HPU2 Journal of Sciences:
Natural Sciences and Technology

journal homepage: https://sj.hpu2.edu.vn

Article type: Review article

Molecular docking and ADMET studies of soluble epoxide hydrolase inhibitors from the leaves of *Paederia foetida* L.

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Abstract

Cardiovascular diseases are one of the leading cause of mortality and morbidity worldwide. Although many efforts have been made in the drug discovery and development process through decades, the number of approved drugs has been declining. In the recent years, soluble epoxide hydrolase (sEH) has been considered as promising target for drug development since inhibiting sEH function would prevent the formation of arterial thrombosis. *Paederia foetida* L. is a folk medicine distributed commonly in Vietnam which is well known for its uses in the treatment of various diseases. This study conducted *in silico* assessment of 21 isolated compounds from leaves of *Paederia foetida* L. against sEH enzyme for potential inhibition activity. Obtained results demonstrated that compound **4** and **9** could be potent, safe and novel inhibitors based on docking conformation and druglikeness properties.

Keywords: Paederia foetida, soluble epoxide hydrolase, molecular docking, ADMET studies; drug discovery

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https://doi.org/10.56764/hpu2.jos.2022.1.2.32-43

Received date: 26-12-2022 ; Revised date: 26-12-2022 ; Accepted date: 28-12-2022

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1. Introduction

Cardiovascular diseases (CVDs) remains the burden of medical system globally nowsaday . It is estimated that about 17,9 million of people die from CVDs in 2019 which representing 32% of all global death. Amongst the cases, 85% were due to heart attack and stroke [1]. Arterial thrombosis is determined as the main causes of CVD-related deaths include ischaemic heart disease or stroke [2]. Recently, the soluble epoxide hydrolase (sEH) appears to be a promising target for the development of antistroke therapies based on a previously unexplored mechanism of action [3]. Epoxide hydrolases are enzymes that add water to three membered cyclic ethers known as epoxides. The soluble epoxide hydrolase in mammalian systems is a member of the a/b-hydrolase fold family of enzymes and it shows a high degree of selectivity for epoxides of fatty acids. The regioisomeric epoxides of arachidonic acid or epoxyeicosanoids (EETs) are particularly good substrates [4]. Previously, EETs was proved to decrease inflammation and platelet aggregation and in general act to maintain vascular homeostasis [5]. However, the EETs are metabolized by sEH to form the responding dihydroxyeicosatrienoic acids [6] and in consequence, the reactions result in diminished cardioprotective effects of EETs. Therefore, it could be interesting to hypothesize that the use of sEH blockers, which prevent EETs degradation, is a promising pharmacological approach to effectively treat CVDs in the future.

Paederia foetida L. is a traditional edible herb widely distributed in Malaysia, Myanmar, Nepal, Thailand, Vietnam, Cambodia and China [7, 8]. The aerial parts of *P. foetida* have been used in traditional and folk medicine for the treatment of various diseases for hundreds of years [7, 9, 10]. The roots and barks of this plant are used as an emetic and also for the treatment of piles and inflammation. Its leaves are used as an antidote for snakebite [11], whereas the leaf juice is given to children with diarrhea and treat toothache also. However, to our best knowledge, none studies have been conducted for potential CVDs treatment.

Computer-aided drug design (CADD) is regularly employed to accelerate the discovery of potent compounds, which are able to inhibit the function of an enzyme, thus reduce the time and cost for the development of a new medication [12, 13]. In CADD, the molecular docking method is commonly used to predict the interaction of a macromolecule (receptor) and a small molecule (ligand). This method predict the binding free ligand-binding free energy (ΔG), strength and stability (binding affinity and binding constant) of complexes using a scoring function [14]. An accurate and precise investigation of the ligand-binding free energy is tremendously critical for searching potential inhibitors.

In this work, a set of compounds originated from *P. foetida* was investigated for sEH enzyme potential inhibition activity using *in silico* approaches. Molecular docking was first used to identify promising inhibitors, "hits", based on binding affinities and docking conformation. The "hits" compounds were then further analyzed for theirs druglikeness properties. Obtained results would establish raw data for rational drug design (structure-based-drug development) of new agents with potentially better efficacy and more specificity against CVDs.

2. Materials and methods

2.1. Protein preparation

The crystal structure of soluble epoxide hydrolase (PDB ID: 4JNC) were downloaded from the Protein Data Bank archive (PDB) [15]. The protein structure was prepared using the Graphical User Interface program named Autodock Tools to produce accurate representation of amino acid residues in terms of ionization and tautomeric states [16]. Procedures of the protein preparation process included removal ofwater molecules, addition of polar hydrogen atoms, and assignment of Kollman united atom partial charges and salvation parameters. Obtained atomic coordinates of the protein were then exported into a PDBQT file which will be used for execution of AutoGrid and AutoDock.

2.2. Ligand preparation

The chemical structures of 20 compounds were visualized using Marvin software. The 3D structure of the compounds were built using Pymol 1.3r1 [17]. The energy minimization was carried out using Gabedit 2.5.0 [18]. In this study, 1-[4-methyl-6-(methylamino)-1,3,5-triazin-2-yl]-N-[2-(trifluoromethyl)benzyl]piperidine-4-carboxamide (PubChem ID: CHEMBL2392714), a well known inhibitor of sEH was selected as reference ligand.

2.3. Molecular docking using AutoDock4

A computer with configurations of Intel®CoreTM i7-9700K CPU @ 3.60 GHz, with 32 GB DDR4 RAM was used to perform docking runs. Four software packages, including PyMOL [17], Discovery Studio Visualizer [19], LigPlus [20] and Maestro [21], were used to analyze the obtained results, which describes distances of hydrogen bonds between the hydrogen and its supposed binding partner.

The operating system in which the compilation of AutoDock 4.2.6 and docking runs was carried out was Ubuntu-Linux 14.04.6 LTS. A grid box comprised of 60 × 60 × 70 points spaced by 0.130 Å was centered on the mortalin-p53 interactions site (x = -13,938, y = 25,535 and z = -14.393, respectively). The software packages that were used to prepare the binding affinity of each ligand’s atom type and perform molecular docking simulation were AutoGrid and AutoDock 4.2.6, respectively. Lamarckian genetic algorithm (LGA) was configured with following parameters: 50 runs; elitism of 1; the mutation rate of 0.02; the population size of 300; a crossover rate of 0.80; number of generations of 27,000; the energy evaluations of 50,000,000 and the root-mean-square (RMS) cluster tolerance was set to 2.0 Å in each run. From the most favored cluster, the ligand conformation for further analysis was selected on the basis of lowest free binding energy.

2.4. Druglikeness properties assessment

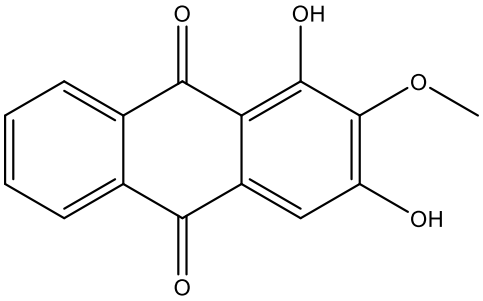
Open bioactivity prediction online server Molinspiration (https://www.molinspiration.com) and pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) were used to evaluate drug-like properties. The admetSAR database was used to calculate the absorption, distribution, metabolism, elimination and toxicity (ADMET) indices of the studied compounds (http://lmmd.ecust.edu. cn/admetsar2/).

3. Results and discussion

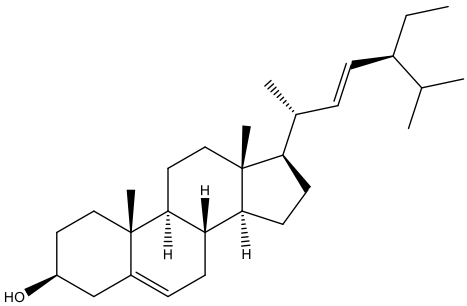
3.1. Ligand structure preparation

The three dimensional structure of studied compounds were prepared using Marvin software and PyMOL. Then, all compounds were processed for energy minimization using Gabedit 2.5.0. Due to

the nature of the compounds that are not peptides, the Gasteiger charge was added and subsequently attached nonpolar hydrogens. The determination of the main chain of the compound is done automatically by the computational tools. The energy-optimized structures are converted to pdbqt files, which are the input files for molecular docking. In total, there are 6 types of atoms that appear in the database: ['A', 'C', 'NA', 'OA', 'N', 'HD'].



Dock 1



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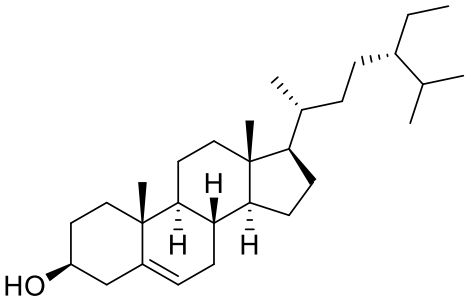

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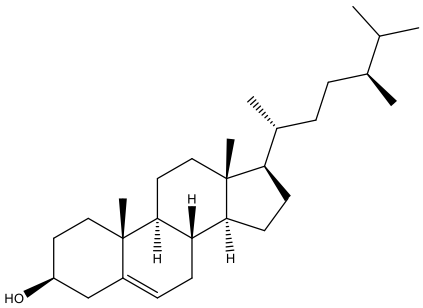
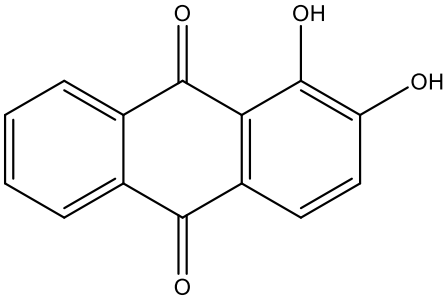
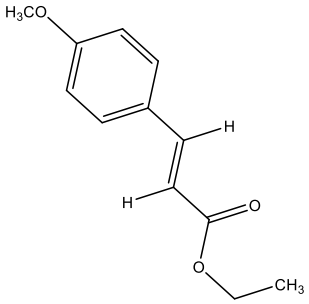


Dock 4



Dock 5



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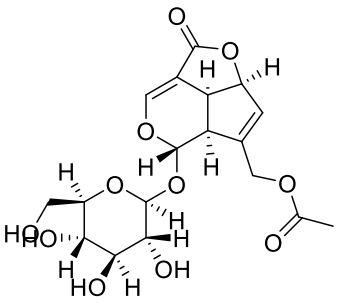

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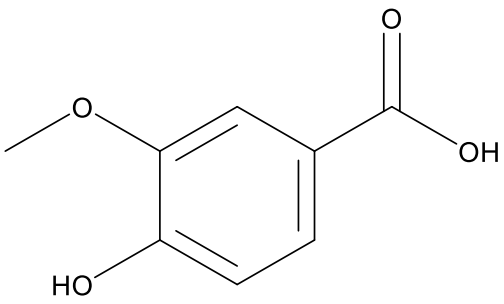

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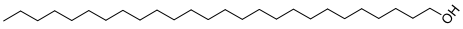

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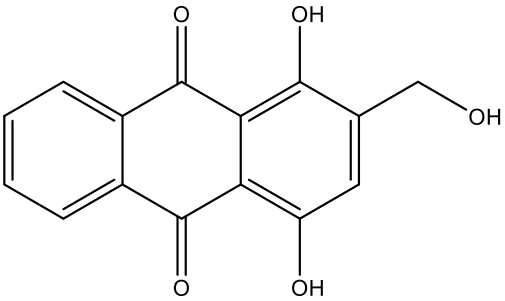

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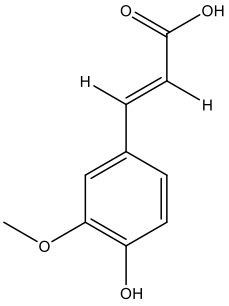

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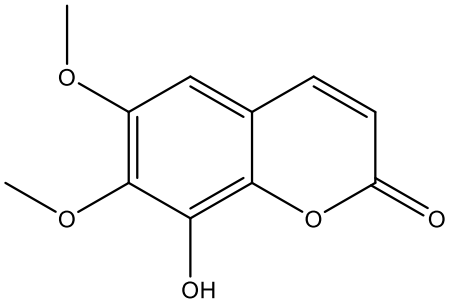

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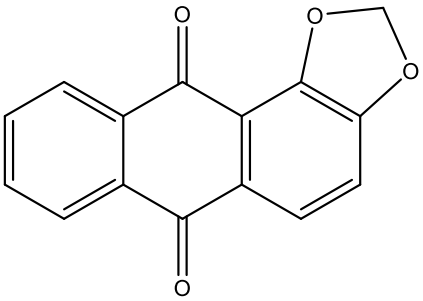
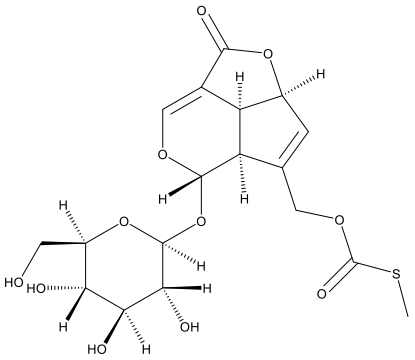


Dock14

H_3C-SH

Dock 13



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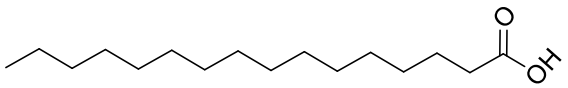

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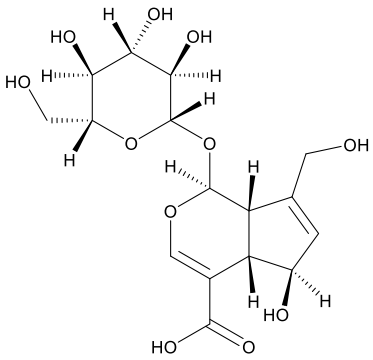

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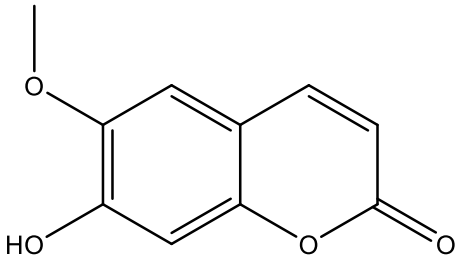

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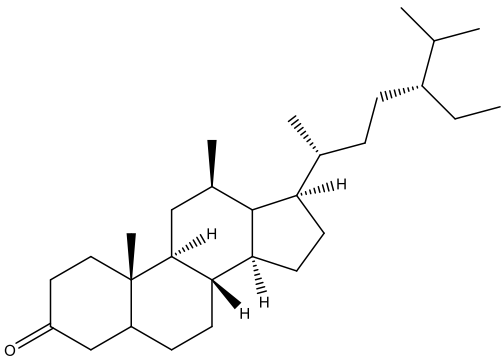
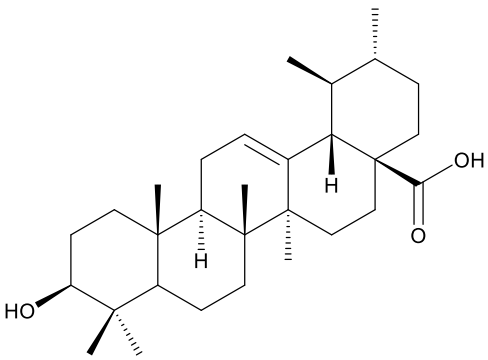
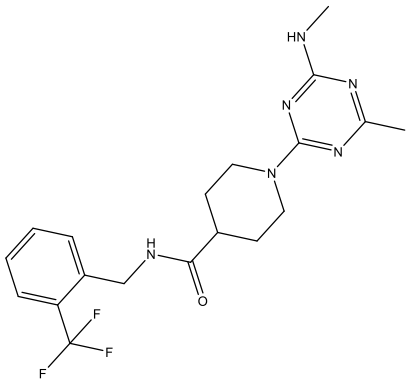


Dock 19



Dock 20



1-[4-methyl-6-(methylamino)-1,3,5-triazin-2-yl]-N-[2-(trifluoromethyl)benzyl]piperidine-4-carboxamide (CHEMBL2392714)

3.2. Molecular docking studies

The docking score of 20 compounds against sEH enzyme are presented in Table 1. According to the ranking criteria of AutoDock, the more negative docking energy suggests the higher binding affinity of the compound towards the targeted receptor [22, 23]. The obtained dock score for the reference inhibitor was -12,20 kcal/mol, thus, any molecules whose docking energies are close to this threshold would be viewed as potential inhibitors of sEH in the virtual screening stage.

Table 1. Docking score of studied compounds against soluble epoxide hydrolase (PDB ID: 4JNC)

Compound	**Binding free energy ΔG_{pred} (kcal/mol)**	**Compound**	**Binding free energy ΔG_{pred} (kcal/mol)**
Dock 1	-9,19	Dock 12	-7,30
Dock 2	-12,17	Dock 13	-2,35
Dock 3	-12,59	Dock 14	-8,42
Dock 4	-13,56	Dock 15	-10,20
Dock 5	-9,45	Dock 16	-6,38
Dock 6	-6,74	Dock 17	-9,17
Dock 7	-9,62	Dock 18	-6,96
Dock 8	-5,14	Dock 19	-13,87
Dock 9	-8,36	Dock 20	-8,10
Dock 10	-8,51	CHEMBL2392714	-12,20
Dock 11	6,16		

In general, amongst studied molecules, compound **2**, **3**, **4** and **19** were determined to exhibit high binding affinity toward sEH enzyme with the binding energy value of -12,17; -12,59; -13,56 and -13,87 kcal/mol, respectively. In which, the dock score of compound **4** and **19** far exceeds the value obtained for the reference ligand CHEMBL2392714.

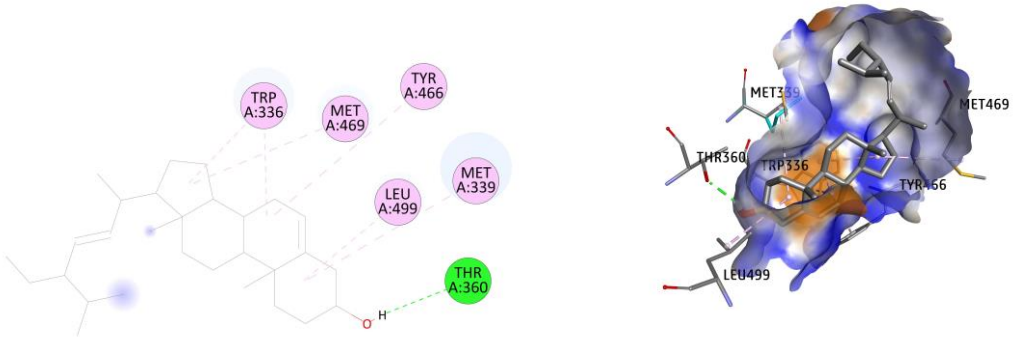
The detailed docking results of high binding affinity compounds are tabulated in table 2. Obtained data indicate that most of the essential residues which participated in constituting the active site of sEH enzyme (Phe267, Pro268, Asp335, Tyr383, Val 498, Leu499, Met503) were involved in forming interaction with reference ligand CHEMBL2392714.

Table 2. Docking results of potential compound against sEH enzyme

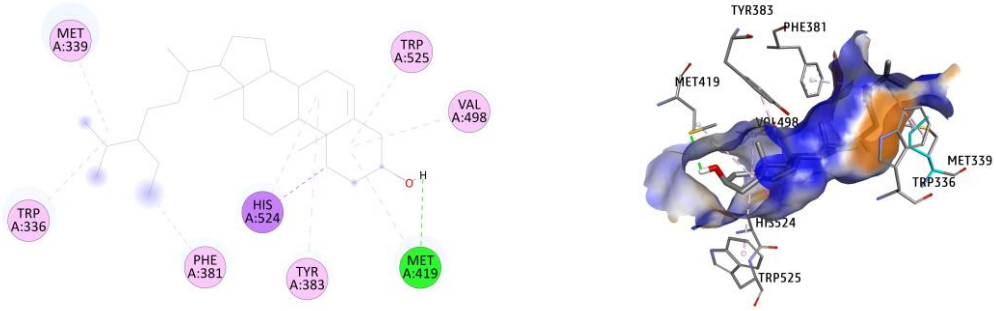
Compound	No. of Hydrogen bond	Residues participating in H-bond	Residues participating in hydrophobic interaction
Dock 2	1	Thr360	Trp336, Met339, Tyr466, Met469, Leu499
Dock 3	1	Met419	Trp336, Met339, Phe381, Tyr383, Val498, His524, Trp525
Dock 4	1	Asp335	Trp336, Met339, Ile363, Phe381, Trp473, Leu499
Dock 19	2	Tyr383, Tyr466	Trp336, Met339, Pro371, Phe381, Trp473, Leu499
CHEMBL2392714	2	Asp335, Tyr383	Phe267, Pro268, Trp336, Met339, Pro361, Ile363, Phe381, Leu408, Met419, Val 498, Leu499, Met503, His524, Trp525

Docking conformation of high ranking compounds are displayed in Figure 2. Interestingly, amongst four candidates, only compound **4** and **19** exhibit potential to inhibit sEH enzyme through direct interaction with essential residues. Compound **2** was observed to form a hydrogen bond with Thr360, on the other hand, Trp336, Met339, Tyr466, Met469, Leu499 were the key residues involved in hydrophobic interactions. Binding orientation analysis exhibited Trp336, Met339, Phe381, Tyr383, Val498, His524, Trp525 initiating the hydrophobic interaction with compound and is further stabilized through a hydrogen bond with Met419. It should be noted that all the residues that participated in hydrogen bond with comopound **2** and **3** are not recorded as an important constituent of the active site of targeted protease; therefore, these compounds are not considered as "hit" for further evaluation.

Docking conformation analysis of compound **4** revealed one hydrogen bonds with Asp335, an array of hydrophobic interactions was observed as contributed by Trp336, Met339, Ile363, Phe381, Trp473, Leu499. The hydrophobic pockets formed with compound **19** are revealed in figure 2 involving residues Trp336, Met339, Pro371, Phe381, Trp473, Leu499. The interaction is further strengthened through two conventional hydrogen bonds with Tyr383, Tyr466.



Dock 2



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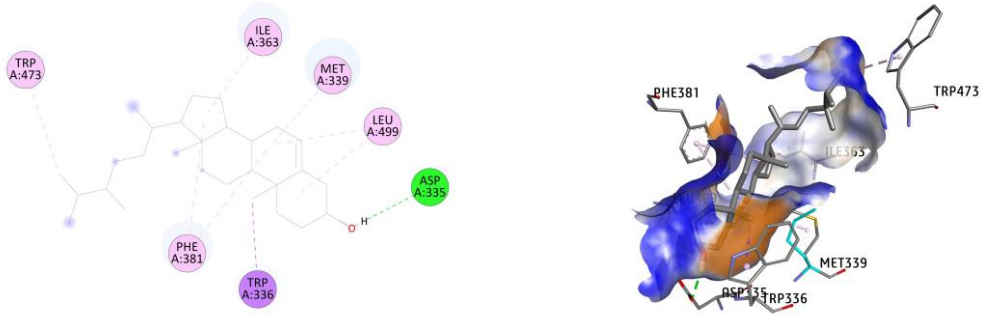
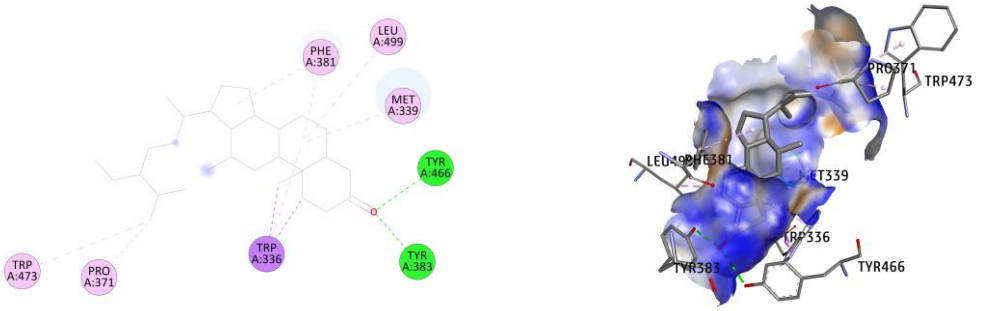


Dock 4



Dock 19

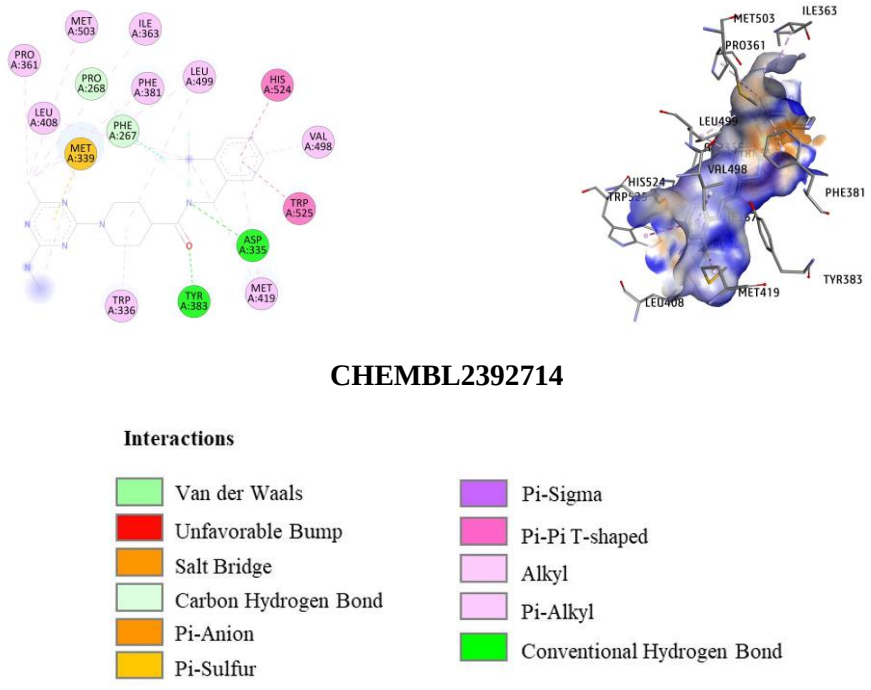


Figure 2. Interaction of studied compounds in the sEH binding site suggested by molecular docking studies

The drug-like properties of the two potential inhibitor compounds were evaluated using Lipinski's Rule of Five (Ro5) to identify suitable compounds for the next stages of drug research and development. In addition, the compounds were further evaluated for their pharmacokinetic properties and predicted toxicity using the Molinspiration and ProTox-II cheminformatic webservers (Table 3).

Table 3. ADMET index and toxicity prediction of potential inhibitors

Compound	MW	HBD	HBA	LogP	MR (cm^3/mol)	LD_{50} (mg/kg)	Toxicity prediction[a]	HIA
Dock 4	400	1	1	7.63	123.59	890	4	1.000
Dock 19	414	0	1	8.16	127.17	775	4	1.000
CHEMBL2392714	408	2	7	2.77	102.33	2000	4	1.000

[a] Toxicity ranking: 1 => 6 (High toxic to non-toxic)

The obtained results indicated that both compounds **4** and **19** were identified possessing favorable properties for oral drug development, with less than twice violations of the criteria of Lipinski's rule. The pharmacokinetic parameters and predicted toxicity data combined with the molecular docking simulation results have contributed useful information for the evaluation of potential compounds capable of inhibiting the sEH enzyme, and the druglikeness properties to conduct further studies for drug development. Calculation results show that compounds **4** and **19** are classified as less toxic (class 4), equivalent to the reference ligand CHEMBL2392714. In addition, it is estimated that compounds with good oral bioavailability will have less than 12 donor (HBD) and accept (HBA) bonds. In this

study, according to the analysis results, both compounds **4** and **19** were observed to have less than 12 HBD and HBA linkages, which met the criteria and were hypothesized to be suitable for oral drug development. In the ADMET study, one of the most important challenges for an oral drug was its movement across the intestinal epithelial barrier, which determines the rate and extent of human drug absorption and ultimately affects to drug bioavailability. According to the HIA value analysis, compounds **4** and **19** have a value of 1, which indicates that they have a high absorption capacity in the human intestinal tract.

4. Conclusions

. In this study, the computational molecular simulation and assessment of drug-like properties were used to gain insight into the interaction of 20 compounds originated from *P. foetida* on the binding site of soluble epoxide hydrolase. The obtained results show that compound **4** and **19** were identified as promising candidates based on high binding affinity and appropiate docking conformation. These contribute information on the interaction mechanism of potential inhibitors for studies to develop drugs that prevent sEH enzyme function.

Declaration of Competing Interest

The authors declare no competing interests.

Author contributions

"Conceptualization: Quang-Huan Duong, Thi Hong-Minh Pham, Anh-Hung Nguyen, ; methodology: Thi Thuy-Huong Le, Viet-Hai Ha and Ngoc-Linh Nguyen; software: Thi Thuy-Huong Le and Thi-Mien Tran; formal analysis: Panyakeo Yuen, Van-Dung Nguyen and Thi-Mien Tran; writing original draft: Quang-Huan Duong, Van-Dung Nguyen and Anh-Hung Nguyen; review and editing: Anh-Hung Nguyen. All authors have read and agreed to the published version of the manuscript."

Acknowledgments

This research was funded by Hanoi Pedagogical University 2 foundation for Sciences and Technology Development via grant number: HPU2.2022-UT-12

Additional notes; Appendix

Biography

Nguyen Anh Hung https://scholar.google.com/citations?user=XEiRcVYAAAAJ&hl=vi&oi=ao

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