_4, X_5, X_8, X_9, X_{10} and X_{11}exhibit a suitable drug-like profile. However, all compounds have a value of blood-brain permeability less than -1 (log BB<-1).This signifies that these molecules are considered to be poorly distributed to the brain. Negative test of Ames indicates that the six flavonoid derivatives (X_4, X_5, X_6, X_8, X_9, $X_{10}$and X_{11}) are not toxic. Additionally, the other PK parameters (intestinal absorption, water solubility, Caco2 permeability) are respected.

4. Conclusion

In this study, we describe the structural binding features of six flavonoid derivatives isolated from the active leaf extracted from Chromolaena odoratawith the human platelet-activating factor receptor (PDB id: 5zkp). Docking, drug-likeness and ADMET studies confirm the potential and drug-likeness of the six compounds X_4, X_5, X_8, X_9, X_{10} and X_{11} as novel inhibitors of PAF receptor.

Acknowledgements

We are grateful to the "*Association Marocaine des Chimistes Théoriciens*" (AMCT) for its pertinent help concerning the programs.

References

[1] R. N. Pinckard, A NEW CLASS OF LIPID. J Biol Chem. 254 (2020) 9355_9358.

[2] P. Detopoulou and T. Nomikos, Platelet Activating Factor in Heart Failure : Potential Role in Disease Progression and Novel Target for Therapy,Curr. Heart. Fail. Rep. 10 (2013) 122–129.

[3] R. Lordan, A. Tsoupras and I. Zabetakis, The Potential Role of Dietary Platelet-Activating Factor Inhibitors in Cancer Prevention and Treatment, Amer. So. for Nut. 10 (2019) 148–164.

[4] V. Melnikova and M. Bar-eli, Inflammation and melanoma growth and metastasis : The role of platelet-activating factor (PAF) and its receptor, Cancer Meta. Rev 26 (2009) 359–371.

[5] V. O. Melnikova and M. Bar-eli, Inflammation and melanoma metastasis, Pigment Cell Melanoma Res. 22 (2007) 257–267.

[6] L. El Mchichi, A. Belhassan, A. Aouidate, A. Ghaleb, T. Lakhlifi and M. Bouachrine, QSAR study of new compounds based on 1,2,4-triazole as potential anticancer agents, Phys. Chem. Res. 8 (2020) 125–137.

[7] J. Summers and D. H. Albert, Platelet Activating Factor Antagonists, Adv. in Pharm. 32(1995).

[8] V. D. Papakonstantinou, N. Lagopati, E.C. Tsilibary, C. A. Demopoulos and A. I. Philippopoulos, A Review on Platelet Activating Factor Inhibitors : Could a New Class of Potent Metal-Based Anti-Inflammatory Drugs Induce Anticancer Properties ?, Bioi. Chem and App 2017 (2017) 1_19.

[9] S. P. Bhatia, D. Mcginty, C. S. Letizia and A. M. Api, Fragrance material review on cedrol, Food and Chem. Tox. 46 (2008)100–102.

[10] H. O. Yang, D. Sal, and B. Ha, Isolation and Characterization of Platelet-Activating Factor Receptor Binding Antagonists from Biota orientalis.Planta Med. 61 (1995).

[11] T. Y. Shen , S. Hwang, N. M. Chang, T. M. Doebber, M. T. Lam, M. S. Wu, X. Wang, G. Q. Han and R. Z. Li, Characterization of a platelet-activating factor receptor antagonist isolated from haifenteng (Piper futokadsura):

Specific inhibition of in vitro and in vivo platelet-activating factor-induced effects, Proc. Nati. Acad. Sci. 82 (1985) 672–676.

[12] L. El Mchichi, A. El Aissouq, A. Belhassan, R, El-Mernissi, A. Ouammou, T. Lakhlifi, M. Bouachrine, "Materials Today : Proceedings In silico design of novel Pyrazole derivatives containing thiourea skeleton as anti-cancer agents using : 3D QSAR , Drug-Likeness studies , ADMET prediction and molecular docking," Mater. Today Proc., 2021, doi: 10.1016/j.matpr.2021.03.152.

[13] A. Adamski, D. Kruszka, Z. Dutkiewicz, M. Kubicki, V. Patroniak and A. Gorczy, Novel family of fused tricyclic [1, 4] diazepines : Design , synthesis , crystal structures and molecular docking studies,Tetrahedron 73 (2017) 3377–3386.

[14] S. K. Ling, M. M. Pisar and S. Man, Platelet-Activating Factor (PAF) Receptor Binding Antagonist Activity of the Methanol Extracts and Isolated Flavonoids from Chromolaena odorata (L .) KING and ROBINSON, Biol. Pharm. Bull. 30 (2007) 1150–1152.

[15] M. Clark, R. D. Cramer and N. Van Opdenbosch, Validation of the General Purpose Tripos5 . 2 Force Field,J. of Comp. Chem. 8 (1989) 982–1012.

[16] W. P. Purcell and J. A. Singer, A Brief Review and Table of Semiempirical Parameters Used in the Huckel Molecular Orbital Method, J. of Chem. and Eng. Data 12 (1967) 235_246.

[17] O. Trott and A. J. Olson, Software News and Update AutoDock Vina : Improving the Speed and Accuracy of Docking with a New Scoring Function , Efficient Optimization , and Multithreading,J. of Comp. Chem. 2 (2009) 456_461.

[18] C. A. Hunter, K. R. Lawson and C. J. Urch, Aromatic interactions.J. Chem. Soc. 2 (2001) 651–669.

[19] DassaultSystemes BIOVIA Discovery Studio Modeling Environment, Release 2017 DassaultSystemes, 2016. http://accelrys.com/products/collaborative-science/biovia-discovery-studio/.

[20] L. El Mchichi, A. Aouidate, F. Z. Chokrafi, A. Ghaleb, T. Lakhlifi and M. Bouachrine, PREDICTION OF BIOLOGICAL ACTIVITY OF PYRAZOLO [3, 4-B] QUINOLINYL ACITAMIDE BY QSAR RESULTS, RHAZES : Grenn and App. Chem. 3 (2018) 79–93.

[21] K.Onodera, K. Satou and H. Hirota, Evaluations of Molecular Docking Programs for Virtual Screening, J. Chem. Inf. Model. 47 (2007) 1609–1618.

[22] L.Gregory, C. Warren, A. Webster, A. Capelli, B. Clarke, J. LaLonde, M. H. Lambert, M. Lindvall, N. Nevins, S. F. Semus, S. Senger, G. Tedesco, I. D. Wall, J. M. Woolven, C. E. Peishoff and M. S. Head, A Critical Assessment of Docking Programs and Scoring Functions,J. Med. Chem. 49 (2006) 5912–5931.

[23] A.Daina, O. Michielin and V. Zoete, SwissADME : a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, Nat. Publ. Gr. 7 (2016) 1–13.

[24] C. A.Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery permeability in drug discovery and development settings, Adv. Drug. Deliv. Rev. 23 (1997) 3_25.

[25] A. K.Ghose, V. N. Viswanadhan and J. J. Wendoloski, A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases,J. Comb. Chem. 1 (1999) 55–68.

[26] D. F.Veber, S. R. Johnson, H. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, Molecular Properties That Influence the Oral Bioavailability of Drug Candidates, J. Med. Chem. 45 (2002) 2615–2623.

[27] W. J.Egan, K. M. Merz and J. J. Baldwin, Prediction of Drug Absorption Using Multivariate Statistics, J. Med. Chem. 43 (2000) 3867–3877.

[28] I.Muegge, S. L. Heald and D. Brittelli, Simple Selection Criteria for Drug-like Chemical Matter, Amer. Chem. soc. 44 (2001)1842_1846.

[29] Y. C.Martin and A. Park, Bioavailability Score, J. Med. Chem. 48 (2005) 3164–3170.

[30] D. E.Pires V, T. L. Blundell and D. B. Ascher, pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures.J Med. Chem. 58 (2015) 4066−4072.

[31] L. Elmchichi, A. Belhassan, T. Lakhlifi, and M. Bouachrine, 3D-QSAR Study of the Chalcone Derivatives as Anticancer Agents, 2020 (2020).

How to Cite This Article

Mohammed BOUACHRINE; Larbi Elmchichi; Abdellah El Aissouq; Assia BELHASSAN; Hanane Zaki; Abdelkrim Ouammou; Tahar Lakhlifi. "Molecular Docking, Drug likeness Studies and ADMET prediction of Flavonoids as Platelet-Activating Factor (PAF) Receptor Binding". Chemical Review and Letters, 4, 3, 2021, 145-152. doi: 10.22034/crl.2021.262806.1098