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Discovery of a potent angiotensin converting enzyme inhibitor via virtual screening

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ABSTRACT

Prompted by the prominent role of angiotensin converting enzyme (ACE) in hypertension, heart failures, myocardial infarction and diabetic nephropathy, we have attempted to discover novel ACE inhibitors through ligand-based virtual screening. Molecular docking method and rigorously validated model was utilized to search a natural compounds database. Finally, 36 compounds were randomly selected and subjected to in vitro ACE kinase inhibitory assay using fluorescence assays method. The results showed that three compounds (Licochalcone A, Echinatin and EGCG) have strong potential to be developed as a new class of ACE inhibitors. Further chemical modification via fragment modifications guided by structure and ligand-based computational methodologies can lead to discover better agents as potential clinical candidates.

Angiotensin converting enzyme (ACE), a type of peptide enzyme, could convert angiotensin-I to angiotensin-II.[1] Angiotensin-II is associated with many cardiovascular diseases such as hypertension, atherosclerosis, hyperlipidemia, and diabetes.[2] Thus, ACE is an ideal target to treat cardiovascular diseases, and some inhibitors targeting ACE have been treated the diseases at the first line therapy, such as Captopril, Enalapril and Lisinopril.[3] However, there are some limitations in clinic for the synthetic ACE inhibitors, because of their undesirable side effects, such as persistent cough, angioedema, renal failure, and postural hypotension.[4–6] Therefore, more efforts are made for safe and effective drug development.

Plant play an important role in healthcare.[7] About more than 50 percent of FDA-approved drugs were natural products or directly derived.[8] Moreover, a large number of studies found that Traditional Chinese medicine (TCM) and Chinese medicine extract effectively inhibited the activity of ACE.[9,10] Therefore, herbal natural products could be a chemical library for ACE inhibitors.[11] Virtual screening has been successful in prioritizing large chemical libraries to identify experimentally active compounds.[12] Methodologies used in virtual screening such as molecular docking and scoring showed a promising predictive power.[12,13] In this study, molecular docking has been utilized for the development of more natural ACE inhibitors.

As a starting point, a data set of 58,147 natural compounds was obtained from Traditional Chinese Medicine Network Pharmacology Intelligent Information Platform (TCMN),[14,15] and fourteen drugs against ACE were chosen from DrugBank (Version 5.0), such as Captopril, Perindopril, Rescinnamine, Fosinopril, Benazepril, Enalapril, Lisinopril, Moexipril, Quinapril, Ramipril, Trandolapril, Spirapril, Cilazapril and Enalaprilat.[16] LigPrep's ligand preparation protocol was used to generate different tautomeric, stereochemical and ionization variants of the small molecules along with energy minimization and flexible filtering.[17]

The crystal structures of ACE were chosen from RCSB Protein Data Bank (http://www.rcsb.org/pdb/home/home.do) by the following criteria[15]: 1. Organism: Homo sapiens. 2. Resolution $\leq$ 2.5 Å. 3. The crystal structure must contain ligand. 4. The ligand should be a classical drug. Finally, two crystal structures were obtained: one is 1UZF (Ligand: Captopril),[18] and the other is 1O86 (Ligand: Lisinopril).[3] Captopril, design by rational drug design approach, is the first ACE inhibitor for hypertension.[19] Lisinopril is the third ACE inhibitor (after Captopril and Enalapril) and is used primarily in treatment of high blood pressure, heart failure, and after heart attacks.[20] As we all know, cross docking is an approach to find the best structures among multiple structures available for a target protein.[21,22] Therefore, the best crystal complex was selected for future study by the method. Protein preparation wizard workflow was applied to prepare the crystal complex structure before receptor grid was generated.[23,24] The active site

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Table 1
RMSD calculated between bioactive and docking conformations.

PDB ID	Lisinopril (PDB code 1O86)			Captopril (PDB code 1UZF)		
	Mean ± SD (Å)	Max	Min	Mean ± SD (Å)	Max	Min
1O86	1.266 ± 0.262	1.896	0.874	1.341 ± 0.478	1.821	0.614
1UZF	1.499 ± 0.138	1.715	1.284	1.261 ± 0.539	1.786	0.537

was defined by the ligand of ACE complex. Flexible docking was then performed using Glide 5.0.[24–27] The molecules were docked into the binding site with the extra precision (XP) mode. Best pose was output on the basis of Glide score and the protein-ligand interactions. Root-mean-square deviation (RMSD) between the bioactive and docking conformations showed that 1O86 was the most suitable one (Table 1). Not only the crystal ligand in 1O86, but the other one was also well docked, which was indicated by the differences mean RMSD values of the same ligand.

Virtual screening approaches by docking reflect ligand-receptor binding process directly. The majority of scoring functions are indeed capable of predicting binding affinities of active compounds.[28,29] In this study, compounds with docking score value greater than 5.270 (the minimum docking score of Captopril) were screened against the crystal structure of ACE. Generally, only docking score is not reliable enough to use it the sole criterion.[30] Therefore, it was essential to consider the real interaction between ligands and targets. In this study, the stereo representations of interaction of Lisinopril or Captopril with ACE were analysis by Discovery Studio 3.0.[31] Fig. 1 showed the binding modes of Lisinopril, Captopril and their docking conformations at ACE active sites. Residues Tyr520, Lys511 and Gln281 in ACE protein were formed

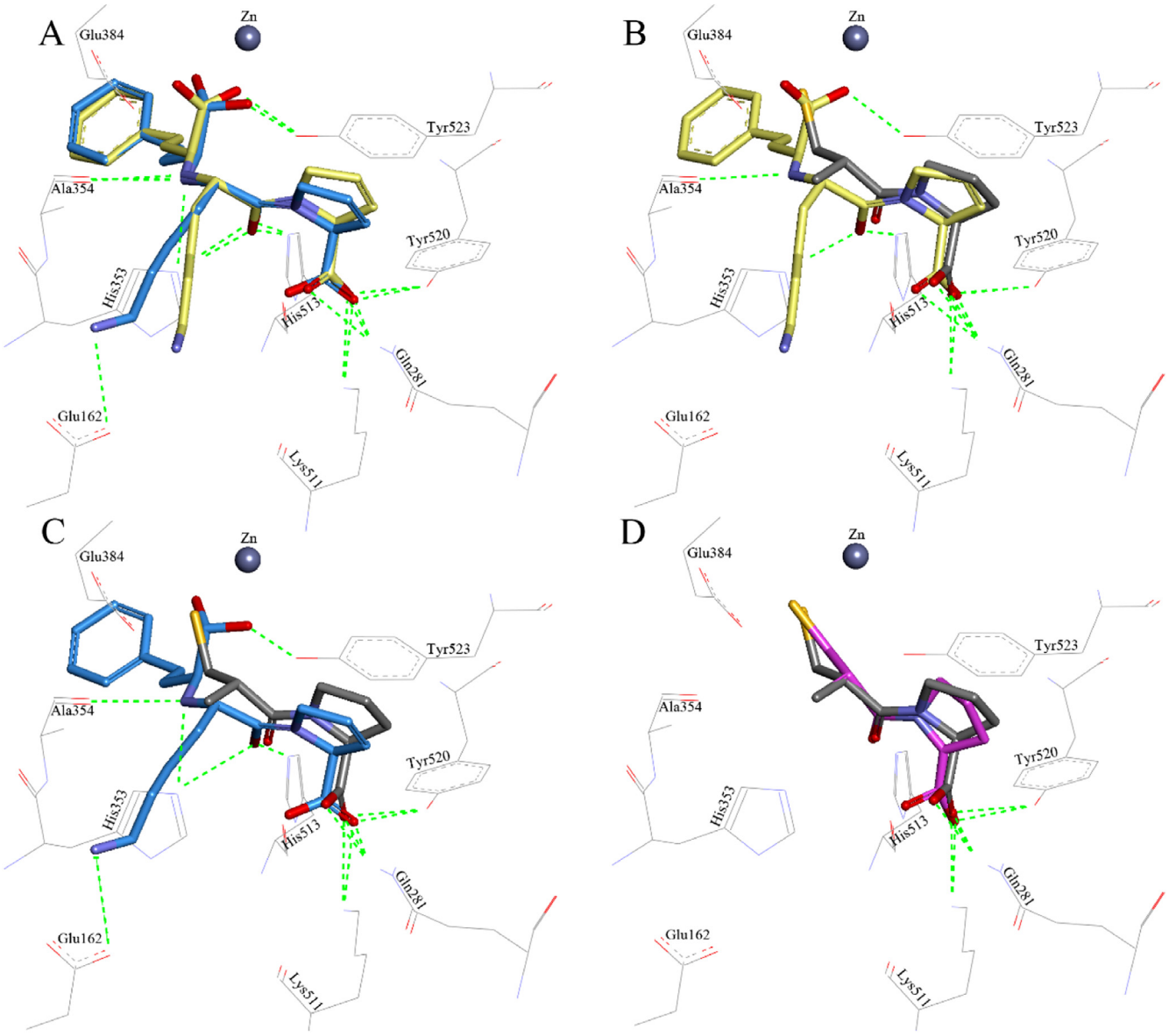

Fig. 1. Stereo representations of interaction for ACE with Lisinopril and Captopril (PDB code 1O86). Lisinopril is shown in yellow, and Captopril in purple. The docking conformation of Lisinopril (RMSD = 0.874, Gscore = −12.086) and Captopril (RMSD = 0.614, Gscore = −5.881) are shown in cyan and gray, respectively. The figure was drawn with Discovery studio visualizer 4.5.[32]