ORIGINAL ARTICLE

In silico molecular docking and ADME/pharmacokinetic prediction studies of Candesartan analogs as inhibitors of angiotensin-converting enzyme 2

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ABSTRACT

A pivotal mediator in the development of hypertension and related cardiovascular diseases is the renin-angiotensin system (RAS). This plays a key role in controlling the blood pressure and maintaining a balance between fluid and salt. Angiotensin-converting enzyme 2 (ACE2) is a part of RAS system and is a potential therapeutic target for cardiovascular disease and hypertension. ACE2 inhibitors are appropriate drugs for the treatment of cardiovascular diseases and related pathophysiology. The Candesartan analogs demonstrated excellent pharmacokinetic properties with strong gastrointestinal absorption, orally bioavailable and less toxic in *in silico* ADME and drug-like prediction. Screened Candesartan analogs were docked with binding pocket of ACE2 protein using molecular docking tool, which show low binding affinity. The findings of this work affirm the importance of these analogs as promising lead candidates for the treatment of cardiovascular diseases that could assist medicinal chemists and pharmaceutical practitioners in further developing and synthesizing more potent candidate drugs.

Keywords: Molecular docking, ADME/Tox, angiotensin-converting enzyme 2, renin-angiotensin system, candesartan

INTRODUCTION

Cardiovascular diseases are a category of heart and blood vessel disorders (CVDs). Typically, heart attacks and strokes are acute events that are caused primarily by a blockage that prevents blood from circulating in the heart or brain. 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. CVDs are the number 1 cause of death globally: More individuals die annually from CVDs than from any other cause. An estimated 17.9 million individuals died in 2016 from CVDs, representing 31 percent of all global deaths. About 85% of these deaths occur due to heart attacks and strokes.[1] High blood pressure is one of the most significant risk factors for cardiovascular disease, which is the primary cause of mortality.[2] Around 54% of strokes and 47% of coronary heart attacks are caused by elevated BP globally.[3] Hypertension is a common health issue, increasing in prevalence with age and affecting 65% of those around 60 years of age.[4,5]

Pharmacological control of the renin-angiotensin pathway is the widely recognized first-line approach to the treatment of hypertension and cardiovascular disease renin-angiotensin system (RAS).[6] Renin, the angiotensin-converting enzyme (ACE), angiotensin II (Ang II), and Ang II receptors are the main components of RAS.[7] The RAS consists of a number of distinct regulatory components and effector peptides that promote complex vascular function regulation for both health and disease. There is a single catalytic metallopeptidase unit in the ACE2 enzyme extracellular domain that shares a 42 percent sequence identity and a 61 percent sequence similarity to the ACE catalytic domain.[8] However, unlike ACE, it functions as a carboxypeptidase rather than a dipeptidase and does not antagonise ACE2 activity with conventional ACE inhibitors.[9] ACE2 catalyzes the synthesis of vasodilator peptides with angiotensin 1 to 7 and is thus responsible for balancing the potent vasoconstrictor effects of Ang II.[10,11] This counterbalancing property of ACE2 is proposed to be significant in the development of novel pharmacotherapy against hypertension and related cardiovascular diseases.[12,13]

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MATERIALS AND METHODS

Virtual Screening

Ligand-based virtual screening of Candesartan against GPCR Ligands (ChEMBL) database using online tool Swisssimilarity.[14]

ADME/Tox Screening

A drug with good oral absorption must comply the following parameters: molecular weight of less than 500 Da, logP (lipophilicity) of less than five; maximum of five groups of hydrogen donors and maximum of ten groups of accepters binding intestinal permeability and consisting of the first steps toward good oral bioavailability. *In silico* physicochemical, pharmacokinetic, and toxicological

properties of Candesartan analogs were performed by SwissADME[15] 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/). To make the ACE2 structure ready for molecular docking processes, all the ligands were removed and polar hydrogen added.

Molecular Docking

Using MTiAutoDock (https://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py#forms::MTiAutoDock), screened Candesartan analogs were docked with ACE2. The most negative binding affinity score of compound chosen as candidate drug compound will be analyzed furthermore.

RESULTS AND DISCUSSION

In Silico ADME/Tox Screening of Candesartan Analogs

Due to 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 for the passive human gastrointestinal (GI) absorption and blood-brain barrier (BBB) permeation of Candesartan analogs are both based on the BOILED-Egg model, as shown in Table 1. Human intestinal absorption properties are a determinant of the development of drugs and must be administered orally. In drug pharmacology, the BBB plays a significant role.[16] Carcinogenicity is a risk in the body that causes cancer. Five distinct rule-based filters such as Lipinski[17] filter implemented rule-of-five, Ghose *et al.*,[18] Veber *et al.*,[19] Egan *et al.*[20] and Muegge *et al.*[21] methods, respectively, were accessed by Candesartan analogs and shown in Table 1. The result presented in Table 1 indicates that high GI absorption and good skin permeation are present in all of the compounds investigated. Five compounds, CHEMBL69221, CHEMBL302815, CHEMBL80220, CHEMBL305936, and CHEMBL311188 failed the drug likeliness examination at the end of the complete ADMET assessment screening.

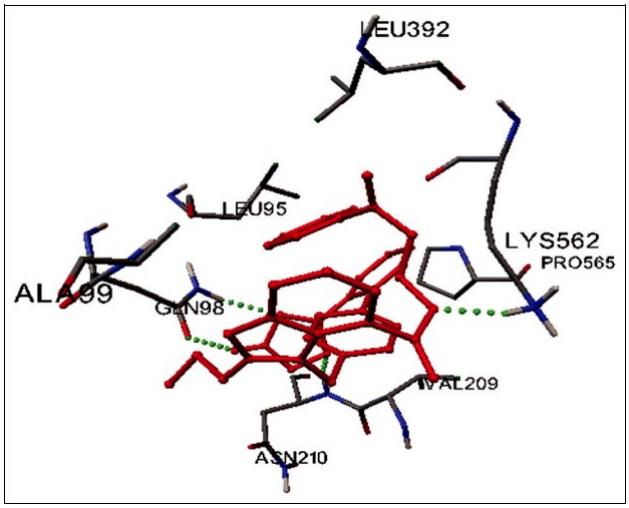

Figure 1: Docking pose of Candesartan analog CHEMBL77294 in binding site of angiotensin-converting enzyme 2. Three H-bonds were formed between amino acid, LYS562, ASN210, and GLN98 of protein with compound, respectively. Hydrogen bonds are represented with spherical line

Analysis of Molecular Docking

Fifty-five Candesartan analogs qualify ADME/Tox parameters out of 60 and were docked in binding site of ACE2 enzyme using MTiAutoDock server. Table 1 showed the binding energy of Candesartan analogs. Binding energy analysis of complexes showed that three analogs, CHEMBL77294, CHEMBL76686, and CHEMBL71545 had a low binding affinity of –10.81 kcal/mol, –9.45 kcal/mol, and –9.34 kcal/ mol, respectively, with ACE2. Predicted docked complexes were analyzed through Python Molecular Viewer[22] for their interaction study shown in Figures 1-3. In the sticks and balls

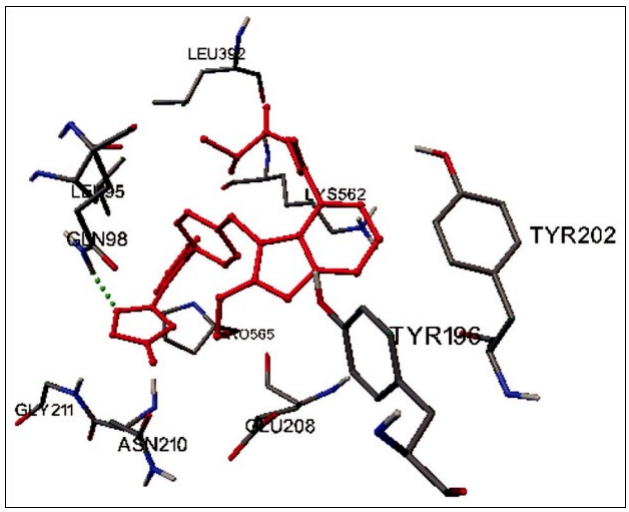

Figure 2: Docking pose of Candesartan analog CHEMBL76686 in binding site of angiotensin-converting enzyme 2. One H-bond was formed between amino acid GLN98 of protein with compound, respectively. Hydrogen bonds are represented with spherical line

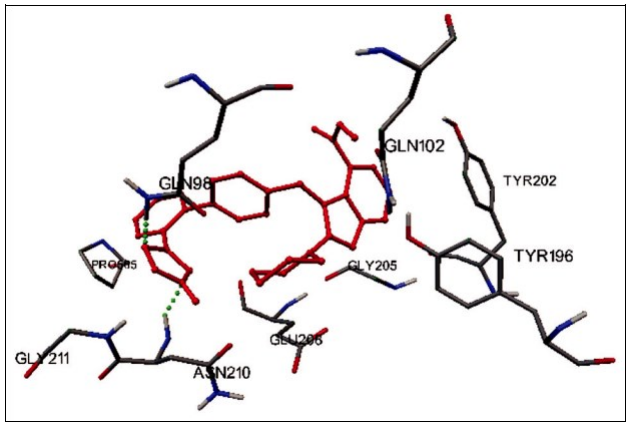

Figure 3: Docking pose of Candesartan analog CHEMBL71545 in binding site of angiotensin-converting enzyme 2. Two H-bonds were formed between amino acid, ASN210, and GLN98 of protein with compound, respectively. Hydrogen bonds are represented with spherical line

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

Sl. No.	GPCR Ligands (ChEMBL)	GI	BBB	LogKp (Cm/s)	Lipinski Rule	Ghose Rule	Veber Rule	Egan Rule	Muegge Rule	Binding energy (kcal/mol)
1	CHEMBL303955	High	No	-5.76	Yes	Yes	Yes	Yes	Yes	–7.5
2	CHEMBL308911	High	No	-6.05	Yes	Yes	Yes	Yes	Yes	–8.4
3	CHEMBL309084	High	No	–6.22	Yes	Yes	Yes	Yes	Yes	–7.25
4	CHEMBL304360	High	Yes	–6.05	Yes	Yes	Yes	Yes	Yes	–6.94
5	CHEMBL303264	High	No	–6.05	Yes	Yes	Yes	Yes	Yes	–7.2
6	CHEMBL71954	High	No	–5.73	Yes	Yes	Yes	Yes	Yes	–6.55
7	CHEMBL328296	Low	No	–6.46	Yes	No	Yes	No	Yes	–8.24
8	CHEMBL302973	Low	No	–5.84	Yes	No	Yes	Yes	Yes	–6.65
9	CHEMBL308884	High	No	–5.90	Yes	Yes	Yes	Yes	Yes	–8.05
10	CHEMBL69221	Low	No	–5.70	No	No	Yes	No	No	-
11	CHEMBL302815	High	No	–5.43	Yes	No	Yes	Yes	No	-
12	CHEMBL68622	High	No	–5.44	Yes	No	Yes	Yes	No	–8.33
13	CHEMBL71038	High	No	–6.08	Yes	Yes	Yes	Yes	Yes	–7.78
14	CHEMBL71550	High	No	–5.77	Yes	No	Yes	Yes	Yes	–8.54
15	CHEMBL69144	High	No	–6.74	Yes	Yes	Yes	Yes	Yes	–7.05
16	CHEMBL69522	High	No	–6.06	Yes	Yes	Yes	Yes	Yes	–8.91
17	CHEMBL68494	High	No	–6.57	Yes	Yes	Yes	Yes	Yes	–7.08
18	CHEMBL71384	Low	Yes	–5.93	Yes	Yes	Yes	No	Yes	–7.59
19	CHEMBL77294	Low	No	–5.46	No	No	No	No	No	**–10.81**
20	CHEMBL77473	Low	No	–6.26	No	No	No	No	Yes	–8.32
21	CHEMBL77050	Low	No	–5.68	No	No	No	No	No	–7.26
22	CHEMBL76850	Low	No	–6.04	No	No	No	No	Yes	–6.83
23	CHEMBL69154	High	No	–5.83	Yes	Yes	Yes	Yes	Yes	–7.64
24	CHEMBL433099	High	No	–5.68	Yes	Yes	Yes	Yes	Yes	–7.86
25	CHEMBL76752	Low	No	–5.68	No	No	No	No	No	–7.47
26	CHEMBL308949	Low	No	–6.01	No	No	No	No	Yes	–8.55
27	CHEMBL76686	Low	No	–5.69	No	No	No	No	No	**–9.45**
28	CHEMBL76150	Low	No	–5.52	No	No	No	No	No	–7.88
29	CHEMBL308290	Low	No	–5.46	No	No	No	No	No	–8.18
30	CHEMBL68732	High	No	–6.01	Yes	No	Yes	Yes	Yes	–8.22
31	CHEMBL303170	High	No	–6.50	Yes	Yes	Yes	Yes	Yes	–7.73
32	CHEMBL305190	Low	No	–5.75	Yes	Yes	No	Yes	Yes	–8.36
33	CHEMBL67636	High	No	–5.44	Yes	No	Yes	Yes	No	–7.98
34	CHEMBL57242	High	Yes	–5.99	Yes	Yes	Yes	Yes	Yes	–7.74
35	CHEMBL310622	Low	No	–4.88	No	No	No	No	No	–8.29
36	CHEMBL302520	High	No	–6.09	Yes	Yes	Yes	Yes	Yes	–7.82
37	CHEMBL70074	High	No	–5.67	Yes	Yes	Yes	Yes	Yes	–8.07
38	CHEMBL292914	Low	No	–5.70	Yes	No	Yes	Yes	Yes	–7.50
39	CHEMBL69124	High	Yes	–5.52	Yes	No	Yes	Yes	Yes	–7.71
40	CHEMBL307861	Low	No	–5.79	No	No	No	No	No	–7.62
41	CHEMBL80220	Low	No	–5.84	No	No	No	No	No	-
42	CHEMBL308651	Low	No	–6.27	Yes	Yes	Yes	Yes	Yes	–7.11
43	CHEMBL302127	High	No	–8.55	Yes	Yes	Yes	Yes	Yes	–7.66
44	CHEMBL307128	High	No	–6.71	Yes	Yes	Yes	Yes	Yes	–7.93
45	CHEMBL305936	Low	No	–5.50	No	No	No	No	No	-
46	CHEMBL311188	High	No	–5.04	Yes	No	Yes	Yes	No	-
47	CHEMBL69236	Low	No	–6.10	Yes	No	Yes	No	Yes	–6.10
48	CHEMBL309348	Low	No	–5.20	No	No	No	No	No	–8.69

(Contd...)

Table 1: *(Continued)*

Sl. No.	GPCR Ligands (ChEMBL)	GI	BBB	LogKp (Cm/s)	Lipinski Rule	Ghose Rule	Veber Rule	Egan Rule	Muegge Rule	Binding energy (kcal/mol)
49	CHEMBL309377	Low	No	–5.44	No	No	No	No	No	–8.28
50	CHEMBL298632	High	Yes	–5.36	Yes	No	Yes	Yes	No	–7.68
51	CHEMBL68597	High	No	–6.20	Yes	Yes	Yes	Yes	Yes	–8.10
52	CHEMBL344546	Low	No	–5.99	Yes	No	Yes	No	Yes	–5.91
53	CHEMBL340612	High	Yes	–5.44	Yes	Yes	Yes	Yes	Yes	–8.88
54	CHEMBL304772	Low	No	–5.47	Yes	No	Yes	No	No	–7.08
55	CHEMBL307018	Low	No	–5.50	No	No	No	No	No	–8.78
56	CHEMBL71545	High	No	–5.83	Yes	No	Yes	Yes	Yes	**–9.34**
57	CHEMBL68516	Low	No	–5.06	Yes	No	Yes	Yes	No	–5.94
58	CHEMBL151436	Low	No	–5.70	Yes	No	Yes	No	No	–7.27
59	CHEMBL70947	Low	No	–6.03	Yes	No	Yes	No	Yes	–6.79
60	CHEMBL5778	High	No	–6.16	Yes	Yes	Yes	Yes	Yes	–8.23

GI: gastrointestinal absorption, BBB: Blood-brain barrier

model, Candesartan analogs were depicted. Candesartan analog CHEMBL77294 interacted with residues LEU392, LEU95, PRO565, LYS562, VAL209, ASN210, GLN98, and ALA99. Candesartan analog CHEMBL76686 interacted with residues LEU392, PRO565, LEU95, LYS562, GLY211, ASN210, GLU208, GLN98, TYR196, and TYR202. Candesartan analog CHEMBL71545 interacted with residues TYR202, GLY205, PRO565, GLU208, GLY211, ASN210, GLN98, GLN102, and TYR196. Interacting residues were represented in lines in Figures 1-3.

CONCLUSION

Current research uses computer-based virtual screening to identify inhibitors of ACE2 for the treatment of cardiovascular disease. Three Candesartan analogs, CHEMBL77294, CHEMBL76686, and CHEMBL71545, were identified from several chemical structures and a sequence of rational refinement steps, including similarity search, ADME properties, and molecular docking, as possible inhibitors for further experimental testing.

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