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Computational assessment of targeting angiotensin-converting enzyme for hypertension management: A structure-based virtual screening approach

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Abstract

Background: Hypertension is a growing public health concern globally. The angiotensin-converting enzyme (ACE) is an enzyme that cleaves the carboxy-terminal His-Leu dipeptide from angiotensin I, yielding the potent vasopressor octapeptide, angiotensin II. ACE inhibitors are a primary treatment option for hypertension, heart failure, and myocardial infarction. However, the use of synthetic ACE inhibitors has been linked to a number of side effects. Therefore, the development of novel and safe ACE inhibitors is a need of time.

Methods: This study used a computational screening of a library of known compounds with anti-inflammatory activities against the active site of ACE using the PyRx-Python 0.8 tool to find more potent ACE inhibitors with less or no side effects. The physicochemical properties of the anti-inflammatory compounds were obtained from the Life Chemicals website.

Result: The five hits, specifically F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060, exhibited notable interactions within the ACE binding pocket and demonstrated greater binding energy compared to the control compound, Lisinopril. All of these compounds displayed favorable physicochemical characteristics and aligned to Lipinski's rule.

Conclusion: The compounds F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060 have the potential to be used as ACE inhibitors; however, further experimental validation is required to optimize them as ACE inhibitors.

Introduction

Hypertension is a formidable threat to global public health and has widespread and increasing prevalence worldwide. The prevalence of diagnosed hypertension continues to rise, with projections predicting nearly 2 billion cases by 2025 [1]. Effective post-manifestation hypertension management remains a challenge, with only a small percentage of patients achieving optimal control. Hypertension's negative consequences extend beyond its primary manifestation, increasing susceptibility to cardiovascular disorders, myocardial infarction, cerebrovascular accidents, renal impairment, intracerebral hemorrhage, end-stage organ dysfunction, and a variety of secondary pathologies [2]. These consequences not only pose a significant threat to patient mortality, but also have a substantial impact on their overall survival and life quality [3]. In addressing the negative effects of hypertension, the imperative pursuit of research and development endeavors aimed at pharmaceutical interventions takes precedence.

The renin-angiotensin system (RAS) and kallikrein-kinin system (KKS) intricately govern blood pressure (BP) regulation in vivo [4]. Renin catalyzes the conversion of angiotensinogen to the inactive Angiotensin I within the RAS, and the subsequent action of angiotensin-converting enzyme (ACE) generates Angiotensin II, which induces vascular smooth muscle activity, causing a rise in BP. Meanwhile, in the KKS, ACE acts to deactivate bradykinin, a key mediator in BP regulation via vasodilation and electrolyte regulation. Unfortunately, the use of synthetic ACE inhibitors such as captopril and enalapril are associated with some adverse effects such as coughing, allergic reactions, and elevated blood potassium levels [5]. Therefore, research into ACE inhibitors derived from natural sources is critical.

ACE inhibitors, also known as ACEIs, are frequently prescribed for the treatment of cardiovascular disorders and kidney disease. Angiotensin II, which is recognized for its strong narrowing of blood vessels and capacity to promote the release of aldosterone, is produced at an accelerated rate in the presence of ACE inhibitors. These inhibitors play a crucial role in renin-angiotensin system regulation, managing vascular tone, and offering therapeutic advantages for cardiovascular health and kidney function [6]. Although ACE inhibitors are commonly prescribed, their use is limited due to potential side effects such as kidney failure, high potassium levels in the blood, low blood pressure, and the development of a persistent wheezing sound after a single dose [7]. ACE inhibitors can benefit individuals with chronic renal failure by reducing systemic vascular resistance. It is important to mention that using this approach may lead to a reduction in filtration pressure, which can worsen negative effects on the kidneys, such as acute renal failure. These adverse effects underscore the significance of exercising caution and monitoring while administering ACE inhibitors, especially in individuals with renal impairment [8,9].

Computer-Aided Drug Design (CADD) tools have become indispensable in the field of drug discovery, influencing the development of new drugs significantly. These tools analyze and simulate the interactions between potential drug candidates and biological targets such as proteins or enzymes using computational methods [10]. The two most common methodologies in CADD are structure-based drug design and ligand-based drug design [11,12]. This study aimed to find potent ACE inhibitors by screening a library of anti-inflammatory compounds using the structure-based virtual screening (VS) approach.

Methods

Protein preparation

The structural configuration of the human ACE-lisinopril complex (PDB ID: 1O8A) was obtained from the Protein Data Bank [13]. Lisinopril is a familiar ACE inhibitor used to treat conditions such as hypertension, heart failure, and myocardial infarction [14]. By removing water and heteroatoms (lisinopril, glycine, zinc, and chloride ion) from the crystal structure using Discovery Studio 2021, it was enabled to prepare it for VS.

Compound library preparation

A collection of more than 2,900 drug-like screening compounds with anti-inflammatory properties was obtained in sdf format from the Life Chemicals website (https://lifechemicals.com/screening-libraries/targeted-and-focused-screening-libraries/anti-inflammatory-library) and was prepared accessible for screening.

Virtual screening

VS is a computational method for identifying novel drug-like compounds by utilizing large and diverse collections of chemical compound libraries [15]. In this study, VS of prepared compounds against ACE protein was carried out using PyRx-Python 0.8 tool integrated with AutoDock 4.2. The energy of all compounds was minimized using a universal force field and were converted to the Autodock-compatible ".pdbqt" format. The coordinates used were X: 41.25, Y: 34.04, and Z: 46.56.

Physiochemical properties prediction

The physicochemical properties of the selected anti-inflammatory compounds were obtained from the Life Chemicals website, where each compound was

extensively documented along with its corresponding characteristics.

Results

Anti-inflammatory drugs, like NSAIDs and corticosteroids, can have a number of side effects, such as irritated stomachs, heart problems, kidney issues, and weakened immune systems [16]. The objective of this research was to identify more effective and potentially fewer harmful therapeutics for hypertension by using computational methods to assess a collection of 2,900 drug-like compounds with anti-inflammatory activities against the ACE active site.

The PDB 3D structure of ACE was obtained and thoroughly studied to understand its structural elements. The emphasis was on analyzing its domains (distinct functional sections) and secondary structures (such as alpha helices and beta sheets) to understand its detailed molecular organization. The data indicates that a specific chain of the ACE protein, consisting of 575 amino acids (protein building blocks), was chosen for this study (Figure 1).

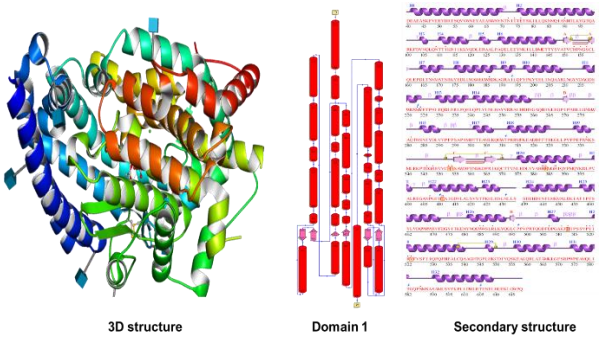

Figure 1: Structural details of the ACE protein. Domain 1 of the ACE protein demonstrates the specific structural components in greater detail. The secondary structure shows the arrangement of alpha-helices, beta-sheets, and random coils.

In this study, the active pocket of the ACE protein was identified and chosen by utilizing the inbound ligand Lisinopril as a positive control. The presence and interaction of Lisinopril in this active pocket were used as a reference or standard for further analysis and comparison with other compounds or molecules being studied. Prior to VS, the compound library was filtered using Lipinski's rule, and 2869 compounds passed the assessment and were used in the screening. Since all the compounds screened in this study had previously demonstrated anti-inflammatory properties, most of them exhibited strong binding, with many showing even better binding than Lisinopril. Table 1 presents a list of the 20 most prominent hits along with their corresponding binding energy.

S. No.	Compounds name/ID	Binding energy (Kcal/mol)
1.	F3398-2114	-10.5
2.	F0193-0245	-10.4
3.	F0163-0089	-10.2
4.	F0193-0237	-10.1
5.	F0302-0060	-10
6.	F0648-0360	-9.8
7.	F0648-0812	-9.8
8.	F3260-0904	-9.8
9.	F1838-0344	-9.6
10.	F0464-0014	-9.6
11.	F2829-0569	-9.4
12.	F5950-0114	-9.3
13.	F5871-3221	-9.3
14.	F0007-1073	-9.3
15.	F2815-0850	-9.3
16.	F5382-0976	-9.1
17.	F0007-0716	-9.1
18.	F1835-0006	-9.1
19.	F2865-1291	-8.8
20.	F1835-0306	-8.8
21.	Lisinopril (Control)	-7.8

Table 1: List of the 20 hits having greater binding energy than the control compound, Lisinopril.

Subsequent in-depth analysis and evaluation of the physicochemical characteristics were performed for the five most promising hits. The compounds F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060 showed significant interactions within the ACE binding pocket. Figure 2 depicts the binding positions of these compounds concerning the control compound within the ACE binding pocket. It shows that these compounds interact with the majority of the active residues in the ACE binding pocket.

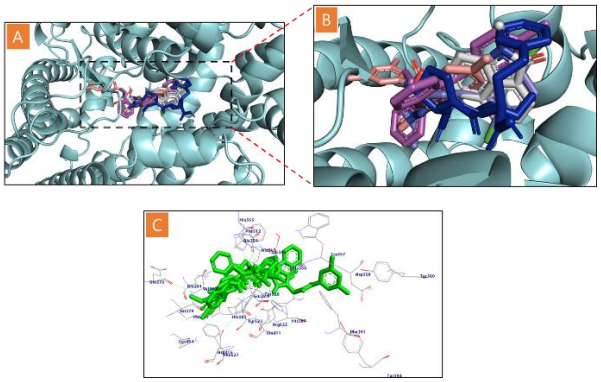

Figure 2: Binding poses of hit compounds in the binding pocket of ACE. The top 5 hits and positive control (blue color) in the pocket of ACE (A), close view (zoom) of the interaction of hit compounds with ACE (B), and interacting residues of ACE with the selected hit compounds (C).

Table 2 presents the chemical names of the top five hits, along with their physicochemical properties including Molecular Weight, clogP, TPSA, Hydrogen Acceptors and Donors, Number of Rotatable Bonds, Heavy Atom Count (HAC), and ALogP.

Further 2D and 3D interaction analyses of the chosen hits (F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060) were performed using Discovery Studio Visualizer.

Name	Chemical Name	MW	clogP	TPSA	HA	HD	RB	HAC	ALogP
F3398-2114	N-(3,5-dimethylphenyl)-2-(9-(3,4-dimethylphenyl)-3-oxopyrazolo[1,5-a][1,2,4]triazolo[3,4-c]pyrazin-2(3H)-yl)acetamide	440.5	5.96	82.83	4	1	4	33	3.976
F0193-0245	N-(4-(2,5-dichlorophenyl)thiazol-2-yl)-2-(naphthalen-1-yl)acetamide	413.32	6.39	70.23	2	1	4	27	5.83
F0163-0089	1-ethyl-N-(2-hydroxyethyl)-2-oxo-1,2-dihydrobenzo[cd]indole-6-sulfonamide	320.36	0.86	95.09	4	2	5	22	0.619
F0193-0237	N-(4-(2,5-dichlorophenyl)thiazol-2-yl)pentanamide	329.24	5.27	70.23	2	1	5	20	4.802
F0302-0060	4-(4-chlorophenyl)-N-(2-methoxyphenyl)quinazolin-2-amine	361.82	6.62	47.04	4	1	4	26	6.054

Table 2: Physicochemical properties of top five hit compounds (F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060).

The results revealed that all of the tested compounds, including the control compound, bind to a common set of amino acid residues in the ACE active site (Figure 3, and Table 3).

Compounds	Interacting residues	H-bonding residues
F3398-2114	Val380, Phe527, Tyr523, Ala354, His353, His513, Phe512, Ser355, Val518, Ala356, Tyr360, Trp357, Asp358, Phe391, Tyr394, His387, Glu411, Glu384, and His383	His353, His387, and Glu411
F0193-0245	Val518, Arg522, Glu411, Val380, His513, Tyr520, Gln281, Tyr523, Phe457, Lys454, Asp415, His353, His383, Phe527, Ala354, Ser355, Glu384, and Phe512	Glu384, Ala354, and His383
F0163-0089	His383, Val380, His513, Ser355, Ala354, Glu384, Ala356, His387, His353, Tyr523, Tyr520, Phe457, Lys454, Phe527, Glu376, and Val379	Ala354, and Glu384
F0193-0237	Tyr523, Lys454, Phe527, Asp415, His383, Phe512, His513, Val518, His353, Ser355, His387, Ala356, Glu411, Ala354, Glu384, Val380, Tyr520, Gln281, and Phe457	His383, and Ala354
F0302-0060	His387, Tyr523, Glu411, Ala356, His383, Asp415, Phe527, Val379, Lys454, Val380, His353, Ala354, Glu384, His513, Phe512, Val518, and Ser355	Tyr523, His383, and Ala354
Lisinopril (Control)	Ala354, His383, Val380, Gln281, Trp279, Asn277, Thr282, Glu376, Val379, Asp453, Asp415, Lys454, Phe527, Glu411, Phe457, Tyr520, Tyr523, Lys511, His513, Phe512, His353, and Glu384	Asn277, and His353

Table 3: Interacting residues of ACE protein with hit compounds (F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060).

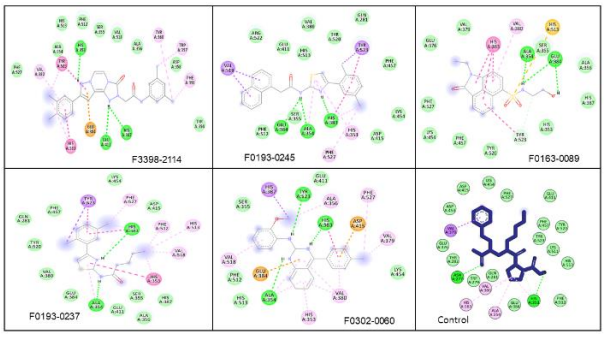

Figure 3: 2D interaction of ACE active site residues with the control and five hit compounds (F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060).

The physicochemical, pharmacokinetic, and drug-likeness properties of the selected compounds were further predicted. This analysis aimed to provide deeper insights into the characteristics of the compounds and to identify potential lead compounds with high efficacy (Table 2).

Discussion

Hypertension is defined as an increase in systemic arterial BP caused by environmental factors, polygenic heredity, and various risk factors. This condition has a significant impact on blood vessel architecture and functionality, frequently resulting in complications affecting the brain, kidneys, and heart. Furthermore, hypertension is a major risk factor for cardiovascular disorders such as coronary heart disease, left ventricular hypertrophy, and arrhythmia [17].

Hypertension management includes both lifestyle and pharmacological interventions. When combined with dietary and lifestyle changes, antihypertensive medications show significant efficacy in lowering BP and heart rate, reducing the risk of cardiovascular morbidity and mortality [18]. However, there are significant drawbacks to using these medications, such as adverse effects, increased costs, and limited accessibility in specific regions of developing countries [19]. Hence, there is a pressing need to investigate novel pharmaceutical agents, with a particular emphasis on those derived from natural sources, in order to advance the development of treatments that are not only more efficacious but also better tolerated by the patient population [20].

In this study, a collection of >2,900 drug-like compounds with anti-inflammatory properties were screened against the ACE protein. Prior to VS, the compound library was filtered using Lipinski's rule, which resulted in 2,869 compounds meeting the criteria for inclusion in the screening process. Given the anti-inflammatory properties of all compounds screened in this study, the majority exhibited strong binding affinity with the ACE protein. Based on their notable binding characteristics, five hits (F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060) were chosen for in-depth interaction analysis.

Hydrogen bonding is crucial in ligand-protein complex interactions [21, 22]. Interestingly, five of the identified hits (F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060) exhibited H-bonding with multiple ACE protein residues. F3398-2114 formed H-bonds with the ACE protein's His353, His387, and Glu411 residues, whereas F0193-0245 formed H-bonds with the Glu384, Ala354, and His383 residues. F0163-0089 H- bonded with Ala354 and Glu384 residues of the ACE protein, while F0193-0237 formed H-bonds with His383 and Ala354 residues. Furthermore, F0302-0060 exhibited H-bonding with the ACE protein's Tyr523, His383, and Ala354 residues.

In docking analysis, a high negative binding energy value indicates a strong and effective interaction between the ligand and the target protein [23-25]. Notably, the identified hits (F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060) had higher binding energy than the control compound, implying that these compounds have potent and efficient interactions with the ACE protein and may be promising lead candidates for ACE inhibitors in the management of hypertension.

Hypertension is a major threat to global public health, with a widespread and rising prevalence worldwide. ACE inhibitors are the primary treatment for hypertension and myocardial infarction. This study elucidates the molecular interactions between the known compounds (with anti-inflammatory activities) and the ACE protein. Notably, F3398-2114, F0193-0245, F0163-0089, F0193-0237, and F0302-0060 demonstrated strong binding affinity with the ACE protein and exhibited favorable physicochemical characteristics, implying that they could be tested further as anti-ACE agents for the effective management of hypertension.

Conflict of Interest

The author declare that there is no conflict of interest regarding the publication of this paper.

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