

TDPBP Derivative Aiding Liquid-Phase Synthesis Strategy and ACE Inhibitory Structure-activity Relationship of Anti-SARS Octapeptide

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Abstract: The tri(4'-diphenylphosphonyloxybenzoyl phenyl) phosphate (TDPBP) derivatives were designed and developed as C-terminal supports to aid the greener and high-efficient liquid-phase peptide synthesis (LPPS) without the need of unrecyclable resin and chromatographic separation, whereby the anti-SARS octapeptide (**2**) (AVLQSGFR) was synthesized with TDPBP-OH support via Fmoc chemistry and support-aided precipitation (SAP) technology. Furthermore, the ACE inhibition and the inhibitory structure-activity relationship (SAR) between the synthetic C-terminal amidated derivate (**1**), anti-SARS octapeptide (**2**) and its alanine-scanning sequence analogues (**3**) to (**9**) were systematically studied by HPLC analysis and 3D-QSAR via molecular docking.

Introduction

More and more attention from pharmaceutical scientists has been given to the development of peptide-based drugs.[1] Compared with small molecule drugs, peptide-based drugs display outstanding edges in affinity, specificity, and metabolic toxicity.[2] Therefore, the innovation of novel peptide-based new drugs or new strategies for peptide-based drug preparation is of considerable significance.[3]

To date, the raw materials of peptide-based drugs were mainly derived from expensive biological extraction technology or chemical pathway with the solid-phase peptide synthesis (SPPS) strategy.[4] For chemical synthesis, SPPS can significantly simplify the cumbersome synthetic processing of peptides. However, SPPS requires expensive and unrecyclable resin as necessary supports.[5] The peptide elongation process requires excessive use of amino acids to participate in the coupling due to the heterogeneous reaction. Besides, the resins attached peptide need a large number of solvents to wash for each step, which leads to an increase in process mass intensity (PMI: the ratio of the entire mass of all raw materials over the mass of target products).[6] Hence, it is challenging to implement large-scale and atomic economic chemical peptide synthesis and preparation.

For homogeneous phase reaction, the soluble polymer supports, such as PEG-modified anchors,[7] multi-attachment sites poly(norbornene)-derived anchor,[8] globular multi-sites anchor,[9] were developed as alternative soluble resin supports. Next, the soluble small molecule supports, such as the OH-Bzl[Bzl(OC₁₈)₃]₃ anchor,[10] the hydrophobic benzyl anchors,[11] the diphenylmethyl-derived anchors,[12] and the N-phosphonyl and BndppOH protecting groups[13] were developed to achieve the equivalent conversion synthesis.

Unwieldy to prepare the supports themselves were extremely adverse to the extensive long-chain peptides synthesis. Also, it was hard to achieve greenness and atomic economy for peptide production.

Based on our group's recent studies regarding TFP, TBP, and DDK derivative supports for resin-free liquid-phase peptide synthesis (LPPS),^[14] we further modified and improved the structure of the above supports. By introducing low-polarity and easily crystallizable group (OPOPh₂) that allows the entire supports molecule to form sizeable aromatic ring system, and effectively lessening the polarity of the molecular system, we successfully acquire a series of new tri (4'-diphenylphosphonyloxybenzoylphenyl) phosphate (TDPBP) derivatives as greener peptide-synthesis supports (GPS). (**Figure 1**). The modified TDPBP supports can perform large-scale and atomic economic liquid-phase Fmoc strategy peptide synthesis in high yields, and effectively obviate the gelation phenomenon of peptide sequences rich in Phe, Val, and Ala residues during the peptide chain extension process.

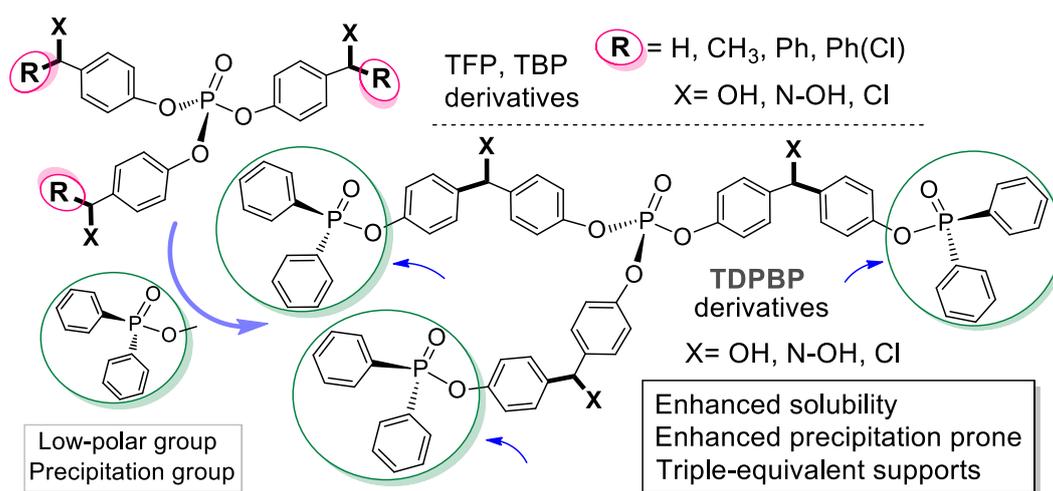


Figure 1. Structure modification of the TBP, TFP and DDK derivatives.

Severe coronavirus infections broke out worldwide in 2019 and 2003, which posed a grave threat to the safety of human life,^[15] necessitating the development of effective

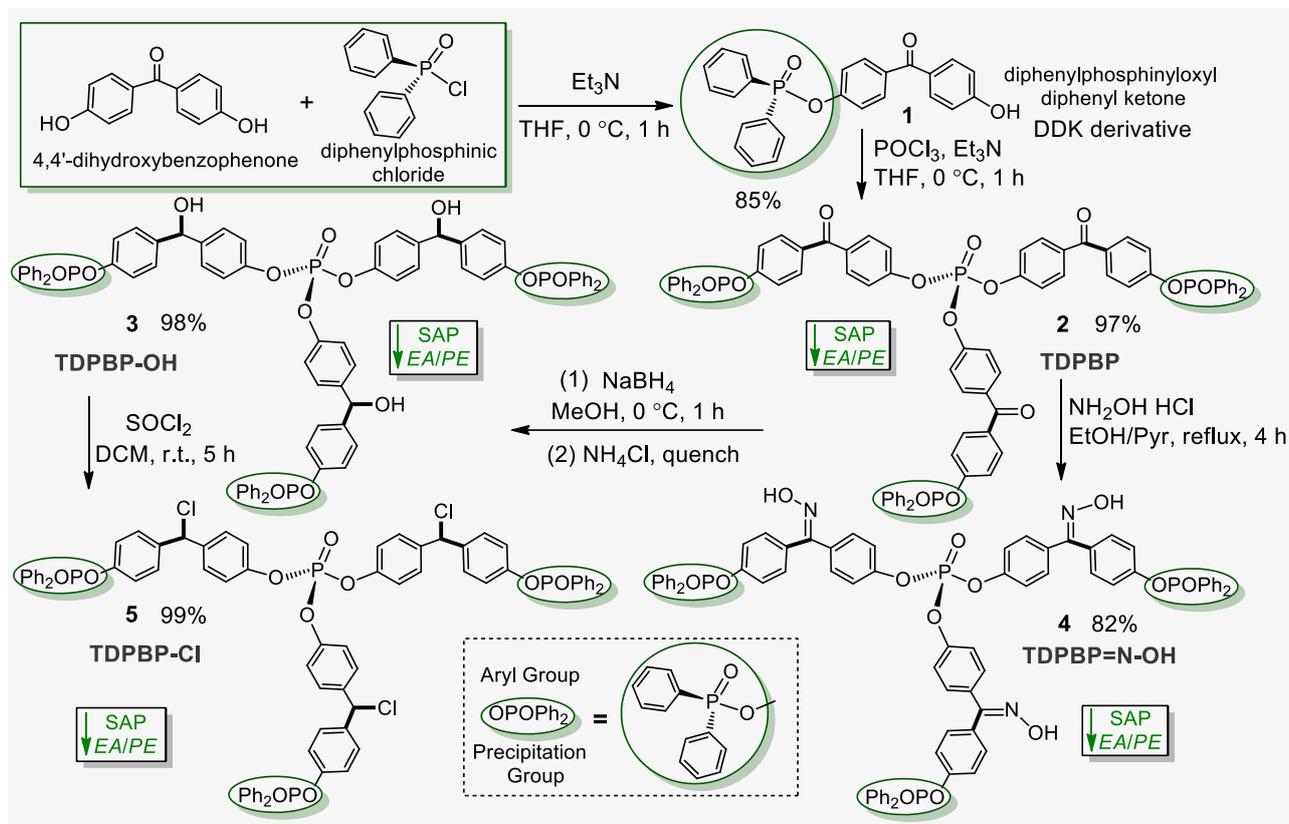
peptide-based antiviral drugs against Covid-19 and SARS-CoV for future latent coronavirus reoccurrence.[15, 16] Meanwhile, the new strategies for peptide-based drugs preparation are also of great significance. The AVLQSGFR octapeptide has been reported to have manifest anti-SARS virus activity.[17] The molecular docking studies of the octapeptide to SARS-CoV M^{pro} based on the three-dimensional structure of the main proteinase in SARS coronavirus have indicated that the anti-SARS octapeptide was bound to the SARS proteinase through six hydrogen bonds, which will further provide a solid foundation for conducting peptide-based drug development against the global outbreak Covid-19 epidemic.[16]

Hence, the anti-SARS octapeptide (**2**) AVLQSGFR containing easily gelation amino acids (Ala, Val, Phe) was selected as the template peptide sequence to verify the superb applicability of the TDPBP derivative support, ensured by realizing a new resin-free, atomic economic, large-scale and green liquid-phase synthesis strategy of anti-SARS octapeptide.

Next, we systematically plumbed the ACE inhibitory activity and the structure-activity relationship (SAR) of anti-SARS octapeptide (**2**) and its alanine-scanning sequence analogues. Furthermore, The 3D-QSAR of C-terminal amidated derivate (**1**), anti-SARS octapeptide (**2**) and its alanine-scanning sequence analogues were investigated as well via molecular docking, and found the potent ACE inhibitory activity of octapeptide AVLQSGFR, which proves that the octapeptide (**2**) is a peptide-based molecule with multiple physiological functions such as inhibition against not only SARS coronavirus main proteinase, but also ACE. This finding may lay a foundation for further understanding the molecular mechanism of how to prevent SARS COV-2 from infecting the human body through its receptor ACE.

Results and discussion

Design and synthesis of TDPBP derivative supports. A high-yield and convenient synthetic route for TDPBP derivatives was demonstrated in **Scheme 1**. The starting material 4,4'-dihydroxybenzophenone was treated with one equivalent Ph_2POCl to afford the intermediate product **1** in 85% yield. Next, three equivalent **1** was processed with POCl_3 to obtain the TDPBP intermediate **2** in 97% yield. Then, **2** was reduced by NaBH_4 to attain the TDPBP-OH support **3** in 98% yield. Afterwards, **2** continued to react with SOCl_2 to derive TDPBP-Cl support **5** in 99% yield. Lastly, **2** reacted with $\text{NH}_2\text{OH}\cdot\text{HCl}$, affording the TDPBP=N-OH support **4** in 82% yield. The TDPBP supports, with high solubility in the medium such as DCM and EA, could be precipitated in EA/PE solvents.

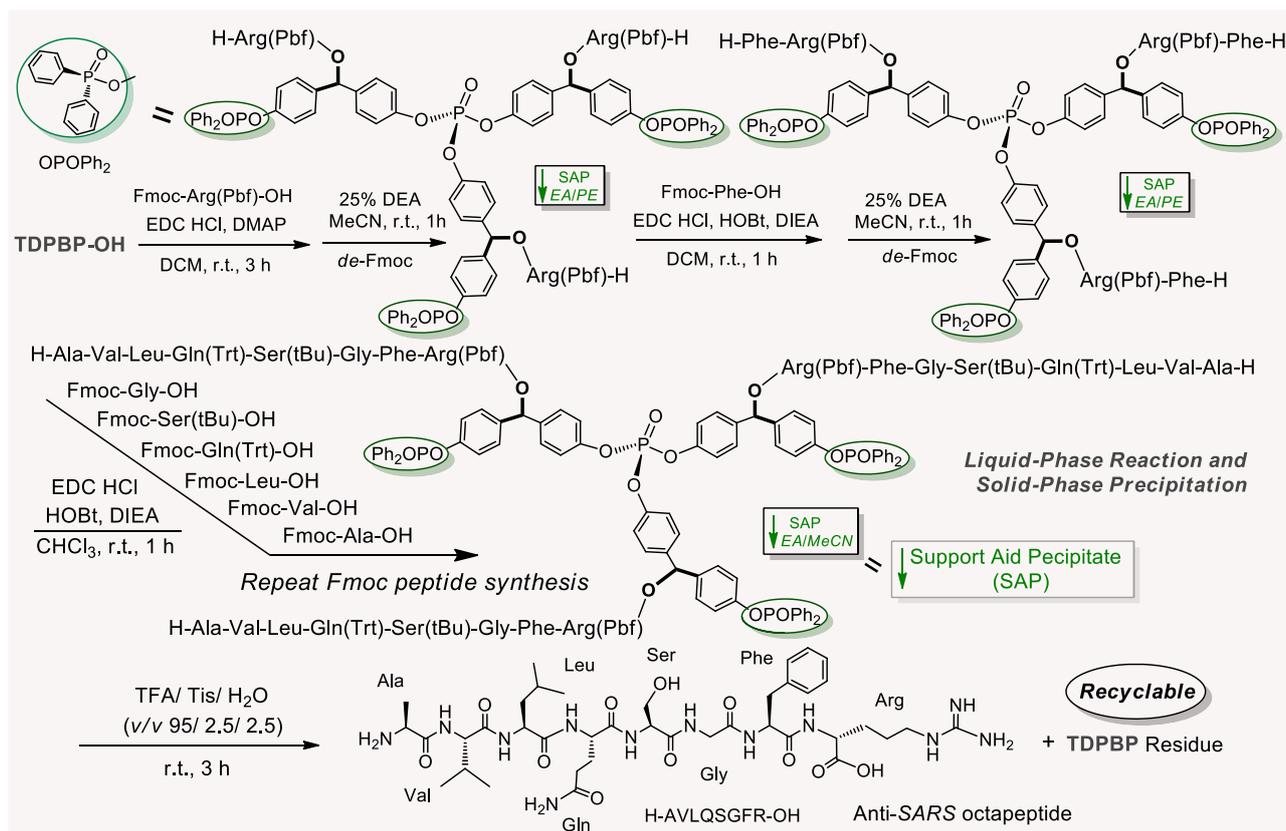


Scheme 1. Synthesis of TDPBP Derivatives as Greener Peptide-synthesis Supports (GPS).

Synthesis of anti-SARS octapeptide. As we expected, TDPBP derivatives still exhibit specific acid-base stability, that was, the coupling product of TDPBP-OH with amino acids was stable in base (25% DEA in MeCN) condition, while the coupling product of TDPBP=N-OH with amino acids was relatively stable in acid (25% TFA in DCM) condition. Therefore, we selected the TDPBP-OH support to conduct the synthesis of anti-SARS octapeptide AVLQSGFR by Fmoc strategy. (**Scheme 2**)

First, three equiv Fmoc-Arg(Pbf)-OH with more substantial steric hindrance was loaded on the TDPBP-OH support via the EDC·HCl/DMAP coupling system. During the coupling process, there was no decrease in yield courtesy of the space crowding, attested by 97% yield of the coupling product [Fmoc-Arg(Pbf)-O]₃-TDPBP in this step, while the coupling time was extended to 3h. The *de*-Fmoc process was carried out under the base condition (DEA/MeCN, *v/v* 1:3), and the *de*-Fmoc, with the yield of 99%, was directly coupled with the following amino acid Fmoc-Phe-OH without further purification to derive the [Fmoc-Phe-Arg(Pbf)-O]₃-TDPBP in 98% yield via the EDC·HCl/HOBt/DIEA coupling system. For the next step, we continued extending the peptide chain to afford the TDPBP-OH attached octapeptide intermediate product [Fmoc-Ala-Val-Leu-Gln(Trt)-Ser(*t*Bu)-Gly-Phe-Arg(Pbf)-O]₃-TDPBP with 61% total yield. It is worth noting that when the peptide chain was extended to the 7th amino acid, Fmoc-Val-OH, a decrease in the solubility of the solution system was invoked, and the reaction solvent changed to chloroform, the precipitation reagent changing to EA/MeCN or EA/MeOH system. Nevertheless, the TDPBP-OH attached octapeptide products were obtained still in high yields.

Next, the shearing reagents system TFA/Tis/H₂O (v/v/v, 95:2.5:2.5), was used to cleave the octapeptide chain from the TDPBP-OH support, the side-chain Pbf, Trt and *t*Bu protecting groups were removed at the same time. In this way, we successfully afford the target anti-SARS octapeptide (**2**) AVLQSGFR in 95% yield.



Scheme 2. The General Synthetic Route of Anti-SARS octapeptide (**2**) AVLQSGFR.

Structural stability of anti-SARS octapeptide (2). The preliminary molecular structural stability analysis for the minimum energy and the number of intramolecular hydrogen bonds of the anti-SARS octapeptide (**2**) indicate that the steric energy of anti-SARS octapeptide (**2**) was -39.895, with six hydrogen bonds in the molecule, relatively stabilizing the molecular structure of anti-SARS octapeptide (**2**). Presented as a linear peptide with many bends in the main chain, the bend is not smooth at Phe-2, Leu-6, Val-7. (see **Figure S9** in the SI)

In vitro ACE inhibitory evaluation. Herein, the HPLC analysis method was used to evaluate the in vitro ACE inhibition of anti-SARS octapeptide (**2**) H-AVLQGFR-OH and its amide octapeptide (**1**) H-AVLQGFR-NH₂. The size of inhibitory activity was calculated by the detection of the content of generated Hip (Hippuric acid: the decomposition product of Angi simulants Hippury-L-Histidyl-L-Leucine (HHL)) after adding the control group captopril, anti-SARS octapeptide and amide octapeptide. The results show that the inhibition rate of anti-SARS amide octapeptide (**1**) varies significantly within the test concentration range. Anti-SARS octapeptide (**2**) and the positive control captopril have significant inhibitory effects on ACE. The IC₅₀ of anti-SARS octapeptides (**2**) and amide octapeptide (**1**) were 34 μmol·L⁻¹ and 240 μmol·L⁻¹, respectively, which indicates that the C-terminal amidation of octapeptide has reduced the ACE inhibitory activity.[\[18\]](#) (See **Figure S5** in the SI)

Structure-activity relationship (SAR) studies of ACE inhibitory peptides[\[19\]](#) illuminate that the interaction of different peptide substrates with ACE was significantly affected by the C-terminal tripeptide sequence. ACE tends to bind with C-terminal hydrophobic amino acid, N-terminal aliphatic amino acid or competitive inhibitor, and the positive charge of the guanidine group on the C-terminal Arg can increase the ACE inhibitory activity of peptides. The hydrophilic-hydrophobicity of peptides is also a pivotal factor that affects ACE inhibitory.

The C-terminal of the H-AVLQSGFR-OH sequence contains aromatic amino acids Phe (F) and Arg (R) with guanidine group, and the N-terminal AVL of the chain are aliphatic amino acids with excellent hydrophobicity. These were consistent with the principle of the structure-activity relationship of ACE inhibitory peptides, which is the leading reason for the prominence of ACE inhibitory activity of the sequence.

In vitro gastrointestinal protease tolerance study. The gastrointestinal protease tolerance of anti-SARS octapeptide (**2**) was studied by simulating the gastrointestinal tract in vitro. After the digestion of anti-SARS octapeptide (**2**) by pepsin for 3h, the difference of ACE inhibitory was not significant, compared with the undigested control group. However, after the digestion of anti-SARS octapeptide (**2**) by trypsin for 3 h, the ACE inhibitory activity was significantly different from that of the control group (**Figure 2A** and **2B**).

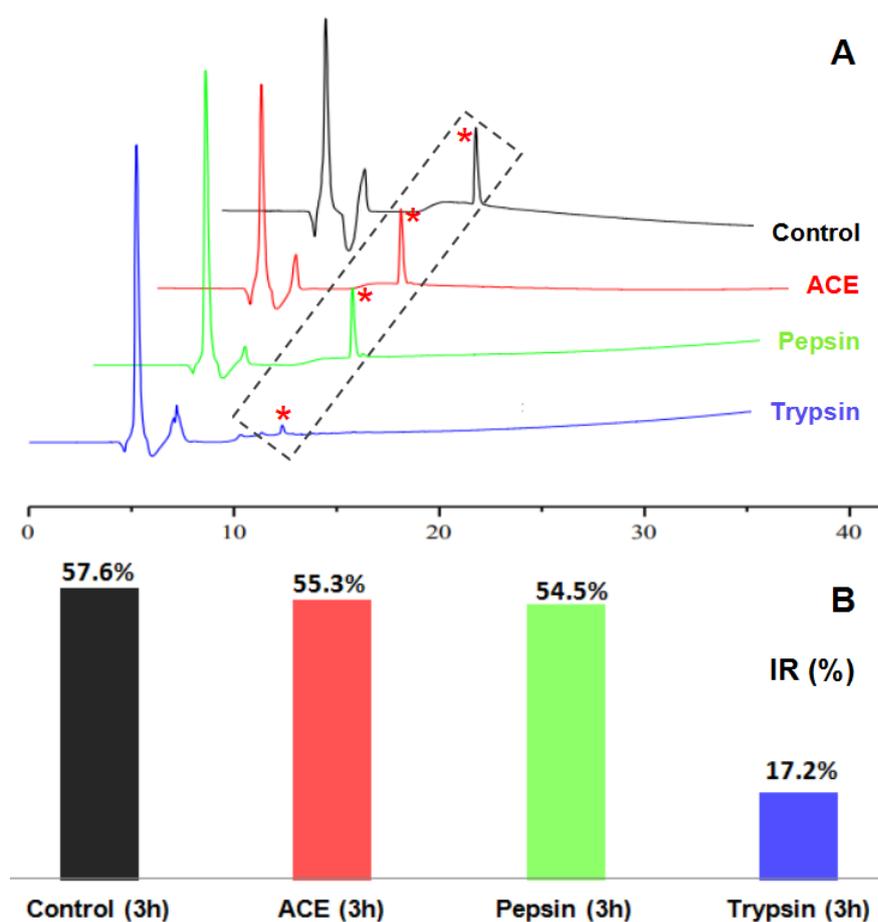


Figure 2. A: HPLC analysis of octapeptide (**2**) before and after ACE treatment and in vitro digestive. Control group; ACE treat for 3 h group; Pepsin digestion for 3 h group; Pepsin digestion for 3h and further trypsin digestion 3h group. **B:** The ACE inhibitory rate of octapeptide (**2**) after gastrointestinal enzyme digestion.

The anti-SARS octapeptide (**2**) can tolerate the pepsin effect in the gastrointestinal tract, and the ACE inhibitory remained almost unchanged before and after digestion. However, its tolerance of the trypsin effect lacks, primarily in that octapeptide (**2**) sequence contains arginine (R) residue, the Asp in the active centre of trypsin is conducive to binding the positively charged Arg. Therefore, the trypsin can hydrolyze the Arg formed peptide, suggesting that anti-SARS octapeptide (**2**) cannot be directly absorbed and utilized by oral administration and then participate in the hypotensive process with high activity.

Temperature and ACE effect on the stability of anti-SARS octapeptide (2). Anti-SARS octapeptide (**2**) was treated under different temperatures, 20 °C, 40 °C, 60 °C, 80 °C, and 100 °C separately for 2h, followed by the test of inhibited ACE activity. The results portrait the subtle change of ACE inhibitory of anti-SARS octapeptide (**2**) with different temperatures, boasting excellent thermal stability within 100°C. (See **Figure S7** in the SI)

Then, we researched the effect of ACE itself on the activity of octapeptide (**2**). Before and after treating octapeptide (**2**) with ACE, the inhibition rate changed slightly, the difference in inhibitory activity was not significant, which indicates that octapeptide was a real inhibitor and will not be affected by ACE itself while maintaining the original activity of anti-SARS octapeptide (**2**). (See **Figure S8** in the SI)

Inhibition mechanism study of anti-SARS octapeptide (2). ACE inhibitory peptides play a role in lowering blood pressure by inhibiting ACE activity in vivo. The inhibitory effect on ACE was divided into three types: [20] the competitive inhibition type; the non-competitive inhibition type; the mixed inhibition type. So, the inhibition kinetics was applied to study the inhibition mechanism of anti-SARS octapeptide (**2**). According to the amount of Hip produced

(decomposed by HHL substrate after treating with ACE with different concentrations) per minute, the reaction speeds V_0 of octapeptide (**2**) with different concentration were calculated pursuant to the Lineweaver-Burk equation as follow (**Equation 1**). Based on the reciprocal of the reaction rate ($1/V_0$) and substrate concentration ($1/[S]$), we derived the Lineweaver-Burk line (**Figure 3**), the slope of the line being K_m/V_{max} , and the intercept being $1/V_{max}$. The type of inhibition of peptides is contingent on K_m and V_{max} . In general, if V_{max} changes significantly, while K_m maintains a specific value, the type of inhibition of ACE was non-competitive, otherwise the opposite.

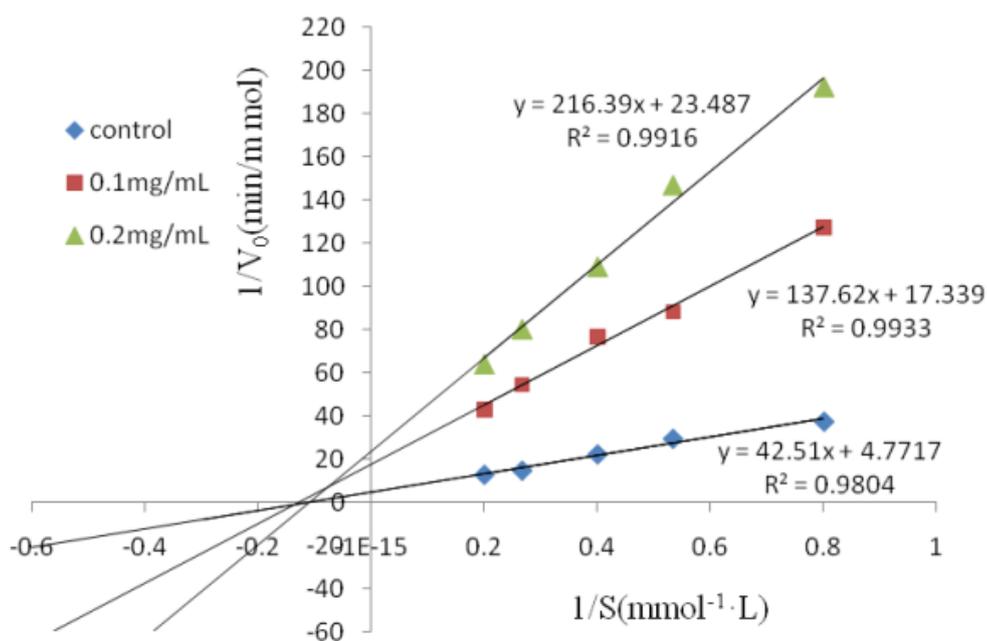


Figure 3. Lineweaver-Burk plot ACE activity in the presence of octapeptide (**2**) at different concentration.

According to the linear equations in **Figure 3**, V_{max} of the control group, octapeptide (**2**) ($0.1 \text{ mg}\cdot\text{mL}^{-1}$) group, and octapeptide (**2**) ($0.2 \text{ mg}\cdot\text{mL}^{-1}$) group were 42.58, 57.67, 209.57 $\mu\text{mol/L min}$, respectively, K_m were 9.22, 7.94, 8.91 $\text{mmol}\cdot\text{L}^{-1}$, respectively, which proves that

V_{max} changes tremendously, while K_m only changes slightly. The result indicates that the type of ACE inhibitor was non-competitive.

$$\frac{1}{V} = \frac{K_m}{[S]} \cdot \frac{1}{V_{max}} + \frac{1}{V_{max}} \quad (1)$$

ACE inhibitory structure-activity relationship of anti-SARS octapeptide and its Alanine scanning analogues. The ACE inhibitory activities of the octapeptide analogues (3) to (9), which were the alanine scanning sequences of anti-SARS octapeptide (2), were evaluated. The results showed the ACE inhibition rates of octapeptides (2) to (9) with different concentrations. The results of **Figure 4** and **Figure S10** in the SI reveal that the inhibition rates of octapeptides (3) to (6) at various concentrations on ACE were similar to that of anti-SARS octapeptide (2), while the inhibition rates of (7), (8), and (9) on ACE were significantly lower than that of octapeptide (2). That meant, the ACE inhibitory activity obviously declined after the Gln (Q), Leu (L) and Val (V) in the octapeptide sequence H-AVLQSGFR-OH was replaced by Ala (A), respectively. However, the ACE inhibitory activity changed little after the C-terminal arginine (R), Phe (F), Gly (G) and Ser (S) was replaced by Ala (A), respectively. The results indicate that V, L, and Q residues in the anti-SARS octapeptide (2) sequence were indeed important for ACE inhibition. The structure-activity relationship of ACE inhibitory peptides suggests that ACE tends to bind with a substrate that contains a hydrophobic amino acid at the C-terminus (F) and an aliphatic amino acid at the N-terminus. The positive charge of the guanidinium group can increase ACE inhibitory activity.^[19] However, in this experiment, it was proved that the C-terminal hydrophobic amino acid (F) and guanidinium-containing Arg (R) exert little effect on ACE inhibitory activity of anti-SARS octapeptide (2).

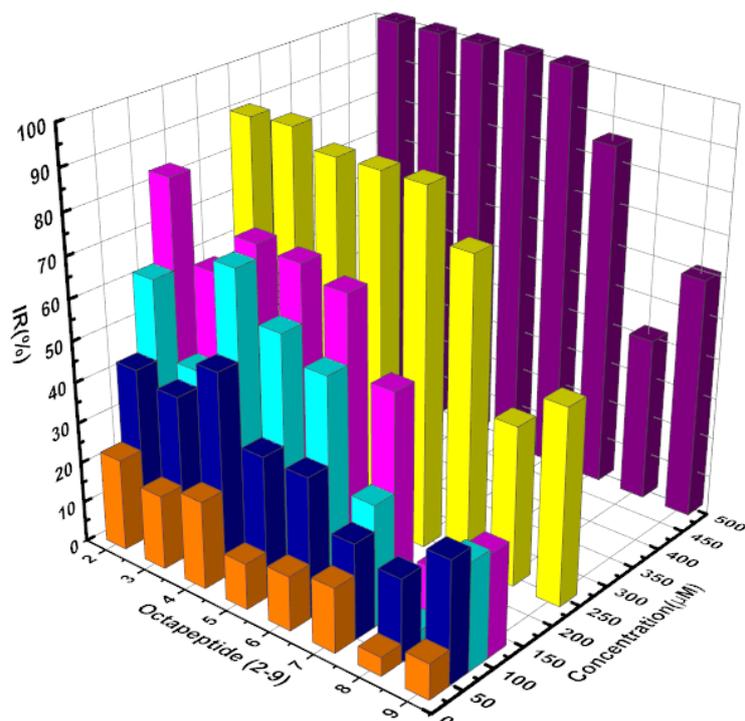


Figure 4. The inhibitory rate of octapeptide (2) and its Ala-substituted analogues (3) to (9) at their different concentrations against ACE.

However, the octapeptide (2), encompassing Arg (R), cannot tolerate the digestion of trypsin, making the oral administration impossible. The results show that when R changed into A, ACE inhibitory activity did not change apparently, meaning that R bears little effect. Consequently, it is worth considering to substitute R with other amino acids to develop a peptide sequence that holds better ACE inhibitory activity and can simultaneously tolerate the gastrointestinal protease digestion for the screening of oral antihypertensive drugs.

In addition, Gan *et al.*[17b] obtained the anti-SARS octapeptide (2) via solid-phase synthesis, and conducted relevant experiments on anti-SARS coronavirus' activity and cytotoxicity. The comprehensive study suggests that this octapeptide (2) can significantly inhibit the replication of SARS coronavirus and simultaneously has ACE inhibitory activity, and was attested by no signs of cytotoxicity in the detected cells within the scope of

concentration. However, the question is why this sequence has these two types of activity? It is admitted that only the angiotensin conversion enzyme 2 (ACE2), discovered in 2000, is homologous to ACE. ACE2 is also involved in renin-angiotensin system (RAS), and has been determined as a functional receptor for COVID-19 and SARS coronavirus.[21, 22, 23] We already know that during the infection process, the combination between the S protein of SARS coronavirus and intracellular ACE2 occurs in the first step,[24] whereas the problem in relation to the process still wants further explanation.

Quantitative structure-activity relationship (QSAR) study of anti-SARS octapeptide (2) and its analogues for ACE inhibiting. Molecular docking technology is constantly employed for virtual screening of bioactive molecules and the rational design of drug candidates. The molecular mechanisms of interactions between ACE and ACE inhibitory peptides have many potentially favorable consequences for further designing and synthesizing their derivatives.[25] To explore the quantitative structure-activity relationship (QSAR) and binding mechanism of anti-SARS octapeptide (2) (ligand 2, H-AVLQSGFR-OH) and its analogues against ACE, the computation of molecular docking was made. The most stabilized pose of the anti-SARS octapeptide (2) (ligand 2) bond with ACE1 (PDB: 1O8A) was obtained, and their 3D and 2D structures were exhibited in **Figure 5A** and **5B**, respectively. The inhibitor combined with the residues of ACE through the main interaction forces of hydrogen bonds, Van der Waals, hydrophobic and electrostatic force. The hydrogen bonds interaction force played the leading role. The molecular docking of anti-SARS octapeptide (2) (ligand 2) on the ACE1 binding site revealed that anti-SARS octapeptide (2) was encompassed by a hydrophilic pocket which formed by the hydrogen bonds of

hydrophilic interactions. The anti-SARS octapeptide (**2**) makes contact via the hydrogen bond interactions with Asn70, Glu162, Thr282, Cys352, Glu384, His387, Glu411 of ACE1, as well the electrostatic interactions with Glu143 and zinc cation as a metal-acceptor of ACE1 (**Figure 5B**). Also, the ligand 2 makes contact via the Van der Waals interactions with Asn66, Thr166, Gln281, Asn277, Trp279, Val351, Trp357, Lys368, Gln369, Cys370, Thr371, Glu376, Phe391, His410, Glu411, Lys454, Phe457, Phe512, Ser516, Val518, Tyr520, Arg522 of ACE1, as well the hydrophobic interactions such as alkyl interaction with Ala356, Val379, Val380, π - π stacking force with His387, π - σ interaction with His383 and unfavorable donor-donor interaction with Ala354 of ACE (**Figure 5C**).

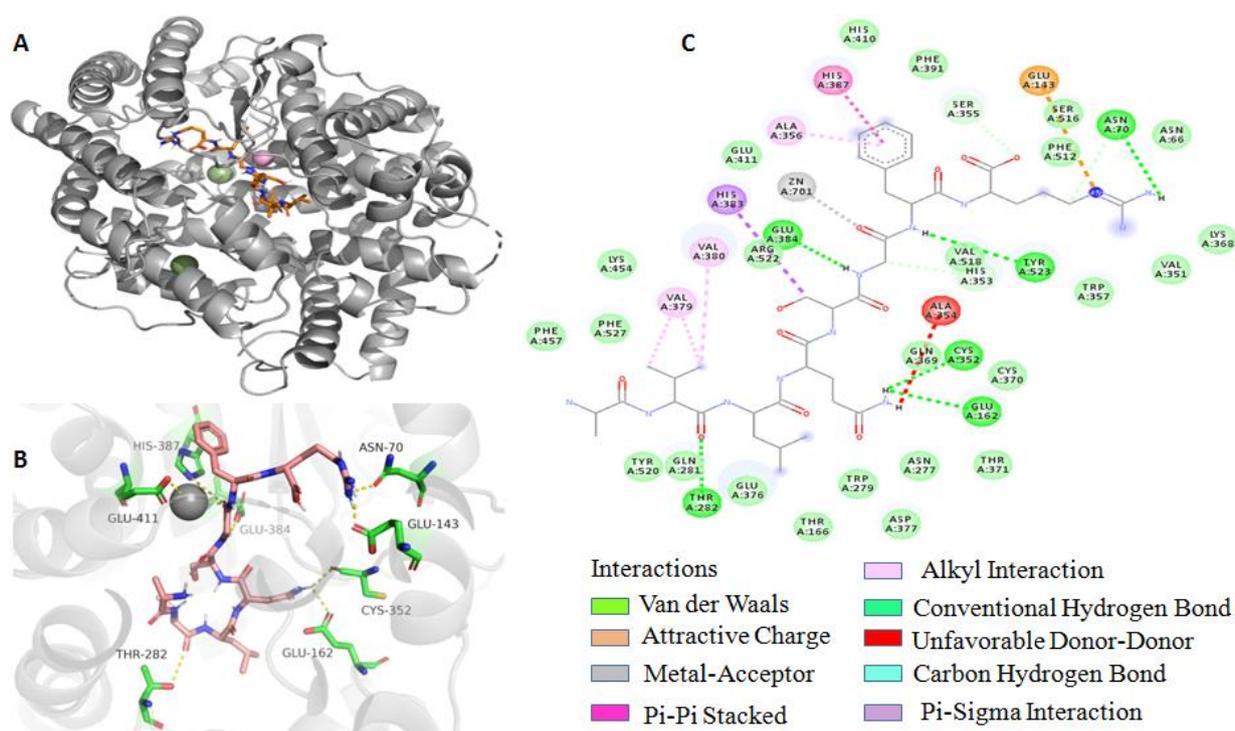


Figure 5. The best ranked docking pose of anti-SARS peptide 2 (AVLQSGFR-OH) binding with ACE1 (PDB: 1O8A). **A:** Full view of ACE1(PDB: 1O8A, Dark gray)-ligand2 (AVLQSGFR-OH, Dark orange) complex; **B:** Binding mode of ACE1 (Light grey and green) with Ligand 2 (H-AVLQSGFR-OH, Dark orange); **C:** All kinds of interactions between ACE1

residues and atoms or atomic groups on Ligand 2.

Table 1. ACE binding energy by docking and measured ACE inhibitory activities of anti-SARS octapeptide and its analogues.

| entry | Ligands | Octapeptide Sequence | Binding Energy (kcal/mol) | | ACE Inhibition IC ₅₀ (μM) |
|-------|---------|----------------------------|---------------------------|-------|--------------------------------------|
| | | | ACE1 | ACE2 | |
| 1 | Ligand1 | H-AVLQSGFR-NH ₂ | -9.5 | -9.3 | 220.7 |
| 2 | Ligand2 | H-AVLQSGFR-OH | -9.7 | -10.2 | 75.3 |
| 3 | Ligand3 | H-AVLQSGFA-OH | -9.2 | -9.5 | 100.5 |
| 4 | Ligand4 | H-AVLQSGAR-OH | -9.2 | -9.0 | 62.5 |
| 5 | Ligand5 | H-AVLQSAFR-OH | -9.5 | -9.4 | 82.3 |
| 6 | Ligand6 | H-AVLQAGFR-OH | -9.5 | -10.1 | 86.4 |
| 7 | Ligand7 | H-AVLASGFR-OH | -9.1 | -9.8 | 131.3 |
| 8 | Ligand8 | H-AVAQSGFR-OH | -9.5 | -9.4 | > 500 |
| 9 | Ligand9 | H-AALQSGFR-OH | -9.2 | -8.9 | 316.5 |

The interaction energies of anti-SARS octapeptide (**2**) (H-AVLQSGFR-OH) and its analogues binding with ACEs (both types 1 and 2) were summarized in **Table 1**. The results by molecular docking indicated that the complexes of ligand 2 (H-AVLQSGFR-OH) with ACE1 and ACE2 were the most stable ones with the interaction energy of -9.7 and -10.2 kcal/mol respectively among those of its analogues. The binding energy of ligand 1 (H-AVLQSGFR-NH₂) in which the C-terminal hydroxyl group was substituted by the amino group decreased to -9.5 kcal/mol with ACE1 and -9.3 kcal/mol with ACE2. The binding energies of the analogues (ligand 3-9), which sequences changed by alanine-scanning one by one, went down to the range of -9.1 to -9.5 kcal/mol with ACE1, and -8.9 to 10.1 kcal/mol with ACE2. It suggested that the residues of four amino acids, such as Arg, Phe, Gln, and Val in the anti-

SARS octapeptide sequence (ligand 2), significantly contributed to the combinative stabilization. (**Figure S12** in the SI)

On the other hand, the inhibitory activities as IC_{50} of anti-SARS octapeptide (**2**) (ligand 2) and its analogues against ACE measured by the experiment were listed in **Table 1**. Except for that of ligand 1 and 8, most of the measured values agree with the simulated theoretical values by molecular docking. It suggested that the C-terminal hydroxyl group and the residue of Leu in the sequence of anti-SARS octapeptide (ligand 2) play a crucial role and have a strong effect on the actual IC_{50} of anti-SARS octapeptide (ligand 2) inhibiting ACE. In summary, anti-SARS octapeptide (**2**) (ligand 2) is indeed an excellent ACEs (both types 1 and 2) inhibitor. No matter theoretically or experimentally, the sequence AVLQSGFR compared with its analogues is the optimal binding ligand to ACEs (both types 1 and 2).

Conclusion

In this work, we utilized the designed TDPBP derivatives as greener support to synthesize the anti-SARS octapeptide template AVLQSGFR. A new simplified liquid-phase strategy was successfully established and demonstrated via Fmoc chemistry and support-aided precipitation for the implementation of large-scale, atom economic synthesis and preparation of biologically active peptides, without the use of resin and chromatographic separation. Additionally, we systematically studied the ACE inhibitory of anti-SARS octapeptide and the ACE inhibitory structure-activity relationship (SAR) of anti-SARS octapeptide and its analogues, and found the critical amino acids sequence for ACE inhibition. This provides a solid foundation for the design and synthesis of peptides to develop bi- or multi-functional therapeutic drugs for antihypertension and anti-SARS CoV in the future.

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Competing financial interests

The authors declare no competing financial interests.

Additional information

Supplementary information and chemical compound linking are available in the online version of the paper.

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