ORIGINAL ARTICLE

In Silico Molecular Docking and ADME/Tox Analysis of Quinapril Analogs as Inhibitors Against Angiotensin-Converting Enzyme 2

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ABSTRACT

The angiotensin-converting enzyme 2 (ACE2) is an important drug target for treating hypertension, heart, lung, and kidney disease. A similar human ACE homolog, named ACE2 has recently been identified and found to be an important new target for cardiorenal disease. We tried a ligand based approach to identify novel potent and selective ACE2 inhibitors. The computational prediction of screened quinapril analogs in ADME/Tox showed excellent pharmacokinetic properties with high gastrointestinal uptake, oral bioavailability, and less toxicity. Further, screened analogs of quinapril were docked using molecular docking program within binding pocket of ACE2 which resulted in low binding affinities. The outcome of this work confirms the importance of these analogs as promising drug candidates for the treatment of hypertention and cardiovascular diseases. Moreover, the finding allows for further development and synthesis of more active drug candidates by medicinal chemists and pharmaceutical scientists.

Key words: Molecular docking, angiotensin converting enzyme 2, RAS, quinapril, ADME/Tox

INTRODUCTION

Cardiovascular disorders (CVDs) are a category of heart and blood vessel diseases (CVDs). The most common cause of this is a build-up of fatty deposits on the inner walls of the blood vessels supplying the heart or brain. Strokes can also be caused by bleeding from a blood vessel in the brain or from blood clots. The leading cause of premature death and disability in humans is CVDs, and their incidence is on the increase globally. In the general population, CVDs often create a high socio-economic burden. Hyperlipidaemia, hypertension, diabetes, obesity, smoking, and lack of physical activity are well known as etiological risk factors contributing to the onset of CVDs.[1] They collectively constitute more than 90% of the CVD threats in all epidemiological studies. Pharmacological control of the renin-angiotensin process is the widely recognized first-line approach to the treatment of hypertension and CVD (RAS).[2] The RAS consists of a number of distinct regulatory components and effector peptides that promote complex vascular function regulation for both health and disease. Renin, the angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and Ang II receptors are the main components of RAS.[3] A single catalytic metallopeptidase unit is included in the ACE2 enzyme extracellular domain that shares a 42% sequence identity and a 61% sequence similarity with the ACE catalytic domain.[4] However, unlike ACE, it functions as a carboxypeptidase rather than a dipeptidase, and typical ACE inhibitors do not antagonise ACE2 activity.[5] ACE2 catalyzes the synthesis of vasodilator peptides with angiotensin 1–7 and is thus responsible for counterbalancing the effective vasoconstrictor effects of Ang II.[6-9]

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MATERIALS AND METHODS

Virtual Screening

Ligand-based virtual screening of quinapril against GPCR Ligands (ChEMBL) using SwissSimilarity web tool.[10] The screenable libraries of the SwissSimilarity tool include drugs, bioactive and commercial compounds, and millions of virtual compounds readily synthesizable from synthetic reagents commercially accessible.

ADME/Tox Screening

In silico physicochemical, pharmacokinetic, and toxicological properties of quinapril analogs were performed by SwissADME[11] web tool.

Preparation of ACE2 Structure

Inhibitor Bound Human angiotensin converting enzyme-Related Carboxypeptidase (ACE2) (PDB ID: 1R4L) was retrieved from the Protein Data Bank (https://www.rcsb.org/). All the ligands were removed and polar hydrogen added to make the structure of ACE2 prepared for molecular docking processes.

Molecular Docking

The method of molecular docking can be used to model the interaction between a small molecule and a protein at

the atomic level, which helps us to explain the behavior of small molecules at the target protein binding site and to elucidate basic biochemical processes. Screened Quinapril analogs were docked with ACE2 using MTiAutoDock (https://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/ portal.py#forms::MTiAutoDock). The most negative binding affinity score of compound chosen as candidate compound will be analyzed furthermore.

RESULTS AND DISCUSSION

In Silico ADME/Tox Screening of Quinapril Analogs

Because of ADME/Tox deficiencies, about half of the drug candidates struggled during development. A series of *in silico* ADME/Tox screens were introduced with the goal of discarding compounds during the discovery process to avoid this production failure. The ADME predictions of Quinapril analogs for passive human gastrointestinal (GI) absorption and permeation of the blood-brain barrier (BBB) are both based on the BOILED-Egg model, as are shown in table 1. The properties of human intestinal absorption are determinant of the drug production and are required to be administered orally. The blood-brain barrier (BBB) plays a significant role in drug pharmacology.[12] Carcinogenicity is a cancer-causing risk in the body. Quinapril analogs were accessed by five different rule-based filters such as Lipinski[13] filter implemented rule-of-five, Ghose *et al*.,[14] Veber *et al*.,[15] Egan *et al*.,[16] and Muegge *et al*.[17] methods, respectively, and shown in table 1. The outcome presented in Table 1 indicates that high GI absorption and strong skin permeation are observed in all of the compounds examined. At the end of the entire ADMET evaluation screening, five compounds, CHEMBL69221, CHEMBL302815, CHEMBL80220, CHEMBL305936, and CHEMBL311188, failed the drug likeliness test.

Analysis of Molecular Docking

Forty-one ADME/Tox parameters qualify Quinapril were docked in binding site of ACE2 enzyme using MTiAutoDock server. Binding energy of Quinapril analogs is shown in table 1. On analysis of binding energy of analogs, it was found that two analogs, CHEBI: 3011 and CHEMBL191751, had low binding affinity –9.06 kcal/mol and –9.70 kcal/mol with ACE2, respectively. Predicted docked complexes were analyzed through Python Molecular Viewer[18] for their interaction study, as shown in Figures 1 and 2. Quinapril

Table 1: The prediction of pharmacokinetics and drug likeliness of quinapril analogs and binding energy with ACE2

Sl. No.	ChEMBL Compound Id	GI	BBB	LogKp (Cm/s)	Lipinski	Ghose	Veber	Egan	Muegge	Binding Energy (kcal/mol)
1.	CHEMBL1592	High	No	–8.09	Yes	Yes	No	Yes	Yes	–8.42
2.	CHEMBL1214049	High	No	–7.99	Yes	Yes	Yes	Yes	Yes	–8.29
3.	CHEMBL198316	High	No	–6.53	Yes	Yes	Yes	Yes	Yes	–7.55
4.	CHEMBL78429	High	No	–6.53	Yes	Yes	Yes	Yes	Yes	–7.99
5.	CHEMBL86475	High	No	–6.49	Yes	Yes	Yes	Yes	Yes	–6.96
6.	CHEMBL1212952	High	No	–8.33	Yes	Yes	Yes	Yes	Yes	–7.76
7.	CHEMBL2114222	High	No	–6.49	Yes	Yes	Yes	Yes	Yes	–6.81
8.	CHEMBL422417	High	No	–6.49	Yes	Yes	Yes	Yes	Yes	–7.66
9.	CHEMBL89388	High	No	–6.49	Yes	Yes	Yes	Yes	Yes	–5.92
10.	CHEMBL571492	High	No	–8.50	Yes	Yes	Yes	Yes	Yes	–8.00
11.	CHEMBL313198	High	No	–6.47	Yes	Yes	Yes	Yes	Yes	–5.55
12.	CHEMBL2177187	High	No	–5.43	No	No	Yes	Yes	No	–7.21
13.	CHEMBL1214050	High	No	–8.40	Yes	Yes	Yes	Yes	Yes	–7.43
14.	CHEMBL315037	High	No	–6.49	Yes	Yes	Yes	Yes	Yes	–7.99
15.	CHEMBL485576	High	No	–8.85	Yes	Yes	Yes	Yes	Yes	–7.56
16.	CHEMBL572543	High	No	–7.84	Yes	No	Yes	No	Yes	–8.91
17.	CHEMBL2207128	High	No	–7.11	Yes	Yes	No	Yes	Yes	–6.08
18.	CHEMBL419499	High	No	–6.67	Yes	Yes	Yes	Yes	Yes	–8.88
19.	CHEMBL87005	High	No	–6.67	Yes	Yes	Yes	Yes	Yes	–6.64
20.	CHEMBL201765	Low	No	–7.44	No	No	No	No	No	–7.41
21.	CHEMBL191751	Low	No	–8.75	Yes	No	No	No	No	**–9.70**
22.	CHEBI:39484	High	No	–7.51	Yes	Yes	Yes	Yes	Yes	–6.66
23.	CHEBI:72723	High	No	–8.81	Yes	Yes	Yes	Yes	Yes	–8.02
24.	CHEBI:74075	Low	No	–9.28	Yes	Yes	Yes	Yes	Yes	–7.34
25.	CHEBI:8025	High	No	–7.90	Yes	Yes	Yes	Yes	Yes	–8.82
26.	CHEBI:3011	High	No	–7.99	Yes	Yes	Yes	Yes	Yes	**–9.06**

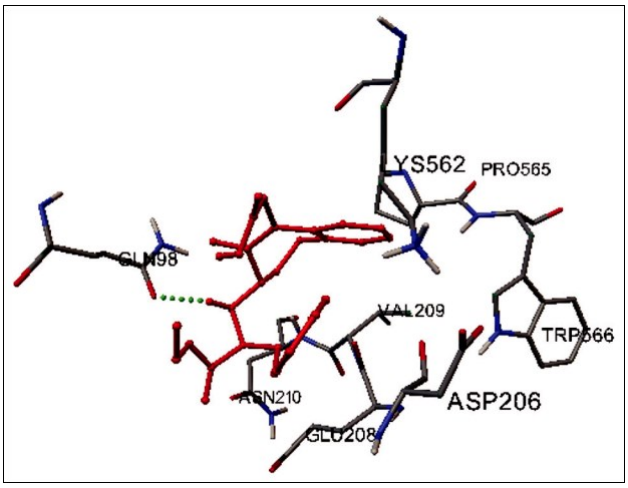

Figure 1: Docking pose of quinapril analog CHEBI:3011 in binding site of angiotensin-converting enzyme 2. One H-bond was formed between amino acid GLN98 of protein with compound, respectively. Hydrogen bonds are represented with spherical line

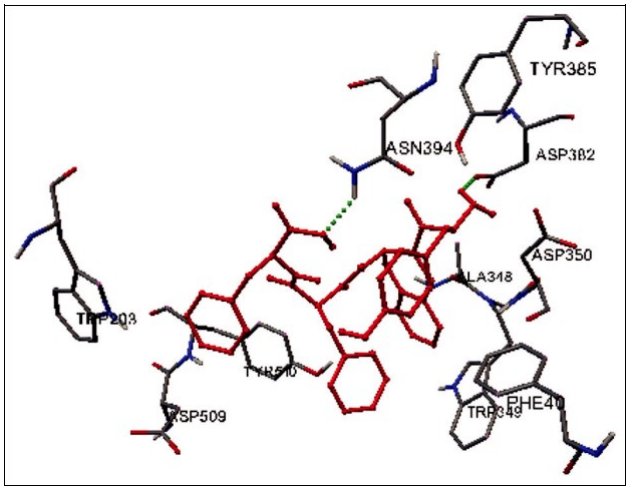

Figure 2: Docking pose of quinapril analog CHEMBL191751 in binding site of angiotensin-converting enzyme 2. Two H-bonds were formed between amino acid, ASP382 and ASN394 of protein with compound, respectively. Hydrogen bonds are represented with spherical line

analogs were represented in sticks and balls model. Quinapril analog CHEBI: 3011 interacted with residues LYS562, PRO565, TRP566, VAL209, GLN98, ASN210, GLU208, and ASP206. Quinapril analog CHEMBL191751 interacted with residues TYR385, ASP382, ASP350, ALA348, TRP349, ASN394, TYR510, ASP509, TRP203, and PHE40. Interacting residues were represented in lines in Figures 1 and 2.

CONCLUSION

The current research utilizes computer-based virtual screening to identify ACE2 inhibitors that are required for CVD treatment. We identified two quinapril analogs, CHEBI: 3011 and CHEMBL191751, from several million chemical structures and a series of steps of logical refinement, including similarity search, ADME properties, and molecular docking, as good inhibitors for further experimental research.

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