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Original article

A class of novel *N*-(3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-amino acid derivatives: their synthesis, anti-thrombotic activity evaluation, and 3D QSAR analysis

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ABSTRACT

To find new anti-thrombotic agents, a natural amino acid was introduced into the 3-position of anti-platelet aggregation active 3*S*-tetrahydroisoquinoline-3-carboxylic acid (THIQA), and 20 novel dipeptide derivatives, 3*S*-tetrahydroisoquinoline-3-carboxyamino acids (**6a**–**t**), targeting the intestinal peptide transport system were provided. In vitro anti-platelet aggregation assay of **6a**–**t** indicated that their potencies of inhibiting adenosine diphosphate (ADP), arachidonic acid (AA), platelet-activating factor (PAF), and thrombin (TH) induced platelet aggregations were higher than that of THIQA, and the in vivo anti-thrombotic assay of **6a**–**t** indicated that their potencies of inhibiting thrombogenesis in rats were also higher than that of THIQA. According to MFA based Cerius2 QSAR module, using training/test set of **6a**,**b**,**d**,**g**–**p**/**6c**,**e**,**f**,**q** and training/test set of **6a**–**p**/**6q**–**t**, two equations (*r*, 0.984 and 0.996) correlating the structures with in vitro or in vivo activity of **6a**–**t** were established.

1. Introduction

Intravascular thrombosis is known as one of the most frequent pathological events and a leading cause of morbidity and mortality all over the world. In the onset and progression of acute coronary syndromes, there are critical steps such as the rift, rupture and pathogenesis of atheromatous plaque with the formation of either partial or complete occlusive thrombus [1–3], while vascular damage, stimulus of platelets, and initiation of the clotting cascade are the essential factors of thrombosis. In the cases of unstable Rougnon–Heberden disease, cardiac infarction, transient attack of myocardial ischemia, apoplexy and atherosclerotic occlusion, the so-called thromboembolic disorders of cardiovascular and cerebrovascular, the subendothelium surfaces of the vessels are injured and function as the adherent target of platelets [3–7]. Though the anti-thrombotic therapy of anticoagulants, anti-platelet drugs and thrombolytic drugs are well established, to improve the prevention and treatment of ischemic symptoms, more potent and safer compounds are urgently needed, and a lot of efforts have been devoted to the design of anti-thrombotic drug. However, many candidates of anti-thrombotic drug fail to exert their therapeutic potential mainly due to their poor bioavailability, which led us to pay more attention to the development of GPIIb/IIIa antagonist of small molecules with desirable pharmacodynamic and pharmacokinetic properties [7–13]. Recently, intestinal peptide transport system is successfully utilized to increase bioavailability [14–16] and we reported our new design as drug candidates in the form of dipeptide analogues that can be readily absorbed across the intestinal brush border membrane *via* the peptide transport system. For instance, 3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (THCA) and 3*S*-1,2,3,4-tetrahydroisoqunoline-3-carbonylamino acid (THIQA), the anti-platelet aggregation compounds, were converted to their dipeptide analogues to enhance their anti-thrombotic activity and permeability [8,9].

Besides a number of bioactivities [17–31], tetrahydroisoquinolines were identified as anti-platelet aggregation agents. The investigations of the anti-platelet aggregation mechanism of tetrahydroisoquinolines indicated that in addition to receptor and β-adrenergic/α_2-adrenergic receptor system [32], thromboxane A_2/prostaglandin H_2 receptor system was commonly involved, for instance they may exert their inhibitory effects on AA-induced platelet aggregation partly by inhibiting the production of TXA2

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from AA and partly by directly blocking the TXA2 receptor [33–35]. Based on the results of these investigations some derivatives of benzyltetrahydroisoquinoline alkaloid were reported having anti-platelet aggregation activities [36–39].

In our previous paper, THIQA was used as the anti-thrombotic pharmacophore and converted to 3*S*-*N*-(L-aminoacyl)-1,2,3,4-tetrahydroisoquinolines for 3D QSAR analysis. The stereoview of individual 3*S*-*N*-(L-aminoacyl)-1,2,3,4-tetrahydroisoquinoline explored that due to proximity its side chain of 2-amino acid residue and the 3-carboxylic group may form hydrogen bonding leading to low anti-thrombotic activity [9], while the corresponding 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonyl- amino acid does not form this kind of intramolecular hydrogen bonding and therefore it will have higher anti-thrombotic activity (Fig. 1). In this context, the present paper introduced the natural amino acids into the 3-position of THIQA to provide 20 novel 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids for anti-thrombotic evaluation and 3D QSAR analysis.

2. Results and discussion

2.1. Preparing 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids

The preparation of 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids (**6a**–**t**) was carried out according to the five-step-route depicted in Scheme 1. Using a common procedure L-Phe was successively converted into THIQA (**2**, 84% yield) and Boc-THIQA (**3**, 80% yield) *via* Pictet–Spengler condensation and amidation, respectively [40,41]. To determine if any racemization of the chiral center in both L-Phe and **2** had occurred during the course of Spengler–Pictet reaction the enantiomeric purity of **2** was determined by analytical HPLC. After 20 μl of the sample of **2** (10 μM) was loaded, the Daicel Chiralpak AS chiral column was eluted with aqueous methanol (50%) for 40 min. The flow rate was 1 ml/min, the sample was monitored with UV detector at 254.8 nm and the peak area was recorded. The relative proportion of the peak area suggested that **2** was a single enantiomer. In the presence of DCC, HOBt and NMM, **3** was conjugated with 20 amino acid methylesters to give 3*S*-*N*-Boc-1,2,3,4- tetrahydroisoquinoline-3-carbonylamino acid methylesters (**4a**–**t**, 45–95% yield). The saponification of **4a**–**t** provided 3*S*-*N*-Boc-1,2,3,4-tetrahydroisoquinoline-3-carbonyl-amino acids (**5a**–**t**, 65–96% yield). Removing Boc groups from **5a**–**t** resulted in 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids (**6a**–**t**, 48–100% yield). The mild condition and the moderate yield of the individual reaction suggest that the present synthetic route is suitable for preparing these novel 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids.

2.2. In vitro anti-platelet aggregation activities of ***6a*–*t***

To evaluate the effect of introducing amino acid into the 3-position of THIQA, the in vitro anti-platelet aggregation activities of **6a**–**t** were measured following the common procedure by using four aggregators, namely platelet-activating factor (PAF, final concentration 0.1 μM), adenosine diphosphate (ADP, final concentration 10 μM), arachidonic acid (AA, final concentration 350 μM), and thrombin (TH, final concentration 0.1 U/ml). The IC_{50} values are listed in Table 1.

The data demonstrate that the IC_{50} values of THIQA against PAF, ADP, AA and TH induced platelet aggregation are 0.55, 0.45, 0.96 and 0.88 μM, respectively. As lead compounds tetrahydroisoquinolines were investigated generally as the inhibitors of ADP or AA and had 270–100 μM and 3.3–140 μM of IC_{50} values, respectively [33,38]. Comparing with them THIQA belongs to desirable lead and is more suitable as the inhibitor of ADP and AA than that of PAF and TH. The IC_{50} values of **6a**–**t** against ADP, AA, PAF and TH range from 0.12 to 0.66, 0.10 to 0.49, 0.14 to 1.40 and 0.16 to 0.97 μM, respectively. Thus these dipeptides similarly belong to desirable leads and are more suitable for inhibiting ADP and AA than that of PAF and TH. It is known that the representatives of tetrahydroisoquinolines, Higenamine, YS-49 and YS-51, are able to inhibit both AA- and ADP-induced platelet aggregation with IC_{50} values ranging from 3.3 to 270 μM, and other analogs give 5.3–800 μM of IC_{50} values in inhibiting U46619-induced platelet aggregation [38]. In Table 1 the inhibitory potencies of 13 and 10 dipeptides are defined as 1.4–4.6 and 1.2–4.3-fold higher than that of THIQA in inhibiting ADP- and AA-induced platelet aggregation, respectively. Therefore the inhibition potencies of both ADP- and AA-induced platelet aggregations derived benefit from the modification. Besides, in AA- and ADP-induced platelet aggregations Table 1 identifies **6a**,**b**,**t** and **6f**,**m**,**s** having the best potency, respectively.

2.3. In vivo anti-thrombotic activities of ***6a*–*t***

To evaluate the effect of the introduction of amino acid into the 3-position of THIQA, the in vivo anti-thrombotic activity of **6a**–**t** were measured by use of an extracorporeal circulation of arterioveinous cannula model of rats. According to the general

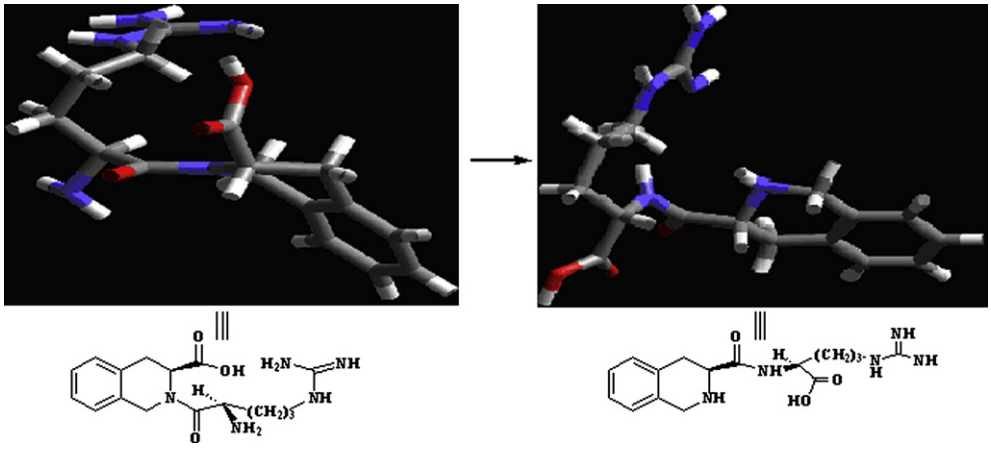
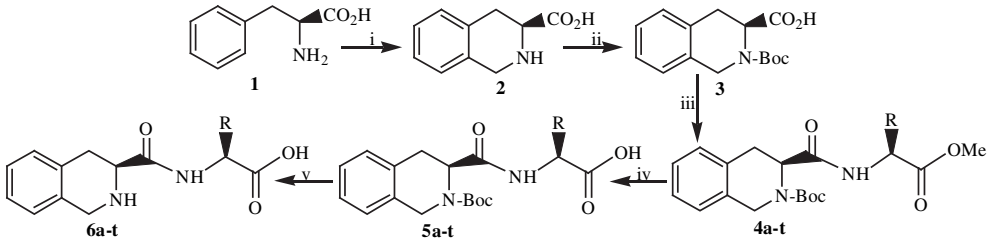


Fig. 1. Stereoview of 3*S*-*N*-(L-argininyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and *N*-(3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-arginine.



Scheme 1. (i) HCHO and HCl; (ii) $(Boc)_2O$, 1 N NaOH; (iii) AA–OCH_3, HOBt, DCC and NMM; (iv) NaOH aqueous (2 N); (v) Hydrogen chloride in ethyl acetate (6 N). In **4a–6a** R = CH_3, **4b–6b** R = H, **4c–6c** R = $CH(CH_3)_2$, **4d–6d** R = $CH_2CH(CH_3)_2$, **4e–6e** R = $CH(CH_3)CH_2CH_3$, **4f–6f** R = indol-2-ylmethylene, **4g–6g** R = CH_2OH, **4h–6h** R = 4-hydroxylbenzyl, **4i–6i** NHCHR = cyclobutylamino, **4j–6j** R = CH_2CONH_2, **4k–6k** R = $CH_2CH_2CONH_2$, **4l–6l** R = imidazol-4-ylmethylene, **4m** R = *N*-benzyloxycarbonylbutylamino-4-yl, **5m** & **6m** R = butylamino-4-yl, **4n** R = methoxycarbonylmethylene, **5n** & **6n** R = carboxylmethylene, **4o** R = methoxycarbonylethylene, **5o** & **6o** R = carboxylethylene, **4p–6p** R = CH_2SH, **4q–6q** R = benzyl, **4r–6r** R = $CH(OH)CH_3$, **4s–6s** AA = $CH_2(CH_2)_2NHC(NH_2)$ = NH, **4t–6t** R = $CH_2CH_2SCH_3$.

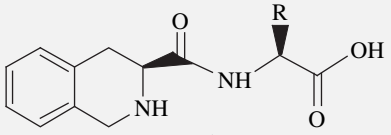
procedure, the individual stock solution of Aspirin (positive control) and **6a–t** in NS was administered intravenously. The thrombus weights were weighed, and the data are listed in Table 2.

The thrombus weights of the rats receiving 5 μmol/kg of **6a–t** range from 18.73 to 23.58 mg, and are significantly lower than that (28.54 mg) of rats receiving NS ($p < 0.001$), which demonstrate that **6a–t** are in vivo anti-thrombotic active. On the other hand, the thrombus weights of the rats receiving 5 μmol/kg of **6b**,**d**,**e**,**j**,**o**,**q**,**s** range from 18.73 to 20.24 mg, and are significantly lower than that (21.52 mg) of rats receiving 15 μmol/kg of THIQA ($p < 0.05$–0.01). The thrombus weights of the rats receiving 5 μmol/kg of **6a**,**f**,**g**,**i**,**k**–**n**,**r**,**t** equal to that of rats receiving 15 μmol/kg of THIQA. In other words, modifying 3-position of THIQA with amino acids leads the anti-thrombotic activity a 2-fold to more than 3-fold increase. Therefore the modification is beneficial to the improvement of in vivo anti-thrombotic activity of THIQA.

From Table 1 it is noticed that **6f**,**q**,**s** are the best inhibitors for ADP-induced platelet aggregation. Parallel with this, except **6f** which has the biggest side chain, indol- 2-ylmethylene, **6q** and **6s** exhibit the highest in vivo anti-thrombotic activity (Table 2). This implies that the dipeptides, of which the side chains are proper, exhibiting the best in vitro inhibitory potency in ADP-induced platelet aggregation will also exhibit the highest in vivo anti-thrombotic activity. In addition, the fact that the thrombus weights of the rats receiving 167 μmol/kg of aspirin and 5 μmol/kg of **6a–t** are comparable indicates that the anti-thrombotic potency of **6a–t** is over 30-fold higher than that of aspirin (Table 2).

To clarify the benefit of 3-position modification the thrombus weights of the rats receiving 5 μmol/kg of 3*S*-*N*-(L-argininyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (**7a–s**), the 2-amino acid modified THIQA, are incorporated into Table 2. The data indicate that the anti-thrombotic activities of **6a–e**,**i**,**k–n** are equal that of **7a–e**,**i**,**k–n**, the anti-thrombotic activities of **6h**,**j**,**o–q**,**s** are significantly higher than that of **7h**,**j**,**o–q**,**s**, and only the anti-thrombotic activities of **6f**,**g**,**t** are significantly lower than that of **7f**,**g**,**t**. Thus, 3-position amino acid modification totally has one advantage over 2-position amino acid modification.

Table 1
IC_{50} of **6a–t** against four aggregators induced aggregation of pig platelets.[a]



6a-t

IC50 (μM)

No/R	ADP	AA	PAF	TH	No	ADP	AA	PAF	TH
IQ	0.552 ± 0.032	0.452 ± 0.016	0.960 ± 0.041	0.881 ± 0.040	IQ	0.552 ± 0.032	0.452 ± 0.016	0.960 ± 0.041	0.881 ± 0.040
6a/CH_3	0.350 ± 0.031	0.104 ± 0.026	0.352 ± 0.018	0.485 ± 0.032	**7a**	0.651 ± 0.026	0.452 ± 0.031	0.945 ± 0.038	0.741 ± 0.042
6b/H	0.496 ± 0.028	0.108 ± 0.031	0.791 ± 0.041	0.306 ± 0.018	**7b**	0.365 ± 0.029	0.440 ± 0.034	0.875 ± 0.042	0.761 ± 0.040
6c/$CH(CH_3)_2$	0.382 ± 0.026	0.388 ± 0.034	0.943 ± 0.034	0.199 ± 0.016	**7c**	0.389 ± 0.033	0.423 ± 0.029	0.632 ± 0.034	0.653 ± 0.031
6d/$CH_2CH(CH_3)_2$	0.478 ± 0.029	0.290 ± 0.025	1.611 ± 0.036	0.454 ± 0.031	**7d**	0.336 ± 0.019	0.573 ± 0.030	0.891 ± 0.040	0.730 ± 0.026
6e/$CH(CH_3)C_2H_5$	0.540 ± 0.034	0.443 ± 0.032	0.938 ± 0.044	0.657 ± 0.026	**7e**	0.315 ± 0.030	0.238 ± 0.019	0.831 ± 0.044	0.674 ± 0.028
6f/indol-2-ylmethylene	0.120 ± 0.019	0.374 ± 0.033	0.668 ± 0.033	0.234 ± 0.028	**7f**	0.194 ± 0.016	0.465 ± 0.032	0.422 ± 0.026	0.720 ± 0.044
6g/CH_2OH	0.388 ± 0.033	0.416 ± 0.026	0.942 ± 0.028	0.841 ± 0.036	**7g**	0.103 ± 0.018	0.572 ± 0.031	0.267 ± 0.021	0.498 ± 0.031
6h/p-HO–$C_6H_4CH_2$	0.481 ± 0.030	0.390 ± 0.030	1.152 ± 0.042	0.970 ± 0.034	**7h**	0.327 ± 0.031	0.535 ± 0.026	0.668 ± 0.032	0.736 ± 0.038
[a]**6i**/cyclobutylamino	0.364 ± 0.021	0.103 ± 0.015	1.398 ± 0.027	0.185 ± 0.021	**7i**	0.373 ± 0.032	0.526 ± 0.025	0.507 ± 0.029	0.590 ± 0.025
6j/CH_2CONH_2	0.470 ± 0.029	0.166 ± 0.018	0.153 ± 0.016	0.551 ± 0.029	**7j**	0.534 ± 0.034	0.430 ± 0.030	0.360 ± 0.018	0.495 ± 0.030
6k/$CH_2CH_2CONH_2$	0.235 ± 0.022	0.494 ± 0.029	0.138 ± 0.021	0.935 ± 0.044	**7k**	0.302 ± 0.023	0.407 ± 0.033	0.392 ± 0.031	0.555 ± 0.031
6l/imidazol-4-ylmethylene	0.661 ± 0.034	0.491 ± 0.034	0.724 ± 0.032	0.370 ± 0.019	**7l**	0.324 ± 0.019	0.351 ± 0.022	0.670 ± 0.026	0.684 ± 0.034
6m/$CH_2(CH_2)_3NH_2$	0.194 ± 0.015	0.277 ± 0.031	1.042 ± 0.034	0.733 ± 0.031	**7m**	0.323 ± 0.021	0.521 ± 0.029	0.472 ± 0.034	0.829 ± 0.042
6n/CH_2CO_2Me	0.329 ± 0.033	0.391 ± 0.029	0.633 ± 0.028	0.157 ± 0.016	**7n**	0.345 ± 0.034	0.344 ± 0.034	0.383 ± 0.022	0.902 ± 0.034
6o/$CH_2CH_2CO_2Me$	0.482 ± 0.026	0.356 ± 0.028	0.176 ± 0.017	0.545 ± 0.041	**7o**	0.494 ± 0.032	0.369 ± 0.026	0.544 ± 0.031	0.589 ± 0.027
6p/CH_2SH	0.231 ± 0.018	0.460 ± 0.034	0.780 ± 0.036	0.386 ± 0.032	–	–	–	–	–
6q/$C_6H_5CH_2$	0.188 ± 0.015	0.553 ± 0.030	0.218 ± 0.021	0.336 ± 0.027	**7q**	0.370 ± 0.029	0.666 ± 0.025	0.527 ± 0.028	0.851 ± 0.039
6r/$CH(OH)CH_3$	0.164 ± 0.022	0.418 ± 0.028	0.588 ± 0.032	0.763 ± 0.031	**7r**	0.240 ± 0.027	0.215 ± 0.019	0.404 ± 0.031	0.879 ± 0.041
6s/$CH_2(CH_2)_2NHC(NH_2)$=NH	0.124 ± 0.020	0.361 ± 0.025	1.344 ± 0.036	0.496 ± 0.030	**7s**	0.210 ± 0.022	0.298 ± 0.027	0.517 ± 0.030	0.565 ± 0.028
6t/$CH_2CH_2SCH_3$	0.229 ± 0.018	0.191 ± 0.015	0.376 ± 0.029	0.312 ± 0.026	**7t**	0.265 ± 0.026	0.382 ± 0.031	0.409 ± 0.026	0.607 ± 0.026

[a] NHCHR = cyclobutylamin, **7a–t** = 3*S*-*N*-(L-aminoacyl)-1,2,3,4- tetrahydroisoquinoline-3-carboxylic acids, $n = 6$.

Table 2
Effect of **6a–t** on the weight of the wet thrombus of rats.[a]

Compd.	Thrombus weight	Compd.	Thrombus weight
NS	28.54 ± 2.62	Aspirin[1]	27.60 ± 1.89
IQ	21.52 ± 1.49[b]	Aspirin[2]	13.22 ± 1.67
6a	21.40 ± 1.39[b]	**7a**	20.30 ± 1.33[c]
6b	20.24 ± 1.37[c]	**7b**	21.17 ± 1.47[b]
6c	19.20 ± 1.57[d]	**7c**	20.12 ± 1.59[c]
6d	20.23 ± 1.49[c]	**7d**	19.12 ± 1.82[d]
6e	20.03 ± 1.29[c]	**7e**	21.14 ± 1.24[b]
6f	21.30 ± 1.06[b]	**7f**	19.47 ± 1.64[d]
6g	23.58 ± 1.93[b]	**7g**	18.00 ± 1.59[d]
6h	19.31 ± 1.48[d]	**7h**	20.92 ± 1.44[b]
6i	20.25 ± 1.50[b]	**7i**	21.09 ± 1.68[b]
6j	20.24 ± 1.50[c]	**7j**	22.66 ± 1.45[b]
6k	22.08 ± 1.54[b]	**7k**	21.30 ± 1.69[b]
6l	20.86 ± 1.94[b]	**7l**	21.78 ± 1.96[b]
6m	21.28 ± 1.17[b]	**7m**	21.31 ± 1.75[b]
6n	21.67 ± 1.91[b]	**7n**	20.30 ± 1.34[c]
6o	19.69 ± 1.25[d]	**7o**	20.87 ± 1.45[b]
6p	20.91 ± 1.27[b]	**7q**	22.23 ± 1.72[b]
6q	19.11 ± 1.58[d]	**7r**	20.73 ± 1.53[b]
6r	21.25 ± 1.93[b]	–	–
6s	18.73 ± 1.56[d]	**7s**	20.06 ± 1.48[c]
6t	21.74 ± 1.50[b]	**7t**	19.56 ± 1.72[d]

[a] Weight of wet thrombus is represented by X ± SD mg, NS = vehicle, $n = 12$; IQ = 3S-isoquinoline- 3-carboxylic acid and intravenous dose = 15 μmol/kg.
[b] Compared to NS $p < 0.001$.
[c] Compared to NS $p < 0.001$ and to IQ $p < 0.05$.
[d] Compared to NS $p < 0.001$ and to IQ $p < 0.01$.
[1] Aspirin intravenous dose = 15 μmol/kg.
[2] Aspirin intravenous dose = 0 μmol/kg; **6a–t** = 3S-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids, **7a–t** = 3S-N-(L-aminoacyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids and dose = 5 μmol/kg.

2.4. In vitro membrane permeation test of *6s*

To gain the proof that amino acid modification can enhance the permeability of THIQA through intestinal peptide transport system **6s**, the most interesting dipeptide in Table 2 was fed to Male Wistar rats orally, THIQA was used as the reference compound, and their oral activities were measured. Accordingly, the membrane permeabilities of THIQA and **6s** were also measured on Caco-2 cell monolayers. The data are summarized in Table 3. The data indicate an orally and dose-dependently anti-thrombotic action for **6s**. The data also indicate that modifying THIQA with L-Arg results in a significant increase of the oral anti-thrombotic activity. The data further indicate that modifying THIQA with L-Arg results in a significant increase of the permeability.

Though the oral bioavailability of a drug is influenced by a series of factors, including dissolution, absorption, pre-systemic and systemic metabolism, and elimination, the intestinal mucosa is a significant barrier to oral delivery of drugs into the systemic circulation. While Caco-2 cells possess many structural and functional similarities to human enterocytes. After converting THIQA into the deceptive analogue **6s**, the permeability can be increased 2.3 folds.

Table 3
Apparent permeability coefficients and oral activities of THIQA and **6s**.

Compd.	Dose, thrombus weight (X ± SD mg)[a]	*Papp* × 10^6 (cm/s)[b]		
		A → B	B → A	A → B/B → A
THIQA	15 μmol/kg, 23.88 ± 2.34	9.00	8.71	1.03
6s	5 μmol/kg, 19.01 ± 2.42[c]	17.12	7.34	2.33
	1 μmol/kg, 24.38 ± 2.61[d]			
	0.2 μmol/kg, 29.11 ± 2.37[e]			

[a] $n = 12$, Thrombus weight of the rats receiving 0.6 ml of NS (vehicle): 29.07 ± 2.62 mg.
[b] THIQA and **6s** were dissolved in HBSS (final concentration: 4 mM), the standard deviations were generally less than 9.2% ($n = 4$); A → B: from apical side to basolateral side; B → A: from basolateral side to apical side.
[c] Compare to 15 μmol/kg of THIQA and 1 μmol/kg of **6s**, $p < 0.01$.
[d] Compare to 15 μmol/kg of THIQA $p > 0.05$ and to 0.2 μmol/kg of **6s**, $p < 0.01$.
[e] Compare to NS $p > 0.05$.

2.5. 3D QSAR analysis of amino acid modified THIQA

To elucidate the effects of 3-position amino acid modification on the anti-thrombotic action the activities were converted into the corresponding anti-platelet aggregation and thrombus weights. The training/test set of **6a**,**b**,**d**,**g–p**/**6c**,**e**,**f**,**q** and training/test set of **6a–p**/**6q–t** selections were done manually such that they populate the wide range of anti-platelet aggregation and anti-thrombotic activities in similar proportions, respectively.

2.5.1. Alignment of amino acid modified THIQA

To establish the valid 3D QSAR models, a proper alignment procedure of **6a**,**b**,**d**,**g–p** or **6a–p** was practiced using the target model align strategy in the align module within Cerius2. Based on the assumption that each structure of **6a**,**b**,**d**,**g–p** or **6a–p** exhibits activity at the same binding site of the receptor, they were aligned in a pharmacological active orientation. To obtain a consistent alignment, the pharmacophore tetrahydroisoquinoline ring was selected as the template for superposing **6a**,**b**,**d**,**g–p** or **6a–p**. The method used for performing the alignment was the maximum common subgraph (MCS) [42]. MCS looks at molecules as points and lines, and uses the techniques out of graph theory to identify the patterns. MCS then finds the largest subset of atoms in tetrahydroisoquinoline ring that shared by **6a**,**b**,**d**,**g–p** or **6a–p**, which was used for the alignment. A rigid fit of atom pairings was performed to superimpose each structure onto the target model tetrahydroisoquinoline ring. Stereoview of aligned **6a**,**b**,**d**,**g–p** or **6a–p** is shown in Fig. 2 or Fig. 7. The alignment stereoview explores that to superimpose onto tetrahydroisoquinoline ring, the introduced amino acid residue on each structure has to take individual conformation. This individual conformation of the amino acid residue will affect the anti-thrombotic activity [9].

2.5.2. MFA based cerius2 QSAR module of amino acid modified THIQA

Molecular field analysis (MFA) was performed for **6a**,**b**,**d**,**g–p** or **6a–p** using the QSAR module of Cerius2 [42]. A five-step-procedure included generating conformers, energy minimization, matching atoms and aligning molecules, setting preferences and regression

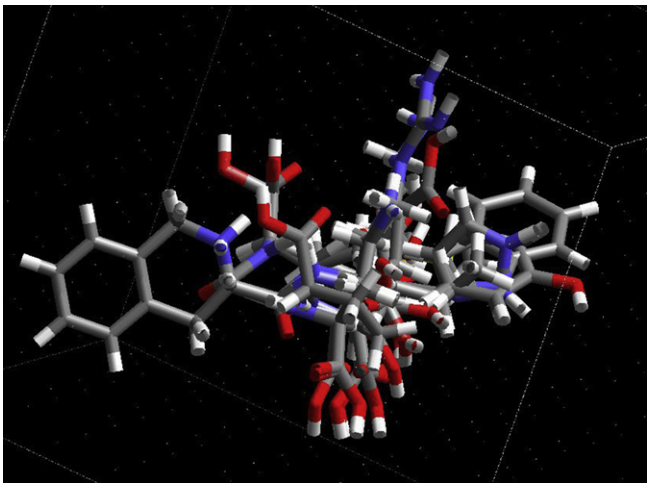


Fig. 2. Alignment stereoview of **6a**,**b**,**d**,**g–p** used for molecular field generation.

analysis was automatically carried out in MFA. By use of proton, methyl, and hydroxyl anion as probes, molecular electrostatic and steric fields were created. These fields were sampled at each point of a regularly spaced grid of 1 Å. A ± 30.0 kcal/mol energy cutoff was set for both electrostatic and steric fields. Totally 672 grid points were generated. Among the considered spatial and structural descriptors such as dipole moment, polarizability, radius of gyration, number of rotatable bonds, molecular volume, principal moment of inertia, *A* log *P*98, number of hydrogen bond donors and acceptors, and molar refractivity, only the highest variance holder proton and methyl descriptors were used. Regression analysis was performed by use of genetic partial least squares (G/PLS) method consisted of 50,000 generations with 100 population size. The component numbers were set to 5. Cross-validation was performed with the leave-one-out procedure. PLS analysis was scaled, with all variables normalized to a variance of 1.0.

2.5.3. 3D QSAR equation of amino acid modified THIQA against ADP-induced platelet aggregation

Based on the module, the regions where variations in the steric or electrostatic features of **6a**,**b**,**d**,**g**–**p** lead to the increase or decrease of their inhibition of ADP-induced platelet aggregation were specified as Fig. 3 corresponding to the IC_{50} values.

The MFA model for the activities of **6a**,**b**,**d**,**g**–**p** inhibiting ADP-induced platelet aggregation in terms of the most relevant descriptors including proton, methyl and hydroxyl anion is expressed by equation (1).

$$\begin{aligned}\text{Activity} = {} & 351.1 + 3.78(H^+/188) + 6.12(H^+/251) \\ & + 2.34(H^+/309) - 5.86(CH_3/179) + 3.78(CH_3/181) \\ & + 2.17(CH_3/182) - 8.56(CH_3/259) + 0.41(CH_3/261) \\ & - 4.73(CH_3/262) - 0.86(CH_3/348) - 8.5(CH_3/413) \\ & - 8.9(HO^-/190) + 6.04(HO^-/251) \end{aligned} \quad (1)$$

The correlation of the activities tested on the in vitro platelet aggregation model and the activities calculated using equation (1) is explained by Fig. 4. In equation (1), the data points (n), correlation coefficient (r), square correlation coefficient (r^2) were 16, 0.984, and 0.968, respectively. The tested activities on ADP-induced platelet aggregation model and the calculated activities based on equation (1) were shown in Fig. 4. The parameters indicated that

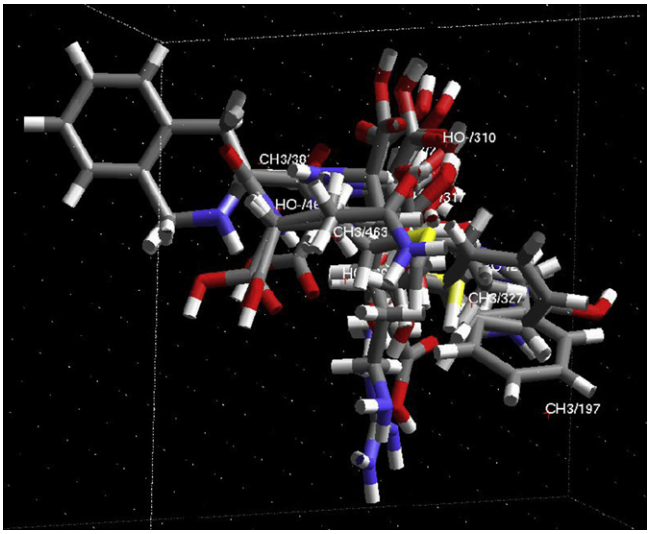


Fig. 3. Steric and electrostatic features of **6a**,**b**,**d**,**g**–**p** leading to the in vitro activity changes.

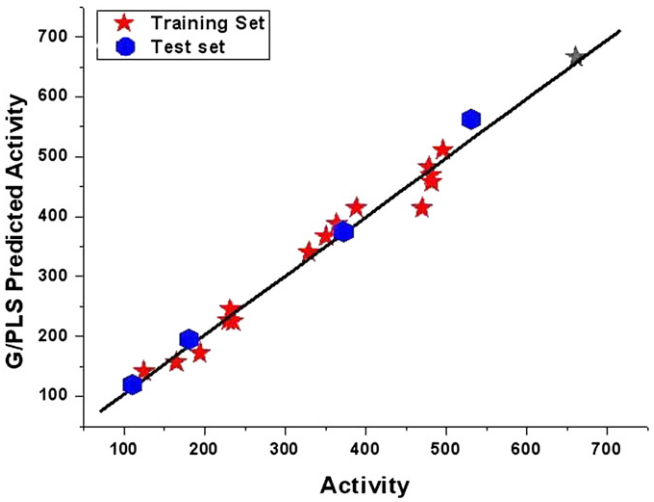


Fig. 4. Graph of tested versus predicted inhibitions of **6a**–**t** to ADP-induced platelet aggregation.

equation (1) is able to predict the in vitro activity for the analogs of **6a**–**t**. Accordingly the 3D QSAR equations for the inhibitions of **6a**,**b**,**d**,**g**–**p** to PAF, AA and TH can be established to reflect the steric and electrostatic effects.

Equation (1) contains 3 terms from proton descriptor, 8 terms from methyl descriptor, and 2 terms from hydroxyl anion descriptor. The terms of 3.78 (H^+/188), 6.12 (H^+/251) and 2.34 (H^+/309) have positive coefficients, which means that at these positions electron-withdrawing groups will increase the activity. The terms of 3.78 (CH_3/181), 2.17 (CH_3/182) and 0.41 (CH_3/261) have positive coefficients, which means that at these positions small groups will increase the activity, while terms of 5.86 (CH_3/179), 8.56 (CH_3/259), 4.73 (CH_3/262), 0.86 (CH_3/348) and 8.5 (CH_3/413) have negative coefficients, which means that at these positions large group will increase the activity. The term of 6.04 (HO^-/251) has positive coefficient, which means that at this position electron-withdrawing group will increase the activity, while the term of 8.9 (HO^-/190) has negative coefficient, which means that at this position electron-releasing group will increase the activity.

Figs. 5 and 6 give four representatives, **6e**,**l**,**r**,**s** as examples. Compounds **6r** has electeon-releasing groups at H^+/251 and OH^-/190, moderate group at CH_3/261 and CH_3/262 as well as small group at CH_3/181 and CH_3/182, and therefore it possesses higher anti-platelet aggregation activity; **6s** has electeon-releasing groups at H^+/188 and OH^-/190, small group at CH_3/261 as well as big group at CH_3/262, CH_3/348 and CH_3/413, and therefore it possesses also higher anti-platelet aggregation activity; **6e** has electeon-releasing group at OH^-/251, and small groups at CH_3/262, CH_3/259 and CH_3/179, and therefore it possesses lower anti-platelet aggregation activity; **6l** has electeo-releasing group at HO^-/251 as well as big group at CH_3/181, CH_3/182 and CH_3/261, and therefore it has lower anti-platelet aggregation activity.

2.5.4. Predicting anti-platelet aggregation activities for *6c*,*e*,*f*,*q*

The predicted power of equation (1) was demonstrated with the comparison of the calculated and tested anti-platelet aggregation activities of **6c**,**e**,**f**,**q** (Table 4). The correlation of the predicted and test values is also shown in Fig. 4. The results indicate that comparing to the test value equation (1) may result in an error% ranging from 1.9 to 3.8% for **6c**,**e**,**f**,**q**, which means that this equation is able to accurately give an anti-platelet aggregation activity for unknown 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids.

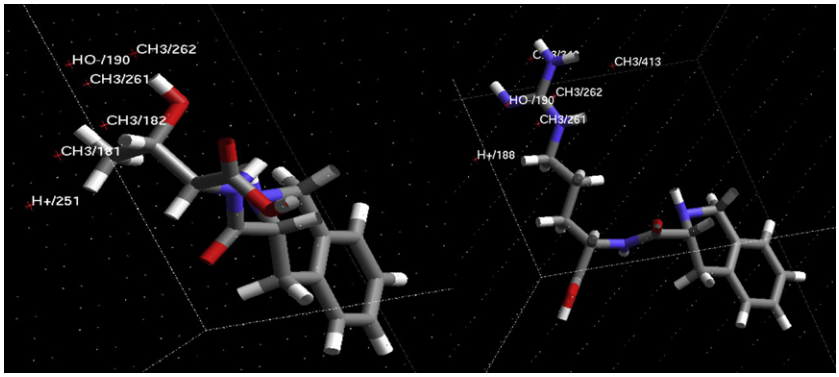


Fig. 5. Steric and electrostatic environments of **6r**,**s** with higher activities within the grid with 3D points of equation (1).

2.5.5. 3D QSAR equation of amino acid modified THIQA inhibiting rat thrombogenesis

Based on the module, the regions where variations in the steric or electrostatic features of **6a–p** lead to the inhibition or enhancement of thrombogenesis on rat model were specified as Fig. 7 corresponding to the thrombus weights of **6a–p**.

The MFA model for anti-thrombotic activities of **6a–p** in terms of the most relevant descriptors including proton, methyl and hydroxyl anions is expressed as equation (2).

$$\begin{aligned}\text{Activity} = {} & 21.57 - 0.023(\mathrm{H^+}/251) + 0.057(\mathrm{H^+}/325) \\ & + 0.020(\mathrm{CH_3}/197) - 0.062(\mathrm{CH_3}/242) + 0.039(\mathrm{CH_3}/322) \\ & - 0.020(\mathrm{CH_3}/327) + 0.023(\mathrm{CH_3}/386) + 0.0043(\mathrm{CH_3}/463) \\ & - 0.023(\mathrm{HO^-}/251) - 0.030(\mathrm{HO^-}/253) + 0.027(\mathrm{HO^-}/310) \\ & - 0.071(\mathrm{HO^-}/317) - 0.032(\mathrm{HO^-}/397) \\ & + 0.0037(\mathrm{HO^-}/461) \end{aligned} \quad (2)$$

The correlation of the activities tested on the in vivo thrombogenesis model and the activities calculated using equation (2) is explained by Fig. 7. In equation (2), the data points (n), correlation coefficient (r), and square correlation coefficient (r^2) were 16, 0.996, and 0.991, respectively. The tested activities on rat thrombogenesis model and the calculated activities based on equation (2) were shown in Fig. 8. The parameters indicated that equation (2) is able to predict the in vivo activity for **6a–p**.

Equation (2) contains 2 terms from proton descriptor, 6 terms from methyl descriptor, and 6 terms from hydroxyl anion descriptor. The terms of 0.057 (H^+/325) has positive coefficient, which means that at this position electron-withdrawing groups will increase the activity, while term of 0.023 (H^+/251) has negative coefficient which means that at this position electron-releasing group will increase the activity. The terms of 0.020 (CH_3/197), 0.039 (CH_3/322), 0.023 (CH_3/386) and 0.0043 (CH_3/463) have positive coefficients, which means that at these positions small groups will increase the activity, while terms of 0.062 (CH_3/242) and 0.020 (CH_3/327) have negative coefficients, which means that at these positions big groups will increase the activity. The term of 0.027 (HO^-/310) and 0.0037 (HO^-/461) have positive coefficients, which means that at these positions electron-withdrawing group will increase the activity, while the term of 0.023 (HO^-/251), 0.030 (HO^-/253), 0.071 (HO^-/317) and 0.032 (HO^-/397) have negative coefficient, which means that at this position electron-releasing group will increase the activity.

Figs. 9 and 10 give four representatives, **6c**,**g**,**h**,**k** as examples. Compound **6c** has electron-releasing groups at H^+/325, OH^-/251, OH^-/253 and OH^-/397, as well as electron-withdrawing groups OH^-/310, and therefore it possesses higher in vivo anti-thrombotic activity; **6h** has electron-releasing groups at OH^-/253 and OH^-/317, an electron-withdrawing group at H^+/325, as well as has small groups at CH_3/197 and CH_3/463, and therefore it possesses higher in vivo anti-thrombotic; **6g** has moderate groups at CH_3/322 and CH_3/386, and an electron-releasing group at OH^-/461, and therefore it possesses lower in vivo anti-thrombotic activity; **6k** has an electron-withdrawing group at HO^-/397 and an electron-releasing group at HO^-/461, as well as a small group at CH_3/197 and CH_3/463, and therefore it has lower in vivo anti-thrombotic activity.

2.5.6. Predicting anti-thrombotic activity for 6q–t

To examine the predicting power of the equations (2) the in vivo anti-thrombotic activities of **6q–t** were calculated, listed in Table 5

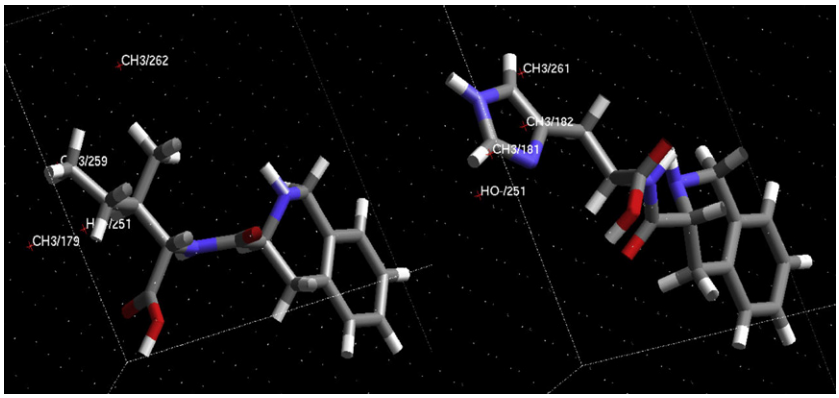


Fig. 6. Steric and electrostatic environments of **6e**,**l** with lower activities within the grid with 3D points of equation (1).

Table 4
Predicted and tested IC_{50} of **6c, e, f, q** against ADP-induced aggregation.

Comp.	IC_{50} (nM)			
	Predict value	Test value	Error	Error%
6c	371.139	382.324	−11.19	2.9
6e	558.254	540.4	17.854	3.3
6f	115.401	119.97	−4.569	3.8
6q	191.319	187.97	3.491	1.9

and compared to the tested values. The correlation of the predicted and tested in vivo anti-thrombotic activities of **6p–t** is also shown in Fig. 8. The results indicate that comparing to the test value equation (2) may predict the anti-thrombotic activities with error% ranging from 0.1 to 6.8% for **6p–t**, which means that this equation is able to accurately predict an anti-thrombotic activity for unknown 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acid.

3. Conclusion

Despite great advances have been made in the prevention of thrombotic disorders by various treatments, thromboembolic diseases are still the leading cause of mortality and morbidity worldwide, and there is still an urgent need for developing anti-thrombotic drugs. In this paper, we modified anti-thrombotic active 3*S*-tetrahydroisoquinoline-3-carboxylic acid with natural amino acids to give 20 novel dipeptide analogs of *N*-(3*S*-tetrahydroisoquinoline-3-carboxyl)amino acids with higher anti-thrombotic activity than 3*S*-tetrahydroisoquinoline-3-carboxylic acid itself. As anti-thrombotic agents, the new candidates were capable of utilizing the intestinal peptide transport system as target for good absorption, optimal aqueous solubility, and good drug-likeness so as to have enhanced anti-thrombotic activity. In a previous paper, it has been demonstrated that the intestinal mucosa is a significant barrier to oral delivery of drugs into the systemic circulation, Caco-2 cells possess many structural and functional similarities to human enterocytes, and the apparent permeability of THCA is increased by amino acid modification [43]. By analyzing their 3D QSAR, the present paper is not only able to help us getting insight into the quantitative correlation of the structure and the in vitro and in vivo activities of these 20 novel dipeptide analogs, but also able to help us predicting the in vitro and in vivo activities of unknown dipeptide analogs.

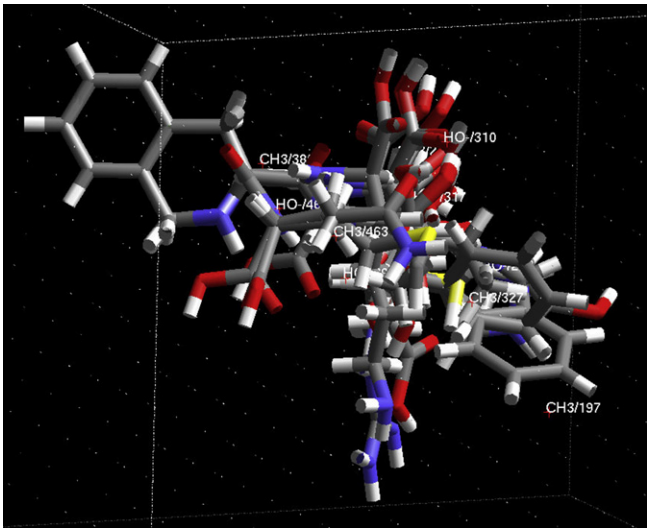


Fig. 7. Steric and electrostatic features of **6a–p** leading to in vivo activity changes.

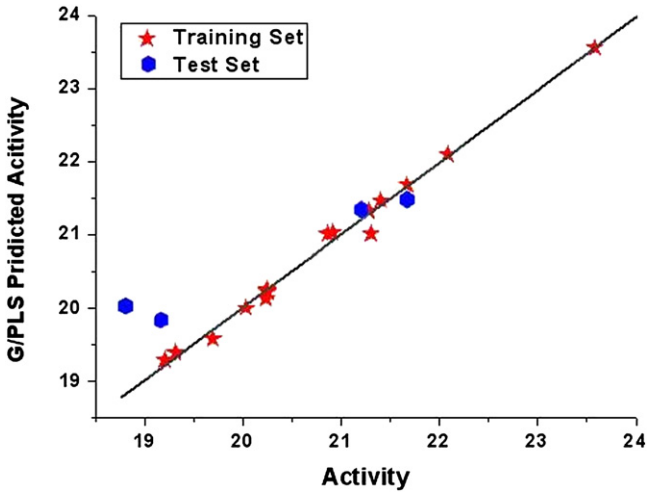


Fig. 8. Graph of tested versus predicted anti-thrombotic activities of **6a–p**.

4. Materials and methods

4.1. General

All the reactions were carried out under nitrogen (1 bar). ^1H (300 and 500 MHz) and ^{13}C (75 and 125 MHz) NMR spectra were recorded on Bruker AMX-300 and AMX-500 spectrometers for solution DMSO-d_6, or $CDCl_3$ with tetramethylsilane as internal standard. IR spectra were recorded with a Perkin-Elmer 983 instrument. FAB/MS was determined on VG-ZAB-MS and TOF-MS was recorded on MDS SCIEX QSTAR. Melting points were measured on a XT5 hot stage microscope (Beijing key electro-optic factory). All L-amino acids were purchased from China Biochemical Corp. TLC was made with Qingdao silica gel GF_{254}. Chromatography was performed with Qingdao silica gel H_{60} or Sephadex-LH_{20}. All solvents were distilled and dried before use by reference to literature procedures. Optical rotations were determined with a Jasco P-1020 Polarimeter at 20 °C. The statistical analysis of all the biological data was carried out by use of ANOVA test, $p < 0.05$ is considered significant.

4.2. Chemical synthesis

4.2.1. (3S)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (**2**)

To the suspension of 5.0 g (0.03 mmol) of L-Phe–OH in 50 ml of chloroform and 27 ml of formaldehyde, 45 ml of concentrated hydrochloric acid was added drop-wise. The reaction mixture was stirred at 80–90 °C for 10 h, and TLC ($CHCl_3/CH_3OH$, 10:1) indicates the complete disappearance of L-Phe. The reaction mixture was cooled to room temperature and the formed precipitates were collected by filtration. The collected solids were successively washed with water (30 ml × 3) and acetone (30 ml × 3) to give 4.5 g (84%) of the title compound as a white powder. Mp 302–303 °C; $[\alpha]_D^{20} = -68$ ($c = 1.0$, H_2O); ESI-MS (m/e) 178$[M+H]^+$; ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.0 (s, 1H), 7.25 (m, $J = 6.4$ Hz, 2H), 7.02 (d, $J = 6.5$ Hz, 1H), 6.98 (t, $J = 6.6$ Hz, 1H), 3.80 (m, 3H), 3.03 (d, $J = 7.5$ Hz, 1H), 2.78(d, $J = 8.4$ Hz, 1H), 2.0(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 174.9, 136.2, 134.2, 127.2, 126.0, 57.6, 47.4, 29.4.

4.2.2. 3S-2-Tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**3**)

To the suspension of 2.49 g (62.2 mmol) of NaOH, 62.2 ml of water, and 10.0 g (56.5 mmol) of 3*S*-1,2,3,4-tetrahydroisoquinoline-

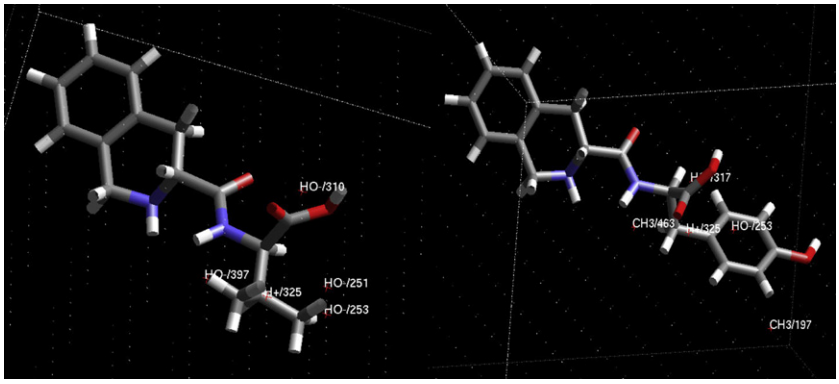


Fig. 9. Steric and electrostatic environments of **6c**,**h** with higher in vivo anti-thrombotic activity within the grid with 3D points of equation (2).

3-carboxylic acid, the solution of 14.8 g (67.8 mmol) of Boc_2O in 40 ml of THF was added at 0 °C. The suspension was stirred at room temperature for 48 h to form a clean solution, and TLC (ethyl acetate/petroleum ether, 1:3) indicated complete disappearance of 3*S*-1,2,3,4-tetra- hydroisoquinoline-3-carboxylic acid. The reaction mixture was evaporated under vacuum, and the residue was dissolved in 100 ml of ethyl acetate. The solution was washed successively with 5% aqueous solution of $KHSO_4$ (30 ml × 3) and saturated aqueous solution of NaCl (30 ml × 3), and dried with anhydrous Na_2SO_4. After filtration, the filtrate was evaporated under vacuum and the residue was triturated with petroleum ether to give 12.5 g (80%) of the title compound as a colorless powder. ESI-MS (*m*/*e*) 278 $[M+H]^+$; $[\alpha]_D^{20} = -6.78$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 11.2 (s, 1 H), 7.56 (d, *J* = 7.5 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.23 (t, *J* = 8.2 Hz, 1 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 4.14 (m, *J* = 5.2 Hz, 3 H), 3.13 (m, *J* = 4.1 Hz, 2 H), 2.72(m, *J* = 4.5 Hz, 2 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 176.8, 169.8, 137.5, 132.8, 129.0, 127.8, 126.9, 125.2, 82.9, 60.7, 56.9, 51.3, 28.2, 25.5.

*4.2.3. General procedure for preparing 3S-2-Boc-1,2,3,4-tetrahydro- isoquinoline-3-carbonylamino acid methylesters (**4a**–**t**)*

At 0 °C and with stirring, to the solution of 0.256 g (0.924 mmol) of 3*S*-2-Boc-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, 2 ml of anhydrous THF 0.151 g (0.109 mmol) of HOBt was added, and stirred for 10 min. And then 0.228 g (0.108 mmol) of DCC was added to form reaction mixture A. To the suspension of 0.102 mmol of HCl·AA-OMe in 4 ml of anhydrous THF, 1 ml of *N*-methylmorpholine was added and stirred at room temperature for 35 min to form reaction mixture B (pH 9). The reaction mixture A and B were combined, stirred at room temperature for 12 h, and TLC (ethyl acetate/petroleum ether, 1:3) indicated the complete disappearance of 3*S*-2-Boc-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid. The formed precipitate of DCU was removed by filtration, and the filtrate was evaporated under vacuum. The residue was dissolved in 50 ml of ethyl acetate, the formed solution was washed successively with saturated aqueous solution of $NaHCO_3$ (30 ml × 3), 5% aqueous solution of $KHSO_4$ (30 ml × 3) and saturated aqueous solution of NaCl (30 ml × 3), and dried with anhydrous Na_2SO_4. After filtration, the filtrate was evaporated under vacuum to give the title compound.

4.2.3.1. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-alanine methylester (**4a**).* Yield: 89%. Colorless powder, M.p. 84–85 °C; ESI-MS (*m*/*e*) 363 $[M+H]^+$; $[\alpha]_D^{20} = -47.46$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.72 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 7.4 Hz, 1 H), 7.34 (d, *J* = 8.1 Hz, 1 H), 7.22 (t, *J* = 7.1 Hz, 1 H), 7.12(t, *J* = 7.3 Hz, 1 H), 4.44 (t, *J* = 5.4 Hz, 1 H), 4.42 (m, *J* = 5.1 Hz, 6 H), 3.13 (m, *J* = 4.4 Hz, 2 H), 2.75 (m, *J* = 5.5 Hz, 2 H), 1.41 (s, 9 H), 1.38 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.8, 168.9, 137.2, 132.4, 129.0, 127.5, 127.1, 124.9, 83.2, 69.5, 57.2, 52.0, 53.1, 49.8, 29.2, 25.6, 16.6. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23; N, 7.73. Found C, 62.70; H, 7.41; N, 7.50.

4.2.3.2. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-glycine methylester (**4b**).* Yield: 85%. Colorless powder, M.p. 125–126 °C; ESI-MS (*m*/*e*) 349 $[M+H]^+$; $[\alpha]_D^{20} = -15.83$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.82 (d, *J* = 8.6 Hz, 1 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.54 (d, *J* = 8.6 Hz, 1 H), 7.43 (t, *J* = 7.4 Hz, 1 H), 7.15 (t, *J* = 8.5 Hz, 1 H), 4.29 (t, *J* = 6.3 Hz, 1 H), 4.15 (m, *J* = 4.3 Hz, 6 H), 3.25 (m, *J* = 5.5 Hz, 2 H), 2.95 (m, *J* = 4.6 Hz, 2 H), 1.52 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.1, 169.1, 168.9, 138.2, 132.3, 128.6, 128.1, 127.6, 124.6, 82.0, 68.1, 57.5, 54.8,

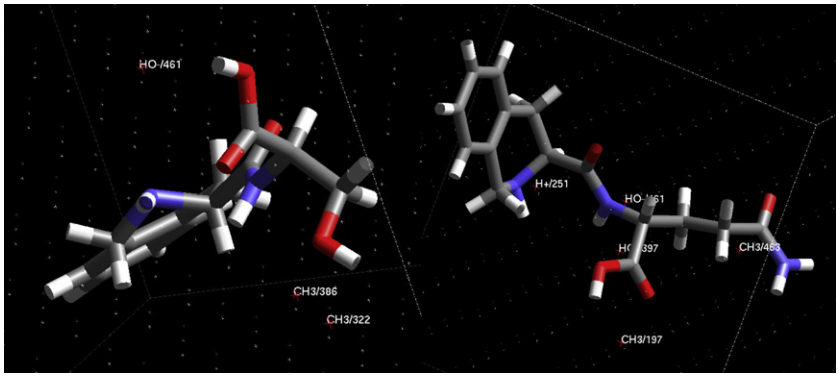


Fig. 10. Steric and electrostatic environments of **6g**,**k** with lower in vivo anti-thrombotic activity within the grid with 3D points of equation (2).

Table 5
Predicted and tested thrombus weights **6q–t**.

Comp.	Thrombus weight (mg)			
	Predict weight	Test weight	Error	Error%
6q	19.83	19.11	−0.72	3.7
6r	21.34	21.25	0.09	0.4
6s	21.47	21.24	0.23	0.1
6t	20.02	18.73	1.29	6.8

51.9, 41.2, 31.0, 26.2. Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found C, 61.82; H, 6.79; N, 8.29.

4.2.3.3. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-valine methylester* (***4c***). Yield: 86%. Colorless powder, M.p. 87–88 °C; ESI-MS (*m*/*e*) 391 $[M+H]^+$; $[\alpha]_D^{20} = -37.57$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.78 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 7.5 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.31 (t, *J* = 7.7 Hz, 1 H), 7.22 (t, *J* = 8.2 Hz, 1 H), 4.45 (m, *J* = 5.4 Hz, 6 H), 4.19 (t, *J* = 5.6 Hz, 1 H), 3.42 (m, *J* = 5.3 Hz, 2 H), 2.91 (m, *J* = 4.4 Hz, 2H), 2.17 (dd, *J* = 5.7 Hz, 2 H), 1.44 (s, 9 H), 0.97 (m, *J* = 3.2 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.8, 171.2, 169.6, 137.2, 133.6, 128.9, 127.8, 127.5, 125.6, 82.0, 68.9, 56.8, 56.0, 53.4, 52.0, 30.1, 29.3, 27.6, 17.6, 17.3. Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found C, 64.36; H, 7.60; N, 6.91.

4.2.3.4. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L- leucine methylester* (***4d***). Yield: 91%. Colorless powder, M.p. 81–83 °C; ESI-MS (*m*/*e*) 405 $[M+H]^+$; $[\alpha]_D^{20} = -14.1$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.72 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 7.5 Hz, 1 H), 7.34 (d, *J* = 8.1 Hz, 1 H), 7.24 (t, *J* = 7.3 Hz, 1 H), 7.14 (t, *J* = 8.2 Hz, 1 H), 4.25 (t, *J* = 5.4 Hz, 1 H), 4.14 (m, *J* = 5.5 Hz, 6 H), 3.14 (m, *J* = 4.3 Hz, 2 H), 2.72 (m, *J* = 5.3 Hz, 2 H), 1.47 (s, 9 H), 1.44 (s, 9 H), 0.93 (m, *J* = 4.1 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.6, 170.2, 168.2, 137.2, 133.9, 128.6, 127.8, 127.3, 125.9, 80.2, 68.9, 55.9, 53.4, 51.8, 49.5, 41.0, 29.5, 27.9, 22.9, 22.2. Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.32; H, 7.97; N, 6.93. Found C, 65.55; H, 7.81; N, 6.70.

4.2.3.5. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-isoleucine methylester* (***4e***). Yield: 89%. Colorless powder, M.p. 73–74 °C; ESI-MS (*m*/*e*) 405 $[M+H]^+$; $[\alpha]_D^{20} = -12.39$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.73 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 7.3 Hz, 1 H), 7.34 (d, *J* = 8.5 Hz, 1 H), 7.27 (t, *J* = 7.3 Hz, 1 H), 7.13 (t, *J* = 8.2 Hz, 1 H), 4.33 (m, *J* = 4.7 Hz, 6 H), 4.29 (t, *J* = 5.6 Hz, 1 H), 3.13 (m, *J* = 4.1 Hz, 2 H), 2.74 (m, *J* = 4.8 Hz, 3 H), 1.29 (dd, *J* = 5.7 Hz, 2 H), 1.56 (s, 9 H), 0.94 (m, *J* = 3.9 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.8, 171.8, 169.9, 137.2, 133.4, 128.9, 127.9, 127.3, 125.6, 81.2, 68.9, 57.0, 53.4, 53.2, 51.8, 36.4, 30.0, 27.2, 26.2, 15.8, 11.5. Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.32; H, 7.97; N, 6.93. Found C, 65.11; H, 7.82; N, 7.19.

4.2.3.6. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-tryptophan methylester* (***4f***). Yield: 87%. Colorless powder, M.p. 71–72 °C; ESI-MS (*m*/*e*) 478 $[M+H]^+$; $[\alpha]_D^{20} = -7.99$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 10.97 (s, 1 H), 9.06 (d, *J* = 8.4 Hz, 1 H), 7.72 (m, *J* = 7.5 Hz, 9 H), 4.38 (m, *J* = 5.3 Hz, 6 H), 4.30 (t, *J* = 5.1 Hz, 1 H), 3.13 (m, *J* = 4.5 Hz, 2 H), 2.69 (m, *J* = 4.0 Hz, 2 H), 1.65 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.9, 171.9, 168.9, 137.6, 136.8, 128.4, 127.9, 127.3, 125.8, 122.9, 122.6, 122.1, 119.8, 112.0, 110.9, 81.2, 68.9, 57.2, 54.3, 51.8, 30.9, 29.4, 27.6. Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found C, 67.68; H, 6.40; N, 8.57.

4.2.3.7. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-serin methylester* (***4g***). Yield: 80%. Colorless powder, M.p. 69–71 °C; ESI-MS (*m*/*e*) 379 $[M+H]^+$; $[\alpha]_D^{20} = -7.45$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.75 (d, *J* = 8.5 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 8.6 Hz, 1 H), 7.32 (t, *J* = 7.7 Hz, 1 H), 7.12 (t, *J* = 8.2 Hz, 1 H), 5.25 (s, 1 H), 4.46 (m, *J* = 5.6 Hz, 6 H), 4.36 (t, *J* = 4.9 Hz, 1 H), 3.15 (m, *J* = 4.9 Hz, 2 H), 2.69 (m, *J* = 4.1 Hz, 3 H), 1.56 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.8, 171.9, 169.7, 137.8, 134.2, 128.9, 127.5, 127.3, 125.9, 81.3, 61.9, 61.2, 57.1, 54.9, 54.4, 51.8, 29.5, 27.9. Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found C, 60.05; H, 6.80; N, 7.16.

4.2.3.8. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-tyrosine methylester* (***4h***). Yield: 82%. Colorless powder, M.p. 62–65 °C; ESI-MS (*m*/*e*) 455 $[M+H]^+$; $[\alpha]_D^{20} = -23.26$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 7.73 (d, *J* = 8.6 Hz, 1 H), 7.56 (d, *J* = 7.4 Hz, 1 H), 7.39 (d, *J* = 8.3 Hz, 1 H), 7.23 (t, *J* = 7.7 Hz, 1 H), 7.13 (t, *J* = 8.2 Hz, 5 H), 4.30 (t, *J* = 4.4 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 2 H), 4.28 (m, *J* = 4.2 Hz, 6 H), 3.13 (m, *J* = 4.3 Hz, 2 H), 2.94 (m, *J* = 4.8 Hz, 3 H), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.9, 171.6, 167.1, 156.8, 133.1, 132.4, 129.9, 129.6, 128.1, 127.8, 125.1, 127.3, 116.1, 115.7, 83.2, 69.1, 57.2, 53.8, 53.1, 52.0, 37.8, 37.2, 29.7, 27.2. Anal. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found C, 66.25; H, 6.79; N, 6.40.

4.2.3.9. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-proline methylester* (***4i***). Yield: 95%. Colorless powder, M.p. 103–104 °C; ESI-MS (*m*/*e*) 388 $[M+H]^+$; $[\alpha]_D^{20} = -22.22$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.75 (d, *J* = 8.4 Hz, 1 H), 7.56 (d, *J* = 7.5 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.20 (t, *J* = 7.7 Hz, 1 H), 7.12 (t, *J* = 8.2 Hz, 1 H), 4.42 (m, *J* = 5.8 Hz, 6 H), 4.28 (t, *J* = 4.3 Hz, 1 H), 3.76 (d, *J* = 6.3 Hz, 1 H), 3.68 (s, 1 H), 3.12 (m, *J* = 4.7 Hz, 2 H), 2.75 (m, *J* = 4.5 Hz, 3 H), 1.97 (d, *J* = 8.7 Hz, 4 H), 1.54 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.8, 172.1, 169.7, 137.1, 133.3, 127.9, 127.5, 127.2, 125.9, 82.1, 65.6, 58.6, 56.8, 53.8, 52.1, 47.1, 29.9, 28.8, 22.6. Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.93; H, 7.27; N, 7.21. Found C, 64.73; H, 7.11; N, 7.45.

4.2.3.10. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-asparagine methylester* (***4j***). Yield: 55%. Colorless powder, M.p. 101–102 °C; ESI-MS (*m*/*e*) 407 $[M+H]^+$; $[\alpha]_D^{20} = -6.50$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.72 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.23 (t, *J* = 7.7 Hz, 1 H), 7.12 (t, *J* = 8.2 Hz, 1 H), 6.20 (s, 1 H), 4.41(m, *J* = 5.4 Hz, 6 H), 4.29 (t, *J* = 4.3 Hz, 1 H), 3.12 (m, *J* = 4.5 Hz, 2 H), 2.74 (m, *J* = 4.5 Hz, 4 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 174.5, 171.8, 168.9, 137.2, 133.7, 128.6, 127.5, 127.3, 125.9, 82.9, 69.0, 53.3, 52.0, 37.2, 17.8. Anal. Calcd for $C_{20}H_{27}N_3O_6$: C, 59.25; H, 6.71; N, 10.36. Found C, 59.07; H, 6.56; N, 10.61.

4.2.3.11. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-glutamine methylester* (***4k***). Yield: 45%. Colorless powder, M.p. 100–102 °C; ESI-MS (*m*/*e*) 420 $[M+H]^+$; $[\alpha]_D^{20} = -28.78$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.72 (d, *J* = 8.5 Hz, 1 H), 8.12 (s, 1 H), 7.55 (d, *J* = 7.7 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.24 (t, *J* = 7.7 Hz, 1 H), 7.13 (t, *J* = 8.2 Hz, 1 H), 4.33 (m, *J* = 5.6 Hz, 6 H), 4.24 (t, *J* = 4.3 Hz, 1 H), 3.13 (m, *J* = 4.8 Hz, 2 H), 2.73 (m, *J* = 4.3 Hz, 6 H), 1.46 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.9, 171.9, 171.6, 168.9, 137.1, 133.5, 127.5, 127.2, 125.8, 82.3, 68.2, 56.1, 53.4, 51.3, 51.2, 34.2, 28.9, 27.2, 26.8. Anal. Calcd for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found C, 60.30; H, 6.81; N, 10.25.

4.2.3.12. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-histidine methylester* (***4l***). Yield: 65%. Colorless powder, M.p. 116–117 °C; ESI-MS (*m*/*e*) 429 $[M+H]^+$; $[\alpha]_D^{20} = -6.67$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 9.12 (s, *J* = 8.0 Hz, 1 H), 8.72 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 7.5 Hz, 1 H), 7.35

(d, $J = 8.0$ Hz, 1H), 7.21 (t, $J = 7.7$ Hz, 1 H), 7.13 (t, $J = 8.2$ Hz, 1 H), 4.29 (t, $J = 4.4$ Hz, 1 H), 4.26 (m, $J = 4.3$ Hz, 6H), 3.15 (m, $J = 5.1$ Hz, 2 H), 3.14 (m, $J = 5.0$ Hz, 2 H), 2.74 (m, $J = 4.5$ Hz, 2 H), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.9, 171.6, 168.9, 137.1, 135.6, 133.8, 133.1, 128.9, 127.5, 127.2, 125.8, 118.7, 81.3, 68.2, 56.1, 53.4, 52.2, 51.3, 30.0, 28.9, 27.2. Anal. Calcd for $C_{22}H_{28}N_4O_5$: C, 61.67; H, 6.59; N, 13.08. Found C, 61.86; H, 6.72; N, 13.34.

4.2.3.13. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-lysine(Z) benzylester (**4m**).* Yield: 95%. Syrupy. ESI-MS (m/e) 630 $[M+H]^+$; $[\alpha]_D^{20} = -19.9$ ($c = 1.0$, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.72 (d, $J = 8.4$ Hz, 1H), 6.99–7.60 (m, 14H), 5.34 (d, $J = 6.3$ Hz, 2H), 4.28 (t, 1H), 4.18 (m, 9H), 3.12 (m, 2H), 2.82 (m, 2H), 2.21 (m, 5H), 1.36 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.9, 171.6, 169.6, 142.8, 137.6, 136.5, 133.7, 125.2–128.9, 82.7, 68.8, 67.8, 56.8, 54.8, 53.7, 52.8, 49.5, 32.0, 30.2, 28.7, 27.9, 21.7. Anal. Calcd for $C_{36}H_{43}N_3O_7$: C, 68.66; H, 6.88; N, 6.67. Found C, 68.47; H, 6.72; N, 6.90.

4.2.3.14. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-aspartic acid dimethylester (**4n**).* Yield: 75%. Colorless powder, M.p. 106–107 °C; ESI-MS (m/e) 407 $[M+H]^+$; $[\alpha]_D^{20} = -3.23$($c = 1.0$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.72 (d, $J = 8.4$ Hz, 1 H), 7.55 (d, $J = 7.6$ Hz, 1 H), 7.35 (d, $J = 8.3$ Hz, 1 H), 7.28 (t, $J = 7.7$ Hz, 1 H), 7.13 (t, $J = 8.2$ Hz, 1 H), 4.31 (m, $J = 4.3$ Hz, 3 H), 4.24 (t, $J = 4.4$ Hz, 1 H), 3.73 (m, $J = 4.6$ Hz, 6 H), 3.12 (m, $J = 4.6$ Hz, 2 H), 2.89 (m, $J = 4.3$ Hz, 3 H), 2.76 (m, $J = 4.5$ Hz, 2 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.1, 172.8, 171.6, 169.6, 137.9, 133.6, 127.6, 127.0, 126.9, 124.1, 81.8, 69.5, 56.7, 53.8, 51.7, 48.2, 37.9, 29.1, 27.6. Anal. Calcd for $C_{21}H_{28}N_2O_7$: C, 59.99; H, 6.71; N, 6.66. Found C, 59.80; H, 6.57; N, 6.91.

4.2.3.15. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L- glutamic acid dimethylester (**4o**).* Yield: 78%. Colorless powder, M.p. 107–109 °C; ESI-MS (m/e) 420 $[M+H]^+$; $[\alpha]_D^{20} = -4.05$ ($c = 1.0$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.72 (d, $J = 8.5$ Hz, 1 H), 7.57 (d, $J = 7.6$ Hz, 1 H), 7.33 (d, $J = 8.7$ Hz, 1 H), 7.28 (t, $J = 7.7$ Hz, 1 H), 7.12 (t, $J = 8.2$ Hz, 1 H), 4.45 (m, $J = 5.6$ Hz, 3 H), 4.29 (t, $J = 5.5$ Hz, 1 H), 3.53 (m, $J = 4.6$ Hz, 6 H), 3.12 (m, $J = 4.5$ Hz, 2 H), 2.72 (m, $J = 4.8$ Hz, 2 H), 1.96 (m, $J = 5.2$ Hz, 4 H), 1.42 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.2, 172.8, 171.6, 169.6, 137.9, 133.6, 127.6, 127.0, 126.9, 124.1, 81.8, 69.5, 56.7, 53.8, 51.6, 50.7, 29.1, 27.8, 27.6, 26.6. Anal. Calcd for $C_{22}H_{30}N_2O_7$: C, 60.82; H, 6.96; N, 6.45. Found C, 60.99; H, 7.13; N, 6.71.

4.2.3.16. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L- cysteine methylester (**4p**).* Yield: 50%. Colorless powder, M.p. 107–110 °C; ESI-MS (m/e) 395 $[M+H]^+$; $[\alpha]_D^{20} = -25.12$ ($c = 1.0$, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, $J = 7.6$ Hz, 1 H), 7.02 (m, $J = 8.2$ Hz, 2 H), 6.95 (d, $J = 8.8$ Hz, 2 H), 4.90 (t, $J = 8.4$ Hz, 1 H), 4.71 (m, 1 H), 4.20 (t, $J = 8.3$ Hz, 2 H), 3.65 (s, 3 H), 3.07 (m, $J = 5.4$ Hz, 4 H), 1.5 (t, $J = 6.4$ Hz, 1 H), 1.41 (s, 9 H). Anal. Calcd for $C_{19}H_{26}N_2O_5S$: C, 57.85; H, 6.64; N, 7.10. Found C, 57.66; H, 6.50; N, 6.89.

4.2.3.17. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylalanine methylester (**4q**).* Yield: 87%. Colorless powder, M.p. 91–93 °C; ESI-MS (m/e) 439 $[M+H]^+$; $[\alpha]_D^{20} = -7.61$ ($c = 1.0$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 9.06(d, $J = 8.4$ Hz, 1 H), 7.25(m, $J = 7.5$ Hz, 9 H), 4.25(t, $J = 5.6$ Hz, 1 H), 4.15(m, $J = 5.2$ Hz, 6 H), 3.02(m, $J = 4.2$ Hz, 4 H), 2.93(m, $J = 5.6$ Hz, 2 H), 1.45(s, 9 H), 1.41(m, $J = 4.1$ Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 169.6, 133.3, 128.2, 128.1, 127.9, 127.5, 127.3, 126.2, 125.7, 80.2, 69.5, 53.9, 53.5, 52.0, 37.5, 29.3, 28.5, 27.5. Anal. Calcd for $C_{25}H_{30}N_2O_5$: C, 68.47; H, 6.90; N, 6.39. Found C, 68.71; H, 7.15; N, 6.63.

4.2.3.18. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-threonine methylester (**4r**).* Yield: 89%. Colorless powder, M.p. 80–81 °C; ESI-MS (m/e) 393 $[M+H]^+$; $[\alpha]_D^{20} = -42.43$ ($c = 1.0$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.73 (d, $J = 8.4$ Hz, 1 H), 7.56 (d, $J = 7.5$ Hz, 1 H), 7.33 (d, $J = 8.1$ Hz, 1 H), 7.22 (t, $J = 7.7$ Hz, 1 H), 7.14 (t, $J = 8.6$ Hz, 1 H), 4.28 (t, $J = 4.5$ Hz, 1 H), 4.29 (m, $J = 4.3$ Hz, 6 H), 3.16 (m, $J = 4.2$ Hz, 2 H), 2.74 (m, $J = 4.1$ Hz, 3 H), 2.15 (s, 1 H), 1.52 (s, 9 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.8, 171.6, 167.9, 137.1, 129.1, 127.9, 127.2, 125.6, 83.1, 68.2, 67.9, 58.2, 53.7, 51.2, 28.2, 27.8, 18.6. Anal. Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found C, 61.00; H, 7.02; N, 7.41.

4.2.3.19. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-arginine methylester (**4s**).* Yield: 51%. Colorless powder, M.p. 151–152 °C; ESI-MS (m/e) 448.3$[M+H]^+$; $[\alpha]_D^{20} = -11.56$ ($c = 1.0$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.99(s, 3 H), 8.72 (d, $J = 8.5$ Hz, 1 H), 7.54 (d, $J = 7.3$ Hz, 1 H), 7.35 (d, $J = 8.4$ Hz, 1 H), 7.24 (t, $J = 7.7$ Hz, 1H), 7.13 (t, $J = 8.3$ Hz, 1 H), 4.24 (t, $J = 5.3$ Hz, 1 H), 4.12 (m, $J = 4.3$ Hz, 6 H), 3.53 (m, $J = 4.6$ Hz, 6 H), 3.15(m, $J = 4.6$ Hz, 2 H), 2.73 (m, $J = 4.3$ Hz, 4 H), 2.11 (m, $J = 4.3$ Hz, 1 H), 1.96 (m, $J = 3.9$ Hz, 1 H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.9, 171.6, 169.6, 149.7, 137.2, 133.6, 128.9, 127.9, 127.2, 125.6, 83.2, 68.5, 57.2, 53.7, 52.7, 51.0, 37.2, 29.1, 28.7, 26.7, 24.5. Anal. Calcd for $C_{22}H_{33}N_5O_5$: C, 59.04; H, 7.43; N, 15.65. Found C, 59.23; H, 7.60; N, 15.81.

4.2.3.20. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-methionine methylester (**4t**).* Yield: 49%. Colorless powder, M.p. 143–144 °C; ESI-MS (m/e) 409 $[M+H]^+$; $[\alpha]_D^{20} = -12.90$ ($c = 1.0$, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.72 (d, $J = 8.7$ Hz, 1 H), 7.55 (d, $J = 7.6$ Hz, 1 H), 7.34 (d, $J = 8.3$ Hz, 1 H), 7.23 (t, $J = 7.7$ Hz, 1 H), 7.12 (t, $J = 8.2$ Hz, 1 H), 4.32 (t, $J = 4.5$ Hz, 1H), 4.25 (m, $J = 4.9$ Hz, 6 H), 3.12 (m, $J = 4.3$ Hz, 2 H), 2.81 (m, $J = 4.9$ Hz, 2 H), 2.35 (m, $J = 4.6$ Hz, 2 H), 1.42 (s, 9 H), 1.27 (m, $J = 4.2$ Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ/ppm = 171.8, 171.6, 169.2, 137.6, 128.9, 127.6, 127.2, 125.8, 81.3, 69.1, 56.7, 53.2, 52.9, 52.3, 31.2, 29.1, 27.9, 17.8. Anal. Calcd for $C_{21}H_{30}N_2O_5S$: C, 59.69; H, 7.16; N, 6.63. Found C, 59.88; H, 7.00; N, 6.88.

*4.2.4. General procedure preparing 3S-2-Boc-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids (**5a**–**t**)*

At 0 °C to the solution of 1.0 mmol of 3*S*-2-Boc-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acid methylester in 5 ml of methanol, was added 7 ml of 2 N aqueous of NaOH to adjust pH 11. The reaction mixture was stirred at 0 °C for 3 h, and TLC (CCl_3/CH_3OH, 5:1) indicated the complete disappearance of 3*S*-2-Boc-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acid methylester. The reaction mixture was adjusted to pH 7 with aqueous solution of $KHSO_4$. The solution was evaporated under vacuum to remove methanol, adjusted pH 2 with aqueous solution of $KHSO_4$ and extracted with ethyl acetate (30 ml × 3). The combined ethyl acetate was successively washed with saturated aqueous solution of NaCl (20 ml × 2) and dried with anhydrous Na_2SO_4. After filtration, the filtrate was evaporated to provide the title compound.

4.2.4.1. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-alanine (**5a**).* Yield: 96%. Colorless powder, M.p. 122–123 °C; ESI-MS (m/e) 348 $[M-H]^-$; $[\alpha]_D^{20} = -7.98$ ($c = 1.0$, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, $J = 7.6$ Hz, 1 H), 7.02 (m, $J = 8.2$ Hz, 2 H), 6.95 (d, $J = 8.8$ Hz, 2 H), 4.93 (d, $J = 5.4$ Hz, 1H), 4.63 (m, 1 H), 4.20(d, $J = 5.4$ Hz, 2 H), 3.18 (d, $J = 5.5$ Hz, 1 H), 2.92 (d, $J = 8.5$ Hz, 1 H), 1.45 (d, $J = 6.3$ Hz, 3 H), 1.41

(s, 9 H). Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found C, 62.24; H, 6.80; N, 7.78.

4.2.4.2. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-glycine (**5b**).* Yield: 99%. Colorless powder, M.p. 147–149 °C; ESI-MS (*m*/*e*) 333 [M-H]$^-$; $[\alpha]_D^{20} = -0.13$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.01 (d, *J* = 7.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.90 (d, *J* = 5.4 Hz, 1 H), 4.21 (m, *J* = 8.2 Hz, 2 H), 4.15(m, *J* = 8.2 Hz, 2 H), 3.15 (d, *J* = 6.2 Hz, 1 H), 2.85 (d, *J* = 6.2 Hz, 1 H), 1.41 (s, 9 H). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found C, 61.25; H, 6.50; N, 8.16.

4.2.4.3. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-valine (**5c**).* Yield: 93%. Colorless powder, M.p. 116–119 °C; ESI-MS (*m*/*e*) 407 [M-H]$^-$; $[\alpha]_D^{20} = -6.53$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 6.7 Hz, 1 H), 7.01 (m, *J* = 8.1 Hz, 2 H), 6.96 (d, *J* = 8.8 Hz, 2 H), 4.90 (d, *J* = 7.4 Hz, 1 H), 4.51 (d, *J* = 5.3 Hz, 1 H), 4.24 (m, 2 H), 3.05 (m, 2 H), 2.80 (m, 1 H), 1.41 (s, 9 H), 1.21 (d, *J* = 8.7 Hz, 6 H). Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found C, 63.60; H, 7.66; N, 7.68.

4.2.4.4. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L- leucine (**5d**).* Yield: 90%. Colorless powder, M.p. 119–120 °C; ESI-MS (*m*/*e*) 389 [M-H]$^-$; $[\alpha]_D^{20} = -8.91$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.02 (d, *J* = 8.6 Hz, 1 H), 7.04 (m, *J* = 8.2 Hz, 2 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 4.90 (d, *J* = 7.4 Hz, 1 H), 4.50 (m, 1 H), 4.22 (m, *J* = 8.6 Hz, 2 H), 3.10 (m, 2 H), 1.78 (m, 3 H), 1.41 (s, 9 H), 1.01 (d, *J* = 7.6 Hz, 6 H). Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found C, 64.80; H, 7.89; N, 7.40.

4.2.4.5. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-isoleucine (**5e**).* Yield: 94%. Colorless powder, M.p. 105–108 °C; ESI-MS (*m*/*e*) 389 [M-H]$^-$; $[\alpha]_D^{20} = -9.13$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CHCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 5.6 Hz, 1 H), 7.01 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.91 (d, *J* = 6.4 Hz, 1 H), 4.51 (m, 1 H), 4.21 (m, *J* = 8.6 Hz, 2 H), 3.10 (m, 2 H), 2.58 (m, 1 H), 1.41 (s, 9 H), 1.29 (m, 2 H), 1.06 (d, *J* = 7.6 Hz, 3 H), 0.96 (d, *J* = 8.5 Hz, 3 H). Anal. Calcd for $C_{21}H_{30}N_2O_5$: C, 64.59; H, 7.74; N, 7.17. Found C, 64.80; H, 7.89; N, 7.51.

4.2.4.6. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-tryptophan (**5f**).* Yield: 90%. Colorless powder, M.p. 115–116 °C; ESI-MS (*m*/*e*) 462 [M-H]$^-$; $[\alpha]_D^{20} = -17.67$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 10.10 (s, 1 H), 8.00 (d, *J* = 5.6 Hz, 1 H), 7.18 (m, *J* = 6.4 Hz, 4 H), 7.02 (m, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2 H), 6.80 (d, *J* = 6.4 Hz, 1H), 4.90 (d, *J* = 7.1 Hz, 1 H), 4.81 (d, *J* = 7.4 Hz, 1 H), 4.21 (m, 2 H), 3.10 (m, 4 H), 1.41(s, 9 H). Anal. Calcd for $C_{26}H_{29}N_3O_5$: C, 67.37; H, 6.31; N, 9.07. Found C, 67.15; H, 6.14; N, 9.30.

4.2.4.7. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-serin (**5g**).* Yield: 93%. Colorless powder, M.p. 102–104 °C; ESI-MS (*m*/*e*) 363 [M-H]$^-$; $[\alpha]_D^{20} = -3.30$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 5.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.83 (m, 1 H), 4.53 (m, 1 H), 4.21 (m, 2 H), 3.96 (m, 2 H), 3.19 (d, *J* = 8.2 Hz, 1 H), 2.95 (d, *J* = 6.4 Hz, 1 H), 1.41 (s, 9 H). Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found C, 59.52; H, 6.79; N, 7.90.

4.2.4.8. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxyl)-L-tyrosine (**5h**).* Yield: 90%. Colorless powder, M.p. 99–100 °C; ESI-MS (*m*/*e*) 439 [M-H]$^-$; $[\alpha]_D^{20} = -11.52$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1H), 8.00 (d, *J* = 8.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.72 (d, *J* = 5.5 Hz, 2 H), 4.92 (m, 3 H), 4.21 (m, 2 H), 3.19 (d, *J* = 5.3 Hz, 1 H), 3.05 (d, *J* = 6.5 Hz, 1 H), 2.92 (m, 2 H), 1.41(s, 9 H). Anal. Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found C, 65.23; H, 6.56; N, 6.60.

4.2.4.9. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-proline (**5i**).* Yield: 93%. Colorless powder, M.p. 169–170 °C; ESI-MS (*m*/*e*) 373 [M-H]$^-$; $[\alpha]_D^{20} = -6.06$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.90 (t, *J* = 7.4 Hz, 1 H), 4.31 (m, 1 H), 4.20 (t, *J* = 8.3 Hz, 2 H), 3.46 (m, 2 H), 3.01 (m, 2 H), 2.20 (m, 2 H), 1.97 (m, 2 H), 1.41 (s, 9 H). Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.15; H, 7.00; N, 7.48. Found C, 64.34; H, 6.84; N, 7.70.

4.2.4.10. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-asparagine (**5j**).* Yield: 90%. Colorless powder, M.p. 137–139 °C; ESI-MS (*m*/*e*) 407 [M-H]$^-$; $[\alpha]_D^{20} = -9.42$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 5.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 5.85 (s, 2 H), 4.85 (m, 1 H), 4.71 (m, *J* = 7.1 Hz, 1 H), 4.21 (m, *J* = 8.0 Hz, 2 H), 3.16 (m, 2 H), 2.68 (m, 2 H), 1.41 (s, 9 H). Anal. Calcd for $C_{19}H_{25}N_3O_6$: C, 58.30; H, 6.44; N, 10.74. Found C, 58.11; H, 6.30; N, 10.52.

4.2.4.11. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-glutamine (**5k**).* Yield: 98%. Colorless powder, M.p. 154–157 °C; ESI-MS (*m*/*e*) 421 [M-H]$^-$; $[\alpha]_D^{20} = -45.38$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 5.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 5.85 (s, 2 H), 4.85 (m, 1 H), 4.51 (m, *J* = 7.1 Hz, 1 H), 4.22 (m, *J* = 8.0 Hz, 2 H), 3.06 (m, 2 H), 2.18 (m, *J* = 7.2 Hz, 2 H), 2.06 (m, 2 H), 1.41 (s, 9 H). Anal. Calcd for $C_{20}H_{27}N_3O_6$: C, 59.25; H, 6.71; N, 10.36. Found C, 59.44; H, 6.56; N, 10.13.

4.2.4.12. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-histidine (**5l**).* Yield: 75%. Colorless powder, M.p. 150–151 °C; ESI-MS (*m*/*e*) 413 [M-H]$^-$; $[\alpha]_D^{20} = -12.8$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 13.40 (d, *J* = 5.6 Hz, 1 H), 11.01 (s, 1 H), 8.00 (s, 1 H), 7.44 (s, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.80 (d, *J* = 7.6 Hz, 1 H), 4.92 (t, *J* = 8.5 Hz, 1 H), 4.80 (t, *J* = 6.4 Hz, 1 H), 4.21 (m, 2 H), 3.17 (m, 2 H), 2.92 (m, 2 H), 1.41 (s, 9 H). Anal. Calcd for $C_{21}H_{26}N_4O_5$: C, 60.86; H, 6.32; N, 13.52. Found C, 60.65; H, 6.48; N, 13.72.

4.2.4.13. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-lysine (**5m**).* The solution of 1.5 g (2.38 mmol) of 3*S*-2-Boc-1,2,3,4-tetrahydroisoquinoline-3- carbonyl-L-lysine(Z) benzylester (**4p**) in 5 ml anhydrous ethanol was mixed with 0.200 g of Pt/C. To the suspension hydrogen was bubbled for 96 h and TLC ($CHCl_3$/CH_3OH, 1:1) indicated complete disappearance of **4p**. After filtration the filtrate was evaporated to give 0.92 g (96%) of title compound as a syrupy. ESI-MS (m/e) 404 [M-H]$^-$; $[\alpha]_D^{20} = -3.4$ (*c* = 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.70 (s, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 7.29 (m, 14H), 4.28 (t, 1H), 4.18 (m, 3H), 3.12 (m, 2H), 2.82 (m, 2H), 2.21 (m, 5H), 1.36 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 172.9, 171.6, 169.6, 142.8, 137.6, 136.6, 134.7, 125.2–128.7, 82.7, 68.8, 67.8, 56.8, 54.8, 53.7, 52.8, 32.0, 30.2, 28.9, 27.9, 22.7. Anal. Calcd for $C_{21}H_{31}N_3O_5$: C, 62.20; H, 7.71; N, 10.36. Found C, 62.00; H, 7.58; N, 13.59.

4.2.4.14. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-aspartic acid (**5n**).* Yield: 65%. Colorless powder, M.p. 131–133 °C; ESI-MS (*m*/*e*) 391 [M-H]$^-$; $[\alpha]_D^{20} = -7.93$ (*c* = 1.0, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 2 H), 8.00 (d, *J* = 8.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.91 (m, 1 H), 4.78 (m, 1 H), 4.21 (m, 2 H), 3.09 (m, 2H), 2.68 (m, 2 H), 1.41 (s, 9 H). Anal. Calcd for $C_{19}H_{24}N_2O_7$: C, 58.16; H, 6.16; N, 7.14. Found C, 58.35; H, 6.30; N, 7.39.

4.2.4.15. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L- glutamic acid (**5o**).* Yield: 89%. Colorless powder, M.p. 125–128 °C; ESI-MS (*m*/*e*) 405 $[M-H]^-$; $[\alpha]_D^{20} = -10.46$ (*c* = 1.0, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 2 H), 8.00 (d, *J* = 8.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.91 (m, 1 H), 4.48 (m, 1 H), 4.21 (m, 2 H), 3.09 (m, 2H), 2.24 (m, 2 H), 2.04 (m, 2 H), 1.41 (s, 9 H). Anal. Calcd for $C_{20}H_{26}N_2O_7$: C, 59.10; H, 6.45; N, 6.89. Found C, 59.30; H, 6.51; N, 7.12.

4.2.4.16. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L- cysteine (**5p**).* Yield:86%. Colorless powder, M.p. 146–148 °C; ESI-MS (*m*/*e*) 757 $[M-H]^-$; $[\alpha]_D^{20} = -25.12$ (*c* = 1.0, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 7.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.90 (t, *J* = 8.4 Hz, 1 H), 4.81 (m, 1 H), 4.20 (t, *J* = 8.3 Hz, 2 H), 3.17 (m, *J* = 5.4 Hz, 2 H), 2.92 (m, *J* = 5.4 Hz, 2 H), 1.5 (t, *J* = 6.4 Hz, 1 H), 1.41 (s, 9 H). Anal. Calcd for $C_{18}H_{24}N_2O_5S$: C, 56.82; H, 6.36; N, 7.36. Found C, 56.61; H, 6.22; N, 7.27.

4.2.4.17. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylalanine (**5q**).* Yield: 96%. Colorless powder, M.p. 121–122 °C; ESI-MS (*m*/*e*) 423 $[M-H]^-$; $[\alpha]_D^{20} = -9.73$ (*c* = 1.0, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 7.6 Hz, 1 H), 7.11 (m, *J* = 8.2 Hz, 2H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.97 (d, *J* = 8.9 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 3 H), 4.92 (d, *J* = 5.5 Hz, 1 H), 4.81 (d, *J* = 6.5 Hz, 1 H), 4.21 (m, *J* = 8.6 Hz, 2 H), 3.17 (m, *J* = 5.6 Hz, 2 H), 2.90 (m, *J* = 5.6 Hz, 2 H), 1.41 (s, 9 H). Anal. Calcd for $C_{24}H_{28}N_2O_5$: C, 67.91; H, 6.65; N, 6.60. Found C, 67.70; H, 6.51; N, 6.38.

4.2.4.18. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-threonine (**5r**).* Yield: 98%. Colorless powder, M.p. 116–117 °C; ESI-MS (*m*/*e*) 377 $[M-H]^-$; $[\alpha]_D^{20} = -59.69$ (*c* = 1.0, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 6.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.80 (t, *J* = 7.6 Hz, 1 H), 4.61 (d, 1 H), 4.35 (m, 1 H), 4.21 (m, 2 H), 3.29 (d, *J* = 8.6 Hz, 1 H), 3.05 (d, *J* = 5.5 Hz, 1 H), 2.0 (s, 1 H), 1.41 (s, 9 H), 1.21 (d, *J* = 7.6 Hz, 3 H). Anal. Calcd for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found C, 60.49; H, 6.80; N, 7.62.

4.2.4.19. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-arginine (**5s**).* Yield: 86%. Colorless powder, M.p. 182–184 °C; ESI-MS (*m*/*e*) 432 $[M-H]^-$; $[\alpha]_D^{20} = -20.52$ (*c* = 1.0, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 5.6 Hz, 2 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.94 (m, 1 H), 4.53 (m, 1 H), 4.21 (m, 2 H), 3.17 (m, 1 H), 2.94 (m, 1 H), 2.65 (m, 2 H), 2.0 (d, *J* = 6.2 Hz, 2 H), 1.79 (m, 2 H), 1.55 (m, 2 H), 1.41 (s, 9 H). Anal. Calcd for $C_{21}H_{31}N_5O_5$: C, 58.18; H, 7.21; N, 16.16. Found C, 58.40; H, 7.36; N, 16.40.

4.2.4.20. N-*(3S-2-Tertbutoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-methionine (**5t**).* Yield: 95%. Colorless powder, M.p. 144–145 °C; ESI-MS (*m*/*e*) 407 $[M-H]^-$; $[\alpha]_D^{20} = -9.83$ (*c* = 1.0, methanol); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 11.00 (s, 1 H), 8.00 (d, *J* = 7.6 Hz, 1 H), 7.02 (m, *J* = 8.2 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 4.90 (t, *J* = 8.4 Hz, 1 H), 4.51 (m, 1 H), 4.20 (t, *J* = 8.3 Hz, 2 H), 3.02 (d, *J* = 5.4 Hz, 2 H), 2.44 (m, 2 H), 2.16 (t, *J* = 6.4 Hz, 2 H), 2.09 (s, 3 H), 1.41 (s, 9 H). Anal. Calcd for $C_{20}H_{28}N_2O_5S$: C, 58.80; H, 6.91; N, 6.86. Found C, 58.99; H, 6.77; N, 7.10.

*4.2.5. General procedure preparing 3S-1,2,3,4-tetrahydroisoquinoline-3-carbonyl-L-amino acids (**6a–t**)*

To the solution of 0.86 mmol of 3*S*-2-Boc-1,2,3,4-tetrahydroisoquinoline-3-carbonyl-L-amino acid in 5 ml of ethyl acetate, 6 ml of 4 N hydrogen chloride/ethyl acetate solution was added at 0 °C. The reaction mixture was stirred at room temperature for 4 h, and TLC (CCl_3/CH_3OH, 5:1) indicated the complete disappearance of 3*S*-2-Boc-1,2,3,4-tetrahydroisoquinoline-3-carbonyl-L-amino acid. The reaction mixture was evaporated under vacuum to dry and the residue was dissolved in 5 ml of ethyl acetate. The solution was evaporated under vacuum to dry and the residue was re-dissolved in 5 ml of ethyl acetate. This procedure was repeated for three times to provide the title compound as colorless powder.

4.2.5.1. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-alanine (**6a**).* Yield: 95%. Colorless powder, M.p. 121–123 °C; ESI-MS (*m*/*e*) 248 $[M+H]^+$; $[\alpha]_D^{20} = -164$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 12.9 (s, 1 H), 8.91 (m, *J* = 5.9 Hz, 1 H), 8.72 (d, *J* = 8.4 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 7.23 (t, *J* = 7.2 Hz, 1 H), 7.13 (t, *J* = 8.2 Hz, 1 H), 4.44 (t, *J* = 8.2 Hz, 1 H), 4.35 (m, *J* = 4.6 Hz, 3 H), 2.73 (m, *J* = 4.3 Hz, 2 H), 1.38 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 174.8, 168.9, 137.2, 132.4, 129.0, 127.5, 127.1, 124.9, 69.5, 57.2, 53.1, 50.8, 25.6, 16.7. Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found C, 63.11; H, 6.64; N, 11.51.

4.2.5.2. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-glycine (**6b**).* Yield: 95%. Colorless powder, M.p. 150–152 °C; ESI-MS (*m*/*e*) 235 $[M+H]^+$; $[\alpha]_D^{20} = -32.0$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 12.9(s, 1 H), 8.91 (m, *J* = 8.1 Hz, 1 H), 8.73 (d, *J* = 8.4 Hz, 1 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.25 (t, *J* = 7.7 Hz, 1 H), 7.13 (t, *J* = 8.3 Hz, 1 H), 4.45 (t, *J* = 5.1 Hz, 1 H), 4.24 (m, *J* = 5.3 Hz, 3 H), 2.74 (m, *J* = 5.6 Hz, 2 H), 1.38 (d, *J* = 4.6 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.1, 169.1, 138.2, 132.3, 128.6, 127.7, 127.1, 124.7, 69.1, 57.2, 54.8, 42.2, 26.2. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found C, 61.34; H, 5.86; N, 11.73.

4.2.5.3. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-valine (**6c**).* Yield: 95%. Colorless powder, M.p. 203–204 °C; ESI-MS (*m*/*e*) 277 $[M+H]^+$; IR (cm^{-1}) 3286, 2963, 1669, 1576, 1457, 1399, 750; $[\alpha]_D^{20} = -14.0$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 12.19 (s, 1 H), 8.91 (m, *J* = 8.7 Hz, 1 H), 8.72 (d, *J* = 8.4 Hz, 1 H), 7.60 (d, *J* = 7.5 Hz, 1 H), 7.43 (d, *J* = 8.1 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H), 7.13 (t, *J* = 8.0 Hz, 1 H), 4.46 (t, *J* = 5.6 Hz, 1 H), 4.13 (m, *J* = 6.1 Hz, 3 H), 2.72 (m, *J* = 4.5 Hz, 2 H), 2.18 (dd, *J* = 5.7 Hz, 1 H), 0.95 (m, *J* = 3.5 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.8, 171.2, 137.2, 133.6, 128.9, 127.8, 127.5, 125.6, 68.9, 56.8, 56.0, 53.4, 30.1, 27.6, 17.8, 17.2. Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found C, 65.39; H, 7.44; N, 10.37.

4.2.5.4. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-leucine (**6d**).* Yield: 90%. Colorless powder, M.p. 145–147 °C; ESI-MS (*m*/*e*) 291 $[M+H]^+$; $[\alpha]_D^{20} = -16$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 12.22 (s, 1 H), 8.92 (m, *J* = 8.7 Hz, 1 H), 8.74 (d, *J* = 8.3 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 7.23 (t, *J* = 7.7 Hz, 1 H), 7.14 (t, *J* = 8.3 Hz, 1 H), 4.46 (t, *J* = 5.3 Hz, 1 H), 4.28 (t, *J* = 5.7 Hz, 1 H), 4.27 (m, *J* = 5.7 Hz, 3 H), 2.74 (m, *J* = 4.7 Hz, 2 H), 1.80 (m, *J* = 4.2 Hz, 3 H), 0.93 (m, *J* = 3.8 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.3, 170.2, 137.2, 134.9, 128.6, 127.8, 127.3, 125.9, 68.9, 55.9, 53.4, 49.5, 41.0, 27.6, 22.4, 21.9. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found C, 66.37; H, 7.79; N, 9.86.

4.2.5.5. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-isoleucine (**6e**).* Yield: 95%. Colorless powder, M.p. 126–129 °C; ESI-MS (*m*/*z*) 291 $[M+H]^+$; $[\alpha]_D^{20} = -10$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 12.91 (s, 1H), 8.92 (m, *J* = 8.7 Hz, 1 H), 8.73 (d, *J* = 8.3 Hz, 1 H), 7.58 (d, *J* = 7.5 Hz, 1 H), 7.33 (d, *J* = 8.1 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.13 (t, *J* = 8.3 Hz, 1 H), 4.53 (t, *J* = 4.7 Hz, 1 H), 4.33 (m, *J* = 5.7 Hz, 3 H), 4.27 (t, *J* = 4.8 Hz, 1 H), 2.74 (m, *J* = 3.9 Hz, 3 H), 1.28 (dd, *J* = 5.7 Hz, 2 H), 0.96 (m, *J* = 3.2 Hz, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.8, 170.8, 137.2, 133.4, 128.9, 127.9, 127.3,

125.6, 68.9, 57.0, 53.4, 53.2, 36.4, 27.2, 16.8, 12.3. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found C, 66.00; H, 7.51; N, 9.88.

4.2.5.6. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-tryptophan (**6f**).* Yield: 91%. Colorless powder, M.p. 146–147 °C; ESI-MS (*m*/*e*) 364 $[M+H]^+$; IR (cm^{-1}) 3056, 1733, 1554, 1500, 1434, 743; $[\alpha]_D^{20} = -152$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 10.97 (s, 1 H), 10.91 (s, 1 H), 9.06 (d, *J* = 8.3 Hz, 1 H), 8.86 (m, *J* = 8.1 Hz, 1 H), 7.21 (m, *J* = 7.1 Hz, 9 H), 4.55 (m, *J* = 4.8 Hz, 3 H), 4.26 (t, *J* = 5.9 Hz, 1 H), 2.81 (m, *J* = 3.8 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.9, 171.9, 168.9, 137.6, 136.8, 128.9, 128.4, 127.9, 127.3, 125.8, 122.9, 122.6, 122.1, 119.7, 112.8, 111.9, 69.9, 57.2, 54.3, 29.5, 26.6. Anal. Calcd for $C_{21}H_{23}N_3O_4$: C, 66.13; H, 6.08; N, 11.02. Found C, 65.92; H, 5.87; N, 11.26.

4.2.5.7. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-serin (**6g**).* Yield: 95%. Colorless powder, M.p. 101–104 °C; ESI-MS (*m*/*z*) 265 $[M+H]^+$; IR (cm^{-1}) 3321, 2982, 1683, 1556, 1500, 1434, 750; $[\alpha]_D^{20} = -22.52$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 11.91 (s, 1 H), 8.86 (m, *J* = 8.3 Hz, 1 H), 8.83 (d, *J* = 8.4 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 7.21 (d, *J* = 8.6 Hz, 1 H), 7.13 (t, *J* = 8.3 Hz, 1 H), 7.03 (t, *J* = 7.7 Hz, 1 H), 5.25 (s, 1 H), 4.33 (m, *J* = 5.3 Hz, 3 H), 4.04 (t, *J* = 5.3 Hz, 1 H), 2.74 (m, *J* = 3.9 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.8, 171.6, 137.8, 134.2, 128.9, 127.5, 127.3, 125.9, 61.9, 61.2, 57.1, 54.9, 54.4, 28.9. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found C, 59.30; H, 6.25; N, 10.39.

4.2.5.8. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-tyrosine (**6h**).* Yield: 96%. Colorless powder, M.p. 120–124 °C; ESI-MS (*m*/*z*) 341 $[M+H]^+$; $[\alpha]_D^{20} = -72$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 11.91 (s, 1 H), 9.06 (d, *J* = 8.3 Hz, 1 H), 8.97 (d, *J* = 7.3 Hz, 1 H), 8.86 (m, *J* = 8.2 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 8.3 Hz, 1 H), 7.22 (t, *J* = 6.8 Hz, 1 H), 7.21 (t, *J* = 8.1 Hz, 1 H), 7.15 (m, *J* = 7.2 Hz, 4 H), 6.70 (d, *J* = 8.4 Hz, 2 H), 4.32 (m, *J* = 5.7 Hz, 3 H), 4.23 (t, *J* = 5.4 Hz, 1 H), 2.94 (m, *J* = 4.5 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.9, 171.6, 156.8, 133.1, 132.4, 129.9, 129.6, 128.1, 127.8, 127.3, 125.1, 117.1, 115.7, 69.1, 57.2, 53.8, 53.1, 37.8, 37.2, 22.2. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found C, 67.24; H, 5.77; N, 8.00.

4.2.5.9. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-proline (**6i**).* Yield: 98%. Colorless powder, M.p. 115–116 °C; ESI-MS (*m*/*z*) 275 $[M+H]^+$; IR (cm^{-1}) 3321, 2949, 1739, 1564, 1448, 1434, 750; $[\alpha]_D^{20} = -14.06$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 11.14 (s, 1 H), 8.87 (m, *J* = 5.7 Hz, 1 H), 7.46 (d, *J* = 7.6 Hz, 1 H), 7.28 (d, *J* = 8.1 Hz, 1 H), 7.21 (t, *J* = 8.1 Hz, 1 H), 7.02 (t, *J* = 6.7 Hz, 1 H), 4.35 (m, *J* = 4.6 Hz, 3 H), 4.25 (t, *J* = 4.5 Hz, 1 H), 3.76 (d, *J* = 6.3 Hz, 1 H), 3.68 (s, 1 H), 2.83 (m, *J* = 5.6 Hz, 2 H), 1.97 (d, *J* = 8.7 Hz, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.8, 172.2, 137.1, 133.3, 127.9, 127.5, 127.2, 125.9, 66.6, 58.6, 56.8, 53.8, 52.1, 28.9, 22.7. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found C, 65.47; H, 6.47; N, 10.00.

4.2.5.10. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-asparagine (**6j**).* Yield: 95%. Colorless powder, M.p. 100–101 °C; ESI-MS (*m*/*z*) 292 $[M+H]^+$; $[\alpha]_D^{20} = -22$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 11.91 (s, 1 H), 9.06 (d, *J* = 8.5 Hz, 1 H), 8.87 (m, *J* = 8.3 Hz, 1 H), 8.73 (d, *J* = 8.3 Hz, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.36 (t, *J* = 6.9 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H), 7.27 (t, *J* = 8.1 Hz, 1 H), 6.21 (s, 1 H), 4.37 (m, *J* = 5.9 Hz, 3 H), 4.27 (t, *J* = 5.6 Hz, 1 H), 2.85 (m, *J* = 5.3 Hz, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.5, 171.8, 137.2, 134.7, 128.6, 127.5, 127.1, 125.9, 69.0, 53.3, 37.3, 17.9. Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found C, 57.91; H, 5.72; N, 14.65.

4.2.5.11. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-glutamine (**6k**).* Yield: 95%. Colorless powder, M.p. 87–89 °C; ESI-MS (*m*/*z*) 306.2$[M+H]^+$; $[\alpha]_D^{20} = -62$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 11.91 (s, 1H), 9.07 (d, *J* = 8.6 Hz, 1 H), 8.87 (m, *J* = 6.7 Hz, 1 H), 8.73 (d, *J* = 8.1 Hz, 1 H), 8.1 (m, *J* = 7.9 Hz, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.29 (d, *J* = 8.7 Hz, 1 H), 7.33 (t, *J* = 6.7 Hz, 1 H), 7.24 (t, *J* = 8.1 Hz, 1 H), 4.28 (t, *J* = 4.9 Hz, 1 H), 4.26 (m, *J* = 5.7 Hz, 3 H), 2.83 (m, *J* = 4.9 Hz, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.8, 172.9, 171.6, 137.1, 133.5, 128.9, 127.5, 127.2, 125.8, 68.2, 56.2, 53.2, 51.3, 34.1, 27.3, 26.8. Anal. Calcd for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76. Found C, 58.83; H, 6.12; N, 13.99.

4.2.5.12. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-histidine (**6l**).* Yield: 82%. Colorless powder, M.p. 126–127 °C; ESI-MS (*m*/*z*) 314 $[M+H]^+$; $[\alpha]_D^{20} = -34$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 9.26 (s, 1 H), 9.05 (m, *J* = 7.6 Hz, 1 H), 8.82 (m, *J* = 8.3 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 1 H), 7.13 (t, *J* = 7.1 Hz, 1 H), 7.07 (t, *J* = 6.9 Hz, 1 H), 4.48 (t, *J* = 5.5 Hz, 1 H), 4.36 (m, *J* = 5.6 Hz, 3 H), 3.19 (m, *J* = 4.7 Hz, 2 H), 2.74 (m, *J* = 4.7 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.9, 171.6, 137.1, 135.6, 133.8, 133.1, 128.9, 127.5, 127.2, 125.8, 118.7, 68.2, 56.1, 53.4, 52.2, 30.0, 27.2. Anal. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.13; H, 5.77; N, 17.82. Found C, 61.35; H, 5.91; N, 18.05.

4.2.5.13. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-lysine (**5m**).* Yield: 86%. Colorless powder, M.p. 106–109 °C; ESI-MS (*m*/*z*) 306 $[M+H]^+$; $[\alpha]_D^{20} = -48$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 9.07 (m, *J* = 8.3 Hz, 2 H), 8.87 (m, *J* = 8.3 Hz, 2 H), 8.73 (d, *J* = 8.6 Hz, 1 H), 7.71 (m, *J* = 7.1 Hz, 4 H), 4.58 (m, *J* = 5.4 Hz, 3 H), 4.28 (t, *J* = 5.1 Hz, 1 H), 2.99 (m, *J* = 5.7 Hz, 2 H), 2.13 (m, *J* = 5.4 Hz, 4 H), 1.29 (m, *J* = 5.5 Hz, 4 H), 0.92 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.9, 171.6, 142.8, 137.6, 136.6, 134.7, 126.2, 68.8, 67.8, 56.8, 54.8, 53.7, 52.8, 32.0, 30.2, 27.9, 22.7. Anal. Calcd for $C_{16}H_{23}N_3O_3$: C, 62.93; H, 7.59; N, 13.76. Found C, 62.70; H, 7.43; N, 13.99.

4.2.5.14. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-aspartic acid (**6n**).* Yield: 95%. Colorless powder, M.p. 109–110 °C; ESI-MS (*m*/*z*) 293 $[M+H]^+$; IR (cm^{-1}) 3451, 2937, 1725, 1455, 1358, 745; $[\alpha]_D^{20} = -34$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 12.4 (s, 1 H), 11.7 (s, 1 H), 9.05 (m, *J* = 8.6 Hz, 1 H), 8.91 (m, *J* = 10.1 Hz, 1 H), 7.58 (d, *J* = 7.5 Hz, 1 H), 7.36 (d, *J* = 8.4 Hz, 1 H), 7.25 (t, *J* = 7.3 Hz, 1 H), 7.13 (t, *J* = 8.2 Hz, 1 H), 4.44 (t, *J* = 5.3 Hz, 1 H), 4.36 (d, *J* = 5.3 Hz, 3 H), 3.02 (d, *J* = 4.6 Hz, 2 H), 2.62 (m, *J* = 5.3 Hz, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.2, 172.8, 171.6, 137.8, 133.6, 127.6, 127.1, 126.9, 124.1, 69.6, 56.7, 53.8, 48.3, 37.9, 28.6. Anal. Calcd for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found C, 57.74; H, 5.69; N, 9.81.

4.2.5.15. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-glutamic acid (**6o**).* Yield: 95%. Colorless powder, M.p. 103–106 °C; ESI-MS (*m*/*z*) 307 $[M+H]^+$; IR (cm^{-1}) 3451, 2981, 1734, 1404, 1358, 754; $[\alpha]_D^{20} = -64$ (*c* = 1.0, H_2O); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 12.51 (s, 1 H), 11.17 (s, 1H), 8.73 (d, *J* = 8.6 Hz, 1 H), 8.49 (m, *J* = 9.2 Hz, 1 H), 7.56 (d, *J* = 7.5 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.28 (t, *J* = 7.7 Hz, 1 H), 7.15 (t, *J* = 8.1 Hz, 1 H), 4.47 (t, *J* = 5.7 Hz, 1H), 4.34 (m, *J* = 5.7 Hz, 3 H), 2.76 (d, *J* = 5.6 Hz, 2 H), 2.16 (m, *J* = 4.6 Hz, 1 H), 1.96 (m, *J* = 3.6 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.1, 172.8, 171.6, 137.9, 127.6, 127.0, 124.1, 123.6, 69.5, 56.7, 53.8, 50.7, 27.8, 27.6, 26.7. Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found C, 58.63; H, 5.77; N, 8.92.

4.2.5.16. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-cysteine (**6p**).* Yield: 93%. Colorless powder, M.p. 195–198 °C; ESI-MS (*m*/*z*) 281 $[M+H]^+$; $[\alpha]_D^{20} = -23$ (*c* = 1.0, H_2O); ^1H NMR

(300 MHz, DMSO) δ/ppm = 11.25 (s, 1 H), 9.86 (m, J = 8.9 Hz, 1 H), 8.92 (d, J = 8.4 Hz, 1 H), 7.54 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1 H), 7.24 (t, J = 7.9 Hz, 1 H), 7.13 (t, J = 8.2 Hz, 1 H), 4.34 (t, J = 5.8 Hz, 1 H), 4.24 (m, J = 5.6 Hz, 3 H), 2.76 (m, J = 4.6 Hz, 2 H), 2.01 (m, J = 4.5 Hz, 1 H), 1.98 (m, J = 4.3 Hz, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.6, 171.2, 137.1, 133.6, 128.6, 127.6, 127.1, 125.1, 68.7, 56.8, 55.2, 53.2, 27.2, 26.7. Anal. Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99. Found C, 55.89; H, 5.91; N, 10.22.

4.2.5.17. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-phenylalanine (**6q**).* Yield: 93%. Colorless powder, M.p. 106–108 °C; ESI-MS (m/e) 325 $[M+H]^+$; IR (cm^{-1}) 3423, 2963, 1670, 1634, 1576, 1457, 1400, 740; $[\alpha]_D^{20} = -42$ (c = 1.0, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 12.68 (s, 1 H), 9.06 (d, J = 8.4 Hz, 1 H), 7.21 (m, J = 8.3 Hz, 9 H), 4.35 (m, J = 5.6 Hz, 3 H), 4.26 (t, J = 5.2 Hz, 1 H), 2.81 (m, J = 4.1 Hz, 2 H), 1.28 (m, J = 3.3 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 174.9, 171.8, 133.4, 128.2, 128.1, 127.9, 127.8, 127.5, 127.3, 126.2, 125.7, 69.5, 53.9, 53.5, 37.5, 27.5. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found C, 70.56; H, 6.37; N, 8.87.

4.2.5.18. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-threonine (**6r**).* Yield: 68%. Colorless powder, M.p. 100–102 °C; ESI-MS (m/z) 279 $[M+H]^+$; $[\alpha]_D^{20} = -14$ (c = 1.0, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 11.91 (s, 1 H), 8.93 (d, J = 8.5 Hz, 1 H), 8.87 (m, J = 8.2 Hz, 1 H), 7.47 (d, J = 7.6 Hz, 1 H), 7.38 (d, J = 8.4 Hz, 1 H), 7.31 (t, J = 8.2 Hz, 1 H), 7.15 (t, J = 7.7 Hz, 1 H), 4.35 (m, J = 5.1 Hz, 3 H), 4.27 (t, J = 5.3 Hz, 1 H), 2.84 (m, J = 4.3 Hz, 2 H), 2.25 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.8, 171.6, 137.2, 129.1, 127.9, 127.2, 125.6, 68.9, 68.2, 58.2, 53.7, 52.2, 27.8, 19.6. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found C, 60.23; H, 6.38; N, 10.30.

4.2.5.19. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-arginine (**6s**).* Yield: 80%. Colorless powder, M.p. 201–204 °C; ESI-MS (m/z) 334 $[M+H]^+$, $[\alpha]_D^{20} = -26$ (c = 1.0, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 11.72 (s, 1 H), 8.93 (s, 3 H), 8.91 (m, J = 7.5 Hz, 1 H), 8.73 (d, J = 8.6 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.26 (t, J = 7.7 Hz, 1 H), 7.21 (t, J = 8.2 Hz, 1 H), 4.47 (t, J = 5.7 Hz, 1 H), 4.15 (m, J = 5.7 Hz, 3 H), 2.74 (m, J = 5.7 Hz, 4 H), 1.96 (m, J = 5.7 Hz, 4 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 171.9, 171.6, 137.2, 133.6, 128.9, 127.9, 127.2, 125.6, 68.5, 57.2, 53.7, 52.7, 37.2, 26.7, 25.5. Anal. Calcd for $C_{16}H_{23}N_5O_3$: C, 57.64; H, 6.95; N, 21.01. Found C, 57.75; H, 7.10; N, 21.26.

4.2.5.20. N-*(3S-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-L-methionine (**6t**).* Yield: 91%. Colorless powder, M.p. 101–105 °C; ESI-MS (m/z) 309 $[M+H]^+$; IR (cm^{-1}) 3451, 2974, 1630, 1455, 1358, 739; $[\alpha]_D^{20} = -48$ (c = 1.0, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ/ppm = 11.93 (s, 1 H), 9.06 (d, J = 8.4 Hz, 1 H), 8.86 (m, J = 7.9 Hz, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.33 (t, J = 6.6 Hz, 1 H), 7.29 (d, J = 8.4 Hz, 1 H), 7.21 (t, J = 8.1 Hz, 1 H), 4.35 (m, J = 4.6 Hz, 3 H), 4.27 (t, J = 5.7 Hz, 1 H), 2.88 (m, J = 5.3 Hz, 2 H), 2.51 (m, J = 5.3 Hz, 5 H), 1.36 (m, J = 3.7 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 172.6, 171.8, 137.6, 128.9, 127.6, 127.3, 125.8, 69.1, 56.7, 53.2, 52.9, 31.2, 27.9, 18.8. Anal. Calcd for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; N, 9.08. Found C, 58.63; H, 6.69; N, 9.31.

4.3. Bioassays

4.3.1. In vitro anti-platelet aggregation activity assay

An H-10 cell counter was used to determine the platelet count and a two-channel Chronolog aggregometer was used to evaluate platelet aggregation. After collection, the pig blood was centrifuged at 1000g for 10 min and the platelet rich plasma (PRP) was removed. The remaining blood was centrifuged for an additional 10 min at 1500g to prepare platelet poor plasma (PPP). The final platelet count of the citrated plasma samples was adjusted to 2×10^8 platelets/ml with autologous PPP. To an optical aggregometry testing tuber, 0.5 ml of the adjusted plasma sample and 5 μl of NS or 5 μl of the solution of **6a–t** (in a series of final concentrations of 100, 10, 1, 0.1, 0.01 and 0.001 μM) was added. After adjustment of the baseline, 5 μl of the solution of platelet-activating factor in NS (PAF, final concentration 0.1 μM) or 5 μl of the solution of adenosine diphosphate in NS (ADP, final concentration 10 μM) or 5 μl of the solution of arachidonic acid in NS (AA, final concentration 350 μM), or 50 μl of the solution of thrombin in NS (TH, final concentration 0.1 U/ml) was added and aggregation was measured at 37 °C for 5 min. The effects of **6a–t** (at a series of concentrations ranging from 10 μM to 10 nM) on PAF or ADP or AA or TH induced platelet aggregation were observed. All these anti-platelet aggregation tests in sixplicate tubers were carried out. The maximal rate of platelet aggregation (A_m%) was represented by the peak height of aggregation curve. The inhibition rate was calculated by % Inhibition = [(A_m% of NS) − (A_m% of **6a–t**)]/(A_m% of NS), where A_m% of NS = 50.16 ± 3.65%. The concentration vs. inhibition rate curve is plotted to determine the IC_{50} values *via* GWBASIC.EXE program.

4.3.2. In vivo anti-thrombotic assay of intravenously injection of *6a–t* in rat model

The assessments described here were performed based on a protocol reviewed and approved by the ethics committee of Capital Medical University. The committee assures the welfare of the animals was maintained in accordance to the requirements of the animal welfare act and according to the guide for care and use of laboratory animals. Aspirin and **6a–t** were dissolved in NS before administration and kept in an ice bath. Male Wistar rats weighing 250–300 g (purchased from Animal Center of Peking University) were used. The rats were anesthetized with pentobarbital sodium (80.0 mg/kg, i.p.) and the right carotid artery and left jugular vein were separated. A weighed 6 cm thread was inserted into the middle of a polyethylene tube. The polyethylene tube was filled with heparin sodium (50 IU/ml in NS) and one end was inserted into the left jugular vein. From the other end of the polyethylene tube heparin sodium was injected as anticoagulant, then NS or **6a–t** was injected, and this end was inserted into the right carotid artery. Blood was allowed to flow from the right carotid artery to the left jugular vein through the polyethylene tube for 15 min. The thread was removed to obtain the weight of the wet thrombus.

4.3.3. In vivo anti-thrombotic assay of orally administration of *6s* in rat model

Three doses (5, 1 and 0.2 μmol/kg) of **6s** in NS or NS (0.6 ml) alone were fed to Male Wistar rats orally. Then the rats were anesthetized with pentobarbital sodium (80.0 mg/kg, ip). 30 min later the right carotid artery and left jugular vein of the rat were separated. A weighed 6-cm thread was inserted into the middle of a polyethylene tube. The polyethylene tube was filled with heparin sodium (50 IU/ml in NS) and one end was inserted into the left jugular vein while another end was inserted into the right carotid artery. Blood flowed from the right carotid artery to the left jugular vein through the polyethylene tube for 15 min. The thread was taken out and the weight of the wet thrombus was recorded.

4.3.4. Apparent permeability coefficient test of THIQA and *6s* [43]

Caco-2 cells (from the American Type Culture Collection, Rockville, MD, USA) were cultivated on polycarbonate filters (transwell cell culture inserts, 12 mm in diameter, 3.0 μM in mean pore size). Caco-2 cells were grown on filter supports and the integrity of

monolayers was routinely checked by measurements of trans-epithelial electrical resistance (approximately 700 $\Omega\,cm^2$). THIQA and **6s** for evaluation were dissolved in HBSS to prepare drug solutions at a final concentration of 4 mM. In apical to basolateral direction, transport was initiated by adding drug solutions (total AP volume, 0.5 ml) to the apical compartment of inserts held in transwells containing 1.5 ml of HBSS (basolateral compartment). In basolateral to apical direction, transport was initiated by adding 1.5 ml of the solution of THIQA or **6s** to basolateral compartment and adding 0.5 ml of HBSS as receiving solution to apical side of the monolayers. The monolayers were incubated in air at 37 °C and 95% relative humidity. At 30, 60, 90, and 120 min, samples were withdrawn from the receiving side, and the concentrations of the samples were determined by HPLC analysis. The resistance of monolayers was checked at the end of each test. Apparent permeability coefficients (P_{app}) were calculated according to $P_{app} = dQ/dt \cdot 1/(A \cdot C_0)$, wherein dQ/dt is the permeability rate, C_0 is the initial concentration in the donor chamber, and A is the surface area of monolayer (1 cm^2).

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