Bioorganic & Medicinal Chemistry 18 (2010) 1536–1554

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

2,3-Diamino acid modifying 3*S*-tetrahydroisoquinoline-3-carboxylic acids: Leading to a class of novel agents with highly unfolded conformation, selective in vitro anti-platelet aggregation and potent in vivo anti-thrombotic activity

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ARTICLE INFO

Article history:
Received 2 November 2009
Revised 1 January 2010
Accepted 5 January 2010
Available online 13 January 2010

Keywords:
Tetrahydroisoquinoline
Modification
Anti-thrombotic
Conformation
3D QSAR

ABSTRACT

In the preparation of anti-thrombotic agents the 2- and 3-positions of 3*S*-tetra-hydroisoquinoline-3-carboxylic acid (THIQA) were simultaneously modified with amino acids to form 20 novel *N*-(3*S*-*N*-amino-acyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)amino acids (**8a**–**t**). On an in vitro platelet aggregation model **8a**–**t** selectively inhibit ADP-induced platelet aggregation and their IC_{50} values are leas than 3.5 nM. On an extracorporeal circulation of arterioveinos cannula model of rats both orally and intravenously effective doses of **8a**–**t** are less than 30 nmol/kg. Cerius^2 based stereoview of explores **8a**–**t** having highly unfolded conformation. 3D QSAR analysis gives the importance of the unfolded conformation to high in vitro anti-platelet aggregation and in vivo anti-thrombotic potency rational understanding.

1. Introduction

Intravascular thrombosis is one of the most frequent pathological events as well as a leading cause of morbidity and mortality all over the world. In the onset and progression of acute coronary syndromes, the rift, rupture and pythogenesis of atheromatous plaque with the formation of either partial or complete occlusive thrombus are critical steps, while vascular damage, stimulus of platelets, and initiation of the clotting cascade are essential factors.[1–3] In the cases of thromboembotic disorders of cardiovascular and cerebrovascular the subendothelium surfaces of the vessels are injured and function as the adherent target of platelets.[3–7] Though anticoagulants, anti-platelet drugs and thrombolytic drugs are clinically used for anti-thrombotic therapy, to improve the treatment of ischemic symptoms, more potent and safer agents are urgently needed, and a lot of efforts have been devoted to anti-thrombotic drug design. However, due to undesirable bioavailability the anti-thrombotic candidates usually fail to exert therapeutic potential, which leads to the development of GPIIb/IIIa antagonists having good pharmacodynamic and pharmacokinetic property.[7–14] On the other hand, intestinal peptide transport system is particularly utilized to increase bioavailability.[15–17] Following this approach 3*S*-1,2,3,4-tetrahydro-isoquinoline-3-carbonylamino acid (THIQA), an anti-platelet aggregation compound, was modified to its dipeptide analogues to improve their permeability and consequently to enhance their anti-thrombotic activity.[9,10]

In addition to a number of bioactivities,[18–32] tetrahydroisoquinolines were also reported as anti-platelet aggregation agents. In the mechanism investigations of anti-platelet aggregation of tetrahydroisoquinolines not only β-adrenergic/α_2-adrenergic receptor system,[33] but also thromboxane A_2/prostaglandin H_2 receptor system was involved. Tetrahydroisoquinolines may exert their inhibitory effects on arachidonic acid (AA) induced platelet aggregation partly by inhibiting the production of TXA_2 from AA and partly by directly blocking the TXA_2 receptor.[34–36] Based on these investigations some derivatives of benzyltetrahydroisoquinoline alkaloid were reported having anti-platelet aggregation activities.[37–40]

In the previous paper, we used THIQA as the anti-thrombotic lead, introducing amino acid into its 2- or 3-position, and prepared two series of pseudopeptides 3*S*-*N*-(L-amino-acyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (**9a–t**),[9] as well as 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids (**10a–t**).[10] In our pre-investigation it was found that a folded (Fig. 1a), unfolded (Fig. 1b) and highly unfolded conformation (Fig. 1c) of **9s, 10s** and *N*-(3*S*-*N*-L-argininyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-arginine matching a low, moderate and high in vivo anti-thrombotic activity,

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doi:10.1016/j.bmc.2010.01.009

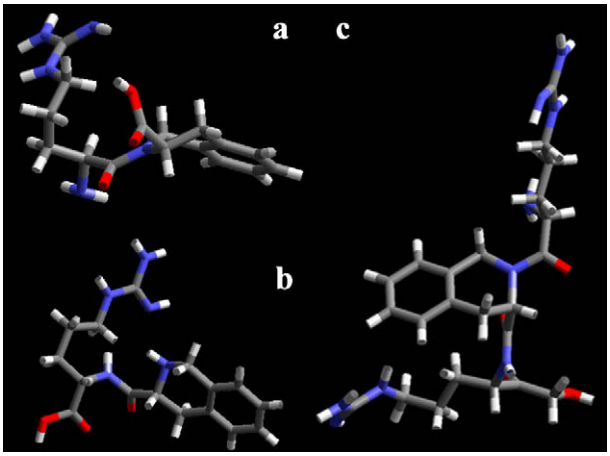


Figure 1. Cerius[2] based stereoview of 3*S*-*N*-(L-argininyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (a) and *N*-(3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-arginine (b) and *N*-(3*S*-*N*-L-argininyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-arginine (c).

respectively. This implies that 2,3-diamino-acid-substituted THIQAs should have highly unfolded conformation and exhibit high in vivo anti-thrombotic potency.

In this context, the present paper prepared 20 novel *N*-(3*S*-*N*-L-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-amino acids (**8a–t**), evaluated their anti-thrombotic activities, examined their conformation, and analyzed their 3D QSAR.

2. Results and discussion

2.1. A seven-step-procedure of preparing 8a–t

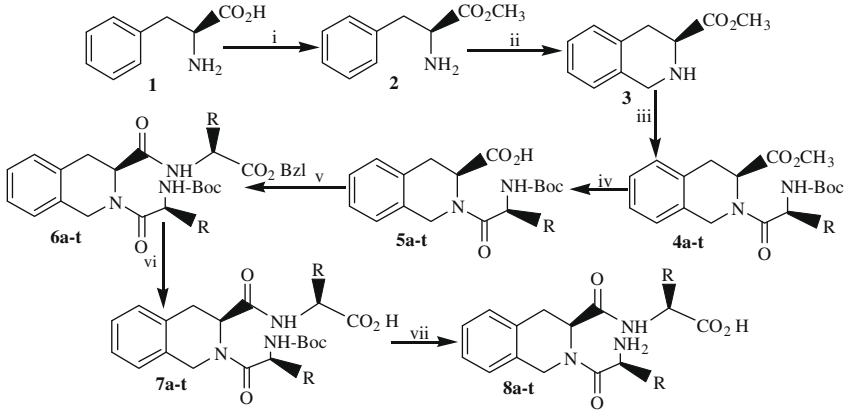
The preparation of *N*-(3*S*-*N*-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)amino acids (**8a–t**) was carried out according to the seven-step-route depicted in Scheme 1. After esterification the formed L-Phe-OMe was treated with formaldehyde in Pictet–Spengler condensation condition to provide methylester of THIQA (**3**, 84% yield).[41,42] In the presence of DCC, HOBt and NMM, **3** was conjugated with 20 amino acids to give 3*S*-*N*-(Boc-aminoacyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl-esters (**4a–t**, 45–95% yield). The saponification of **4a–t** provided 3*S*-*N*-(Boc-aminoacyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (**5a–t**, 51–96% yield). In the presence of DCC, HOBt and NMM, **5a–t** were conjugated with 20 amino acid benzylesters to give *N*-(3*S*-*N*-Boc-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)amino acid banzylesters (**6a–t**, 46–96% yield). Catalytic hydrogenation of **6a–t** provided *N*-(3*S*-*N*-Boc-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)amino acids (**7a–t**, 83–97% yield). Removing Boc groups from **7a–t** resulted in *N*-(3*S*-*N*-aminoacyl-1,2,3,4-tetrahydro-isoquinoline-3-carbonyl)amino acids (**8a–t**, 85–98% yield). The mild condition and the acceptable yield of the individual reaction suggest that the present synthetic route is suitable for preparing these novel *N*-(3*S*-*N*-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)amino acids.

2.2. 2,3-Diamino acid modification of THIQA enhancing the in vitro activity

To evaluate the effect of 2,3-diamino acid modification of THIQA on the in vitro activity, the in vitro anti-platelet aggregation assays of **8a–t** were performed by following the common procedure and 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 against the aggregation induced by them are listed in Table 1.

In the literature a number of tetrahydroisoquinolines were reported as selective inhibitors of ADP and AA and the IC_{50} values against platelet aggregation induced by them range from 100 to 270 μM and 3.3 to 140 μM, respectively.[40,41] Our assay indicates that the IC_{50} values of THIQA against platelet aggregation induced by ADP and AA are 0.55 and 0.45 μM, respectively. The IC_{50} values of THIQA are 182–491 and 7–311-fold lower than that of the mentioned tetrahydroisoquinolines. Therefore as the lead of anti-platelet aggregators THIQA obviously possesses advantage.

In Table 1 the IC_{50} values of **8a–t** against ADP, AA, PAF and TH induced platelet aggregation are less than 3.73, 10.04, 6.32 and 11.35 nM, respectively. The IC_{50} values of **8a–t** against four aggregator induced platelet aggregation are totally less than 11.35 nM identifies **8a–t** as excellent anti-platelet aggregators. Among the mentioned IC_{50}, the values of **8a–t** against ADP-induced platelet aggregation are the smallest ones (<3.73 nM). The mean IC_{50} values



Scheme 1. Synthetic route of *N*-(3*S*-2-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-amino acids. Reagents: (i) $SOCl_2$ and CH_3OH; (ii) HCHO and HCl; (iii) Boc-AA, HOBt, DCC and NMM; (iv) 2 N NaOH; (v) AA-OBzl, HOBt, DCC and NMM; (vi) Pd/C; (vii) hydrogen chloride in ethyl acetate (6 N). In **(4–8)a** R = CH_3, **(4–8)b** R = H, **(4–8)c** R = $CH(CH_3)_2$, **(4–8)d** R = $CH_2CH(CH_3)_2$, **(4–8)e** R = $CH(CH_3)CH_2CH_3$, **(4–8)f** R = indol-2-ylmethylene, **(4–8)g** R = CH_2OH, **(4–8)h** R = 4-hydroxylbenzyl, **(4–8)i** NHCHR = cyclobutylamino, **(4–8)j** R = CH_2CONH_2, **(4–8)k** R = $CH_2CH_2CONH_2$, **(4–8)l** R = imidazol-4-ylmethylene, **(4–7)m** R = *N*-*tert*-butoxy, **8m** R = aminobutyl, **(4–6)n** R = benzyloxycarbonylmethylene, **7n** and **8n** R = carboxylmethylene, **(4–6)o** R = benzyloxycarbonylethylene, **7o** and **8o** R = carboxylethylene, **(4–6)p** R = CH_2S–Bu^t, **7p** and **6p** R = CH_2SH, **(4–8)q** R = benzyl, **(4–6)r** R = $CH(OCH_2C_6H_5)CH_3$, **7r** and **8r** R = $CH(OH)CH_3$, **(4–6)s** AA = $CH_2(CH_2)_2NHC(NHNO_2)$═NH, **7s** and **8s** AA = $CH_2(CH_2)_2NHC(NH_2)$═NH, **(4–8)t** R = $CH_2CH_2SCH_3$.

Table 1
IC_{50} of **8a–t** against four aggregators induced aggregation of pig platelets[a]

Compd	ADP	AA	PAF	TH
IQ	552 ± 3.25	960 ± 2.32	452 ± 2.21	881 ± 2.52
8a	2.36 ± 0.44	8.73 ± 0.51	5.60 ± 0.86	9.48 ± 0.28
8b	2.44 ± 0.21	7.95 ± 0.59	5.15 ± 0.64	10.64 ± 0.82
8c	2.57 ± 0.35	9.08 ± 0.27	5.87 ± 0.62	9.25 ± 0.74
8d	2.57 ± 0.25	8.17 ± 0.55	5.03 ± 0.38	10.02 ± 0.87
8e	2.89 ± 0.17	8.92 ± 0.24	5.64 ± 0.39	11.35 ± 0.41
8f	2.42 ± 0.33	9.31 ± 0.29	4.88 ± 0.98	9.18 ± 0.50
8g	2.17 ± 0.47	7.99 ± 0.16	5.36 ± 0.65	10.24 ± 0.92
8h	2.58 ± 0.22	8.83 ± 0.31	4.52 ± 0.18	9.84 ± 0.40
8i	3.13 ± 0.63	8.54 ± 0.34	5.55 ± 0.11	10.01 ± 0.26
8j	3.07 ± 0.89	8.28 ± 0.64	5.39 ± 0.23	8.43 ± 0.15
8k	2.55 ± 0.31	8.37 ± 0.48	5.72 ± 0.91	9.13 ± 0.22
8l	2.84 ± 0.42	9.38 ± 0.56	5.57 ± 0.30	10.04 ± 0.82
8m	3.73 ± 0.18	9.64 ± 0.27	5.67 ± 0.34	8.98 ± 0.13
8n	3.48 ± 0.51	9.55 ± 0.42	4.37 ± 0.62	11.12 ± 0.95
8o	2.19 ± 0.58	9.86 ± 0.54	4.19 ± 0.25	10.27 ± 0.53
8p	3.26 ± 0.19	8.18 ± 0.43	6.32 ± 0.57	9.64 ± 0.20
8q	2.23 ± 0.31	7.84 ± 0.46	4.92 ± 0.68	8.87 ± 0.43
8r	2.89 ± 0.43	10.04 ± 0.68	4.14 ± 0.72	10.83 ± 0.57
8s	3.15 ± 0.64	9.17 ± 0.41	6.07 ± 0.50	9.87 ± 0.28
8t	3.42 ± 0.25	8.19 ± 0.57	4.91 ± 0.57	9.99 ± 0.38

[a] IC_{50} is represented by mean ± SD nM.

of **8a–t** against four aggregators induced aggregation of pig platelets are 2.55 nM, 8.80 nM, 5.244 nM and 9.859 nM, respectively. The potency of **8a–t** inhibiting ADP induced aggregation is 2.0–3.9-fold higher than the other three aggregators.

In respect of ADP-induced platelet aggregation the IC_{50} values of THIQA and **8a–t** are 552 nM and 2.17–3.73 nM, respectively, **8a–t** are 159–254-fold lower than THIQA. According to the literature some representatives of tetrahydroisoquinolines such as Higenamine, YS-49 and YS-51, effectively inhibit ADP-induced platelet aggregations and the IC_{50} values range from 3.3 to 800 μM,[40,41,43] which are 1520–214477-fold higher than **8a–t**. Therefore 2,3-diamino acid modification of THIQA greatly enhances the in vitro anti-platelet aggregation potency.

To clarify the benefit of 2,3-diamino acid modification of THIQA in Table 2 the IC_{50} values of **8a–t** against ADP-induced platelet aggregation are compared with those of 2-(**9a**–**t**) and 3-monoaminoacid modified THIQA (**10a–t**). The IC_{50} values of **8a–t, 9a–t** and **10a–t** against ADP induced aggregation range from 2.17 to 3.73, 103 to 534 and 120 to 661 nM, respectively. Comparing to 2- and 3-monoaminoacid modification 2,3-diamino acid modification of THIQA results in a 47–143 and 55–177-fold increase for the in vitro inhibition to ADP-induced platelet aggregation.

Table 2
IC_{50} of **(8–10)a–t** against ADP-induced platelet aggregation[a]

Compd	IC_{50}	Compd	IC_{50}	Compd	IC_{50}
8a	2.36 ± 0.44[a]	**9a**	651 ± 26	**10a**	350 ± 31
8b	2.44 ± 0.21[a]	**9b**	365 ± 29	**10b**	496 ± 28
8c	2.57 ± 0.35[a]	**9c**	389 ± 33	**10c**	382 ± 26
8d	2.57 ± 0.25[a]	**9d**	336 ± 19	**10d**	478 ± 29
8e	2.89 ± 0.17[a]	**9e**	315 ± 30	**10e**	540 ± 34
8f	2.42 ± 0.33[a]	**9f**	194 ± 16	**10f**	120 ± 19
8g	2.17 ± 0.47[a]	**9g**	103 ± 18	**10g**	388 ± 33
8h	2.58 ± 0.22[a]	**9h**	327 ± 31	**10h**	481 ± 30
8i	3.13 ± 0.63[a]	**9i**	373 ± 32	**10i**	364 ± 21
8j	3.07 ± 0.89[a]	**9j**	534 ± 34	**10j**	470 ± 29
8k	2.55 ± 0.31[a]	**9k**	302 ± 23	**10k**	235 ± 22
8l	2.84 ± 0.42[a]	**9l**	324 ± 19	**10l**	661 ± 34
8m	3.73 ± 0.18[a]	**9m**	323 ± 21	**10m**	194 ± 15
8n	3.48 ± 0.51[a]	**9n**	345 ± 34	**10n**	329 ± 33
8o	2.19 ± 0.58[a]	**9o**	494 ± 32	**10o**	482 ± 26
8p	3.26 ± 0.19[a]	**9p**	—	**10p**	231 ± 18
8q	2.23 ± 0.31[a]	**9q**	370 ± 29	**10q**	188 ± 15
8r	2.89 ± 0.43[a]	**9r**	240 ± 27	**10r**	164 ± 22
8s	3.15 ± 0.64[a]	**9s**	210 ± 22	**10s**	124 ± 20
8t	3.42 ± 0.25[a]	**9t**	265 ± 26	**10t**	229 ± 18

[a] IC_{50} is represented by mean ± SD nM, **9a**–**t** = 3*S*-*N*-(L-aminoacyl)-1,2,3,4-tetrahydroisoquino line-3-carboxylic acids, **10a**–**t** = 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids.

2.3. 2,3-Diamino acid modification enhancing the in vivo activity

To get insight into the effect of 2,3-diamino acid modification of THIQA on in vio activity **8a–t** were assayed on an extracorporeal circulation of arterioveinos cannula model of rats. The individual stock solution of aspirin (positive control) and **8a–t** in NS was administered intravenously, the thrombus weights were weighed and the data are listed in Table 3. The thrombus weights of the rats receiving 30 nmol/kg of **8a–t** range from 10.61 (**8s**) to 25.20 mg (**8b**), which are significantly lower than that (28.54 mg) of the rats receiving NS (p <0.01). Thus, **8a–t** are highly anti-thrombotic agents and **8s** the most potency agent.

To clarify the benefit of 2,3-diaminoacid modification of THIQA in Table 3 the in vivo anti-thrombotic activities of **8a–t** are compared with those of 2-(**9a**–**t**) and 3-monoaminoacid modification as well as THIQA itself (**10a–t**). The thrombus weights of the rats intravenously receiving 30 nmol/kg of **8a–t,** 5 μmol/kg of **9a–t** and **10a–t,** as well as 15 μmol/kg of THIQA are 10.61–25.20, 18.00–22.66, 18.73–23.58 and 21.52 mg, respectively. Thus even in the case that the dose of **8a–t** is 167 and 500-fold lower than that of **(9,10)a–t** and THIQA, respectively, **8a–t** still possess the comparable in vivo anti-thrombotic potency to that of **(9,10)a–t** and THIQA. Therefore comparing to 2- and 3-modifications 2,3-diaminoacid modification of THIQA results in a greatly increase of the in vivo anti-thrombotic activity.

2.4. Highly unfolded conformation of 2,3-diamino-acid modified THIQAs

To understand the structural basis of 2-/3-monoaminoacid and 2,3-diamino acid modifications of THIQA resulted in different in vitro anti-platelet aggregation as well as in vivo anti-thrombotic activities the Cerius[2] based stereoview of **9a–t** (Fig. 2a)**, 10a–t** (Fig. 2b) and **8a–t** (Fig. 2c) was compared. Figure 2 indicates that the conformational extensibility is **8a–t** > **10a**–**t** > **9a**–**t**. As mentioned above, the in vitro anti-platelet aggregation and the in vivo anti-thrombotic activities are also **8a–t** > **10a**–**t** > **9a**–**t**. The consistence of these orders reflects the correlation of conformational extensibility with the in vitro anti-platelet aggregation and/or the in vivo anti-thrombotic activities, as well as explores the importance of highly conformational extensibility of 2,3-diamino-acid modifications of THIQA to enhancing the in vitro anti-platelet aggregation and/or the in vivo anti-thrombotic activities.

2.5. Dose dependence of in vivo anti-thrombotic activities of intravenous 8a,r,s

The effect of dose on the in vivo anti-thrombotic activity of the mice of intravenously receiving **8a, 8r** and **8s**, the compounds possessing the highest activities at 30 nmol/kg of dose, was observed. The doses of **8a,r** are 30.00, 3.00 and 0.30 nmol/kg, of **8s** are 30.00, 3.00 and 0.03 nmol/kg. The thrombus weights of the treated rats are listed in Table 4. The data demonstrate that **8a,r,s** dose-dependently inhibit the thrombosis of the treated rats.

To clarify the benefit of 2,3-diamino acid modification of THIQA the dose dependent in vivo anti-thrombotic activities of **8a,r,s** are compared with those of 2- (**9g**) and 3- (**10s**) mono-aminoacid modification of THIQA in Table 4. The thrombus weight of the rats

Table 3
Effect of **8a–t** on the thrombus weight of intravenously treated rats[a]

Compd	Thrombus weight	Compd	Thrombus weight	Compd	Thrombus weight
NS	28.54 ± 2.62	IQ	21.52 ± 1.49[e]	Aspirin	13.22 ± 1.67[e]
8a	17.12 ± 1.31[d]	**9a**	20.30 ± 1.33[e]	**10a**	21.40 ± 1.39[e]
8b	25.20 ± 1.13[e]	**9b**	21.17 ± 1.47[e]	**10b**	20.24 ± 1.37[e]
8c	19.42 ± 1.55[e]	**9c**	20.12 ± 1.59[e]	**10c**	19.20 ± 1.57[e]
8d	19.53 ± 1.64[e]	**9d**	19.12±1.82[e]	**10d**	20.23 ± 1.49[e]
8e	24.30 ± 1.88[e]	**9e**	21.14 ± 1.24[e]	**10e**	20.03 ± 1.29[e]
8f	20.11 ± 1.74[e]	**9f**	19.47 ± 1.64[e]	**10f**	21.30 ± 1.06[e]
8g	20.97 ± 1.89[e]	**9g**	18.00 ± 1.59[e]	**10g**	23.58 ± 1.93[e]
8h	18.79 ± 2.03[e]	**9h**	20.92 ± 1.44[e]	**10h**	19.31 ± 1.48[e]
8i	19.27 ± 1.98[e]	**9i**	21.09 ± 1.68[e]	**10i**	20.25 ± 1.50[e]
8j	17.95 ± 1.72[e]	**9j**	22.66 ± 1.45[e]	**10j**	20.24 ± 1.50[e]
8k	18.13 ± 1.48[e]	**9k**	21.30 ± 1.69[e]	**10k**	22.08 ± 1.54[e]
8l	20.91 ± 1.98[e]	**9l**	21.78 ± 1.96[e]	**10l**	20.86 ± 1.94[e]
8m	18.65 ± 1.31[e]	**9m**	21.31 ± 1.75[e]	**10m**	21.28 ± 1.17[e]
8n	20.49 ± 1.46[e]	**9n**	20.30 ± 1.34[e]	**10n**	21.67 ± 1.91[e]
8o	18.95 ± 2.69[e]	**9o**	20.87 ± 1.45[e]	**10o**	19.69 ± 1.25[e]
8p	19.35 ± 2.23[e]	**9p**	—	**10p**	20.91 ± 1.27[e]
8q	22.51 ± 0.91[e]	**9q**	22.23 ± 1.72[e]	**10q**	19.11 ± 1.58[e]
8r	14.32 ± 1.29[c]	**9r**	20.73 ± 1.53[e]	**10r**	21.25 ± 1.93[e]
8s	10.61 ± 1.85[b]	**9s**	20.06 ± 1.48[e]	**10s**	18.73 ± 1.56[e]
8t	19.36 ± 2.37[e]	**9t**	19.56 ± 1.72[e]	**10t**	21.74 ± 1.50[e]

[a] Weight of wet thrombus is represented by mean ± SD mg, NS = vehicle, n = 12; IQ = 3*S*-isoquinoline-3-carboxylic acid and intravenous dose = 15 μmol/kg; Aspirin intravenous dose = 165 μmol/kg; **8a–t** dose = 30 nmol/kg; **9a–t** = 3*S*-*N*-(L-aminoacyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids and dose = 5 μmol/kg; **10a–t** = 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonylamino acids and dose = 5 μmol/kg.
[b] Compared to NS and **8a–r,t** p <0.01.
[c] Compared to NS and **8a–q,t** p <0.01.
[d] Compared to NS and **8b–g,l,n,q** p <0.01, to **8h,i,p,t** p <0.05.
[e] Compared to NS p <0.01.

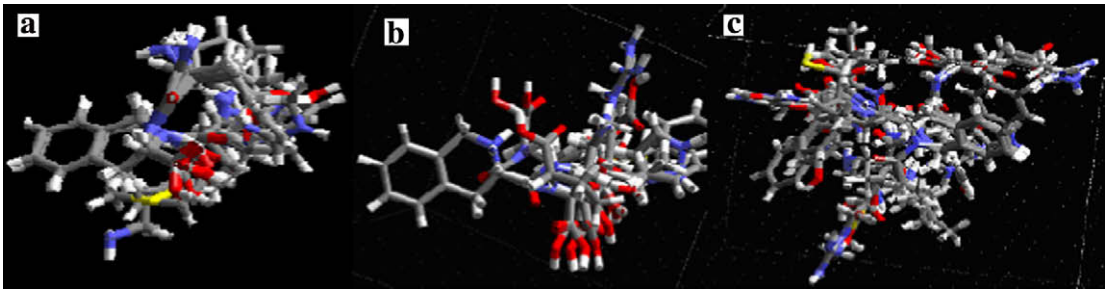


Figure 2. Cerius[2] based stereoview of 3*S*-*N*-(L-aminoacyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (a), *N*-(3*S*-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-amino acids (b) and *N*-(3*S*-*N*-L-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-amino acids (c).

receiving intravenous 3 nmol/kg of **8a** equals those of 50 nmol/kg of **9g** and 1 μmol/kg of **10s**, the thrombus weight of the rats receiving intravenous 3 nmol/kg of **8r** is significantly lower than those of the rats receiving intravenous 50 nmol/kg of **9g** and 1 μmol/kg of **10s**, while the thrombus weight of the rats receiving intravenous 3 nmol/kg of **8s** is significantly lower than those of the rats receiving intravenous 5 μmol/kg of **9g** and **10s**. These comparisons demonstrate that the in vivo anti-thrombotic activity of 2,3-diaminoacid modified THIQA is at least 17–333-fold higher than those of 2- and 3-monoaminoacid modified THIQA.

2.6. In vivo anti-thrombotic activity of oral 8a,j,k,m,r,s

To explore the possibility of oral administration **8a,j,k,m,r,s** were selected as the representatives of **8a–t**, their oral activities were evaluated on an extracorporeal circulation of arterioveinos cannula model of rats and the data are listed in Table 5. The evaluation explores that the thrombus weights of the rats receiving orally administering of 30 nmol/kg of **8a,j,k,m,r,s** are significantly lower than that of the rats receiving NS. The evaluation also explores that 4 (**8a,j,k,m**) of these 6 compounds (**8a,j,k,m,r,s**) possess identical intravenous and oral activity, and the oral activities of two (**8r,s**) are significantly lower than thir intravenous activities. These results imply that **8a–t** could be orally effective anti-thrombotic agents, and their oral potencies are either at the same level as that of intravenous potencies or below the level of intravenous potencies.

2.7. Computational chemistry

To quantitatively analyse the relationship of the conformation and anti-thrombotic activity of **8a–t** on the valid 3D-QSAR models a proper alignment procedure was performed by using the target model align strategy in the align module within Cerius[2]. With an assumption that each structure of **8a–t** binds the same site of the receptor and exhibits activity, they were aligned in a pharmacological active orientation. To obtain a consistent alignment the tetrahydroisoquinoline ring was used as the template for superposing **8a–t**. The maximum common subgraph (MCS) was used to perform this alignment.[44] The alignment of **8a–t** were shown as Figure 3, which explored that to superimpose onto tetrahydroisoquinoline ring the side chains of amino acid residue in each structure had to take its individual conformation and finally affected their in vitro anti-platelet aggregation and in vivo anti-thrombotic activities.

Table 4
Effect of dose of **8a,r,s** on the thrombus weight of intravenously treated rats[a]

Compd	Dose	Thrombus weight (mg)
NS	—	28.80 ± 1.40[a]
Aspirin	165 μmol/kg	13.22 ± 1.67
	50 μmol/kg	27.60 ± 1.89
8a	30 nmol/kg	17.12 ± 1.31[b]
	3 nmol/kg	23.35 ± 1.81[c]
	0.3 nmol/kg	29.77 ± 2.52[c]
8r	30 nmol/kg	14.32 ± 1.29[b]
	3 nmol/kg	20.95 ± 1.88[c]
	0.3 nmol/kg	28.63 ± 0.70
8s	30 nmol/kg	10.61 ± 1.85[b]
	3 nmol/kg	16.29 ± 2.41[d]
	0.03 nmol/kg	19.71 ± 1.85
9g	5 μmol/kg	18.00 ± 1.59
	50 nmol/kg	22.54 ± 3.40
	5 nmol/kg	28.58 ± 1.56
10s	5 μmol/kg	18.73 ± 1.56
	1 μmol/kg	24.38 ± 2.61
	0.2 μmol/kg	29.11 ± 2.37

[a] Weight of wet thrombus is represented by mean ± SD mg, NS = vehicle, n = 12, 3 nmol/kg of **8a** compared with 50 nmol/kg of **9g** and 1 μmol/kg of **10s** p >0.05, 3 nmol/kg of **8r** compared with 50 nmol/kg of **9g** and 1 μmol/kg of **10s** p <0.05, 3 nmol/kg of **8s** compared with 5 μmol/kg of **9g** and **10s** p <0.05.
[b] Compared with NS, 3 nmol/kg and 0.3 nmol/kg of **8a,r,s** p <0.01.
[c] Compared with NS and 0.3 nmol/kg of **8a,r** p <0.01.
[d] Compared with NS and 0.03 nmol/kg of **8s** p <0.01.

Table 5
Effect of oral **8a,j,k,m,r,s** on thrombus weight of the treated rats[a]

Compd	Thrombus weight	Compd	Thrombus weight
NS	28.80 ± 1.40	Aspirin	14.99 ± 1.71[b]
8a	18.89 ± 2.49[b]	**8m**	19.72 ± 1.88[b]
8j	16.88 ± 1.71[b]	**8r**	17.53 ± 1.71[b]
8k	18.23 ± 1.60[b]	**8s**	15.15 ± 2.23[b]

[a] Weight of wet thrombus is represented by X ± SD mg, NS = vehicle, n=12; Dose of **8a,j,k,m,r,s** = 30 nmol/kg; Dose of Aspirin = 165 μmol/kg.
[b] Compared with NS p < 0.01.

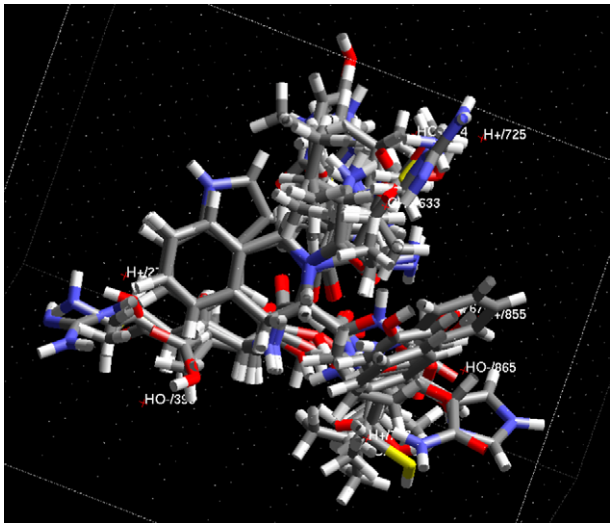


Figure 3. Alignment of **8a–t** used for molecular field generation.

2.7.1. 3D QSAR analysis of 8a-t inhibiting ADP-induced platelet aggregation

After energy-minimization using the MMFF94 (Merck Molecular Force Field), the Molecular Field Analysis (MFA) was performed for **8a–t** using the QSAR module of Cerius[2].[45] Training set (**8a–c,f–i,k–q,s,t**)/test set (**3d,e,j,r**) selections were done manually such that they populate the wide range of activities in similar proportions. Based on the QSAR module of Cerius[2] the MFA was performed by use of the training set. Three probes were chosen to describe 16 molecules. Methyl group was used to account for steric contacts, while proton and hydroxyl ion probes were used to evaluate electrostatic potential fields on each ligand structure. The MFA model of **8a–c,f–i,k–q,s,t** inhibiting ADP-induced-platelet aggregation in terms of the descriptors proton, methyl and hydroxyl ion was expressed by Eq. 1. The data points (n), correlation coefficient (r) and square correlation coefficient (r^2) of Eq. 1 were 16, 0.996 and 0.992, respectively. The tested and calculated anti-platelet aggregation induced by ADP is graphically shown in Figure 4:

$$\begin{aligned}\text{Activity} = {} & 2.755 + 0.021(H^+/725) + 0.0080(H^+/448) \\ & - 0.064(H^+/876) - 0.0059(H^+/773) \\ & - 0.0018(H^+/855) + 0.0029(CH_3/785) \\ & - 0.010(CH_3/633) + 0.011(HO^-/285) \\ & + 0.011(HO^-/396) + 0.0041(HO^-/577) \\ & + 0.0053(HO^-/767) + 0.0019(HO^-/865) \\ & - 0.0090(HO^-/624) \end{aligned} \quad (1)$$

Eq. 1 contains 5 terms from proton descriptor, 2 terms from methyl descriptor, and 5 terms from hydroxyl anion descriptor. The terms of $0.021(H^+/725)$ and $0.0080(H^+/448)$ have positive coefficients, which means that at these positions electron-releasing groups will increase the activity, while the terms of $0.064(H^+/876)$, $0.0059(H^+/773)$ and $0.0018(H^+/855)$ have negative coefficients, which means that at these positions electron-withdrawing groups will increase the activity. The term of $0.0029(CH_3/785)$ has positive coefficient, which means that at this position small group will increase the activity, while term of $0.010(CH_3/633)$ has negative coefficients, which means that at these positions large groups will increase the activity. The terms of $0.011(HO^-/285)$, $0.011(HO^-/396)$, $0.0041(HO^-/577)$, $0.0053(HO^-/767)$ and $0.0019(HO^-/865)$ have positive coefficients, which means that at these positions electron-withdrawing groups will increase the activity, while term of $0.0090(HO^-/624)$ has negative coefficients, which means that at these positions electron-releasing groups will increase the activity.

As examples, Figures 5 and 6 give the electrostatic and environments of **8a,o,p,t** within the grid with 3D points of Eq. 1. Figure 5 indicates that besides the isoquinoline ring has same electrostatic

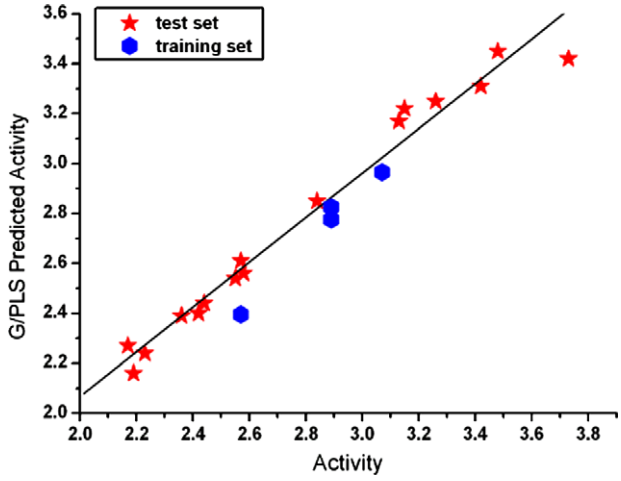


Figure 4. Graph of tested versus predicted activities of **8a–t** inhibiting ADP-induced platelet aggregation.

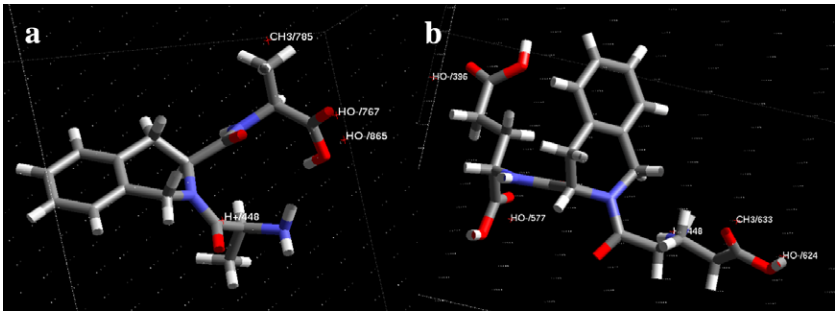


Figure 5. Electrostatic and steric environments of **8a** (a) and **8o** (b) with higher in vitro activity within the grid with 3D points of Eq. 1.

and environments, **8a** has a small group near CH_3/785 region, electron-withdrawing group near H^+/448, as well as hydrogen bond forming groups near OH^-/767,865 region and thus totally results in great increase of in vitro anti-platelet aggregation activity; **8o** has small group near CH_3/633 region, electron-withdrawing group near H^+/448 and hydrogen bond forming group near OH^-/396,577,624 region and thus totally results in increase of in vitro anti-platelet aggregation activity. Figure 6 indicates that besides isoquinoline ring has same electrostatic and environments, **8p** has electron-withdrawing group near H^+/855, small group near CH_3/785 region and hydrogen bond forming group near OH^-/577,865 region, and thus totally results in no increase of in vitro anti-platelet aggregation activity, while **8t** has small groups near CH_3/633,785 region, hydrogen bond forming group near OH^-/577 region and thus totally results in no increase of in vitro anti-platelet aggregation activity.

The predict power of Eq. 1 was examined by comparing the calculated and measured anti-platelet aggregation activities of **8d,e,j,r** in Table 6. The predicting and measuring activities of them are also graphically shown in Figure 4. The results indicate that Eq. 1 rationally gives anti-platelet aggregation activities of **8d,e,j,r** with errors ranging from −0.03 to −0.19. Most of the calculated activities close the measured activities means that Eq. 1 is able to accurately predict the inhibition of the derivatives of 2,3-diamino acid modified THIQA to ADP-induced-platelet aggregation.

2.7.2. 3D QSAR analysis of 8a-t inhibiting thrombosis of treated rats

Using the same protocol as that of item 2.4.1 and the training set (**8a–d,f,h–i,k–o,q–t**)/test (**8e,g,j,p**) were selected. The MFA model of thrombus weights of the rats receiving intravenous **8a–d,f,h–i,k–o,q–t** in terms of the descriptors proton, methyl and hydroxyl ion was expressed by Eq. 2. The data points (n), correlation coefficient (r) and square correlation coefficient (r^2) of Eq. 2 were 16, 0.995 and 0.990, respectively. The tested and calculated anti-thrombotic activities (thrombus weights) are graphically shown in Figure 7:

$$\begin{aligned}\text{Activity} = {} & 20.978 + 0.21(H^+/646) + 0.24(H^+/856) \\ & - 0.27(H^+/536) - 0.31(H^+/634) \\ & - 0.068(H^+/475) - 0.029(H^+/766) \\ & - 0.015(H^+/863) + 0.011(CH_3/874) \\ & - 0.093(CH_3/449) - 0.030(CH_3/733) \\ & - 0.027(CH_3/623) - 0.10(HO^-/773) \\ & - 0.0061(HO^-/376) \end{aligned} \quad (2)$$

Eq. 2 contains 7 terms from proton descriptor, 4 terms from methyl descriptor, and 2 terms from hydroxyl anion descriptor. The terms of 0.21(H^+/646) and 0.24(H^+/856) have positive coefficients, which means that at these positions electron-releasing groups will increase the activity, while the terms of 0.27(H^+/536), 0.31(H^+/634), 0.068(H^+/475), 0.029(H^+/766) and 0.015(H^+/863) have negative coefficients, which means that at these positions electron-withdrawing groups will increase the activity. The term of 0.011(CH_3/874) has positive coefficient, which means that at this position small group will increase the activity, while terms of 0.093(CH_3/449), 0.030(CH_3/733) and 0.027(CH_3/623) have negative coefficients, which means that at these positions large groups will increase the activity. The terms of 0.10(HO^-/773) and 0.0061(HO^-/376) have negative coefficients, which means that at these positions electron-releasing groups will increase the activity.

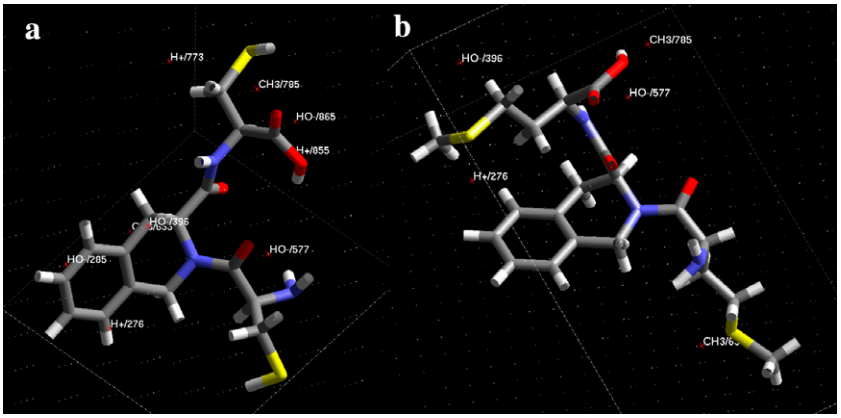


Figure 6. Electrostatic and steric environments of **8p** (a) and **8t** (b) with lower in vitro activity within the grid with 3D points of Eq. 1.

Table 6
Predicted and tested IC_{50} of **8d,e,j,r** against ADP-induced platelet aggregation

Compd	IC_{50} (nM)			
	Predict value	Test value	Error	Error%
8d	2.39	2.57	−0.19	7.2
8e	2.78	2.89	−0.11	3.9
8j	2.97	3.07	−0.10	3.4
8r	2.86	2.89	−0.03	1.0

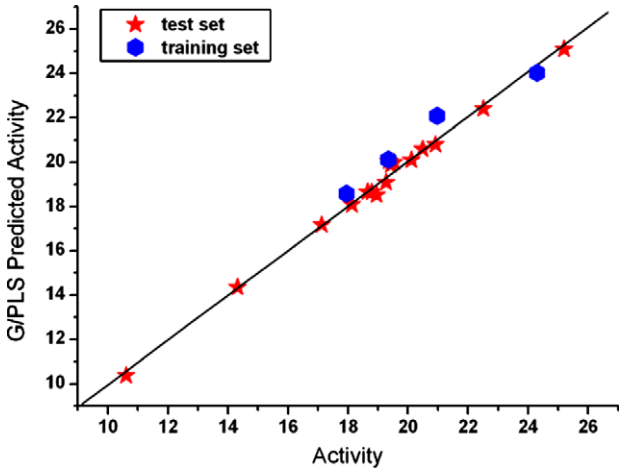


Figure 7. Graph of tested versus predicted activities of **8a–t** inhibiting thrombosis.

As examples, Figures 8 and 9 give the electrostatic and environments of **8a,l,q,r** within the grid with 3D points of Eq. 2. Figure 8 indicates that besides the isoquinoline ring has same electrostatic and environments, **8a** has a small group near CH_3/733 region, electron-withdrawing group near H^+/766, electron-releasing group near H^+/646, as well as electron-releasing group near OH^-/773 region and thus totally results in increase of in vitro anti-platelet aggregation activity; **8r** has large group near CH_3/449 and CH_3/733 regions, electron-releasing groups near H^+/646 and OH^-/376 regions and thus totally results in increase of in vivo anti-thrombotic activity. Figure 9 indicates that besides isoquinoline ring has same electrostatic and environments, **8l** has electron-releasing group near H^+/863 H^+/863, large group near CH_3/874 and CH_3/975 region, small group near CH_3/623 region and thus totally results in no increase of in vivo anti-thrombotic activity, while **8r** has large group near CH_3/449 and CH_3/623 regions, electron-releasing groups near H^+/863 region, electron-withdrawing group near H^+/766 region and thus totally results in no increase of in vivo anti-thrombotic activity.

The predict power of Eq. 2 was examined by comparing the calculated and measured anti-thrombotic activities of **8e,g,j,p** in Table 7. The correlations of predicting and measuring values are also graphically shown in Figure 6. The results indicate that Eq. 2 rationally gives anti-thrombotic activities of **8e,g,j,p** with errors ranging from −0.28 to 1.11 mg. The calculated activity closes the measured activity means that Eq. 2 is able to accurately predict the in vivo anti-thrombotic activity of the derivatives of 2,3-diamino acid modified THIQA.

3. Conclusion

In conclusion, an unfold conformation is crucial for enhancing the activity of amino acid modified THIQA. Comparing with 2- (**9a–t**) or 3-mono amino acid modified THIQAs (**10a–t**), 2,3-diamino acid modified THIQAs (**8a–t**) possess highly unfolded conformation. This leads **8a–t** having selective in vitro inhibition to ADP-induced platelet aggregation, and potential in vivo inhibition to thrombosis of the orally and intravenously treated rats. The IC_{50} values of 2- or 3-monoaminoacid modified THIQAs against ADP-induced platelet aggregation are 47–143 and 55–177-fold higher than that of 2,3-diamino acid modified THIQAs, respectively. To reach the same in vivo anti-thrombotic potency the dose of 2- or 3-monoaminoacid modified THIQAs has to be 167-fold higher than that of 2,3-diamino-acid modified THIQAs. The effect of the highly unfolded conformation on the in vitro anti-platelet aggregation and the in vivo anti-thrombotic activities could be explained with 3D QSAR.

4. Experimental section

4.1. General method

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 according 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.

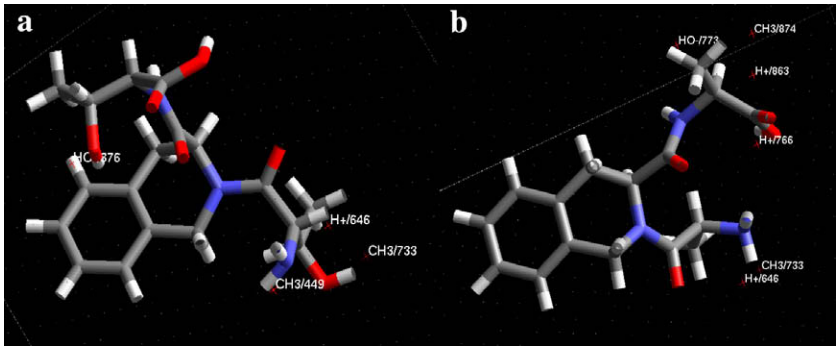


Figure 8. Electrostatic and steric environments of **8r** (a) and **8a** (b) with higher in vitro activity within the grid with 3D points of Eq. 2.

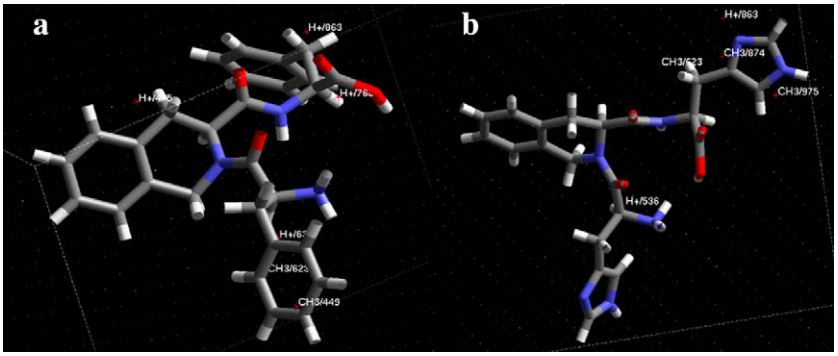


Figure 9. Electrostatic and steric environments of **8q** (a) and **8l** (b) with lower in vitro activity within the grid with 3D points of Eq. 2.

Table 7
Predicted and tested thrombus weight of **8e,g,j,p** treated rats

Compd	Thrombus weight (mg)			
	Predict value	Test value	Error	Error%
8e	24.02	24.30	−0.28	−1.2
8g	22.08	20.97	1.11	5.1
8j	18.58	17.95	0.63	3.4
8p	20.19	19.35	0.84	4.2

4.2. Preparing compounds

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

At 0 °C to 20 ml of methanol 5.2 ml of thionyl chloride was added dropwise, which took 10 min. To this mixture 5.37 g (0.03 mmol) of Phe-OCH_3 was added. The reaction mixture was stirred at room temperature for 100 h, and TLC (CCl_3/CH_3OH = 10:1) indicated the complete disappearance of Phe-OCH_3. The reaction mixture was evaporated under vacuum. The residue was dissolved in 20 ml of methanol and evaporated under vacuum. This procedure was repeated for three times. The residue was dissolved in 50 ml of chloroform and 27 ml of formaldehyde. To this solution 45 ml of concentrated hydrochloric acid was added dropwise. 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 Phe-OCH_3. 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 colorless powder. This procedure was repeated for three times. The residue was crystallized in the mixture of methanol/ether to provide 5.41 g (94%) of the title compound as a colorless powder. Mp 262–264 °C, $[\alpha]_D^{20}$ = −61.0 (*c* = 1.2, CH_3OH), ESI-MS (*m/e*) 192 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.0 (m, 4H), 3.80 (m, 3H), 3.67 (s, 3H), 3.13 (d, *J* = 8.6 Hz, 1H), 2.78 (d, *J* = 7.4 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.

4.3. General procedure of preparing 3*S*-*N*-(Boc-aminoacyl)-1,2,3,4-tetrahydroisoquino-line-3-carboxylic acid methylesters (4a–t)

At 0 °C and with stirring to the solution of 1.0 mmol of Boc-AA in 10 ml of anhydrous THF 0.14 g (1.0 mmol) of HOBt was added to form reaction mixture A. The solution of 0.23 g (0.91 mmol) of 3*S*-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester in 5 ml of anhydrous THF was adjusted pH 9 with triethylamine and stirred for 30 min to form mixture B. At 0 °C the mixture A and B were mixed and then 0.26 g (0.12 mmol) of DCC was added. The reaction mixture was stirred at 0 °C for 2 h, at room temperature for 12 h and TLC (ethyl acetate/petroleum ether, 1:2) indicated the complete disappearance of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester. The formed precipitates of DCU were 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 **4a–t**.

4.3.1. 3*S*-*N*-(Boc-L-alaninyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4a)

Using the general procedure of preparing **4a–t** from 1.93 g (10.21 mmol) Boc-Ala and 1.50 g (7.85 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 2.57 g (90%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 363 $[M+H]^+$; IR (cm^{-1}) 2968, 1734, 1648, 1497, 1457, 1395,1380, 1365, 1198, 1111, 750, 600; $[\alpha]_D^{20}$ = −28.5 (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, *J* = 6.6 Hz, 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),4.83 (d, *J* = 7.5 Hz, 1H), 4.68 (m, 1H), 4.55 (d, *J* = 5.6 Hz, 1H), 4.49 (d, *J* = 8.6 Hz, 1H), 3.63 (s, 3H), 3.30 (d, *J* = 7.5 Hz, 1H), 3.10 (d, *J* = 8.6 Hz, 1H), 1.46 (d, *J* = 5.4 Hz, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 172.9, 155.1, 132.1, 131.7, 127.2, 80.8, 55.8, 52.2, 46.9, 44.6, 28.4, 27.0, 19.0.

4.3.2. 3*S*-*N*-(Boc-glycinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4b)

Using the general procedure of preparing **4a–t** from 1.19 g (6.81 mmol) Boc-Gly and 1.0 g (5.24 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 1.73 g (95%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 349 $[M+H]^+$; IR (cm^{-1}) 2969, 1735, 1648, 1496, 1457, 1395, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20}$ = −11.7 (*c* = 1.1, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, *J* = 5.6 Hz, 1H), 7.22 (m, *J* = 6.4 Hz, 2H), 7.05 (d, *J* = 6.6 Hz, 1H), 6.95 (t, *J* = 6.5 Hz, 1H), 4.80 (d, *J* = 6.4 Hz, 1H), 4.51(m, 2H), 3.85 (d, *J* = 7.5 Hz, 2H), 3.63 (s, 3H), 3.25 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 168.6, 155.8, 131.9, 130.9,128.4,127.2, 126.6, 80.8, 55.8, 52.0, 44.6, 43.0, 28.4, 27.0.

4.3.3. 3*S*-*N*-(Boc-L-valinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4c)

Using the general procedure of preparing **4a–t** from 1.48 g (6.81 mmol) Boc-Val and 1.0 g (5.24 mmol) of (3*S*)-1,2,3,4-tetrahy-

droisoquinoline-3-carboxylic acid methylester 1.28 g (63%) of the title compound was obtained as colorless syrupy. ESI-MS (*m/e*) 391 $[M+H]^+$; IR (cm^{-1}) 2970, 1734, 1648, 1498, 1457, 1395, 1385, 1375, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -15.8$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, *J* = 6.6 Hz, 1H), 7.22 (m, *J* = 6.4 Hz, 2H), 7.07 (d, *J* = 6.5 Hz, 1H), 6.96 (t, *J* = 6.6 Hz, 1H), 4.80 (d, *J* = 5.4 Hz, 1H), 4.61 (d, *J* = 6.4 Hz, 1H), 4.51 (m, 2H), 4.24 (m, 1H), 3.63 (s, 3H), 3.25 (m, 2H), 2.0 (s, 1H), 1.41 (s, 9H), 1.21 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl) δ/ppm = 171.6, 168.6, 155.8, 135.9, 133.9, 128.4, 127.2, 126.6, 80.8, 67.8, 58.4, 55.8, 52.0, 44.6, 28.4, 27.0,18.9.

4.3.4. 3*S*-*N*-(Boc-L-leucinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4d)

Using the general procedure of preparing **4a–t** from 2.36 g (10.21 mmol) Boc-Leu and 1.5 g (7.85 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 1.44 g (45%) of the title compound was obtained as colorless syrupy. ESI-MS (*m/e*) 405 $[M+H]^+$; IR (cm^{-1}) 2970, 1734, 1648, 1497, 1457, 1395, 1385, 1375, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -16.3$ (*c* = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, *J* = 6.6 Hz, 1H), 7.02 (m, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.80 (d, *J* = 8.4 Hz, 1H), 4.51 (m, 3H), 3.63(s, 3H), 3.10 (m, 2H), 1.78 (m, 3H), 1.41 (s, 9H), 1.01(d, *J* = 7.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 135.9, 134.2, 128.4, 127.2, 126.6, 79.5, 55.8, 52.0, 50.7, 44.6, 41.6, 28.4, 27.0, 22.3.

4.3.5. 3*S*-*N*-(Boc-L-isoleucinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl-ester (4e)

Using the general procedure of preparing **4a–t** from 2.36 g (10.21 mmol) Boc-Ile and 1.5 g (7.85 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 1.62 g (51%) of the title compound was obtained as colorless syrupy. ESI-MS (*m/e*) 405 $[M+H]^+$; IR (cm^{-1}) 2969, 1734, 1648, 1497, 1457, 1395,1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -13.4$ (*c* = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, *J* = 7.6 Hz, 1H), 7.02 (m, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.80 (d, *J* = 5.4 Hz, 1H), 4.51 (m, 3H), 3.63 (s, 3H), 3.10 (m, 2H), 2.5 (m, 1H), 1.41 (s, 9H), 1.29 (m, 2H), 1.06 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 8.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 135.9, 134.2,128.4, 127.2, 126.6, 79.5, 55.8, 52.0, 44.6, 28.4, 27.0, 24.3, 14.6, 10.9.

4.3.6. 3*S*-*N*-(Boc-L-tryptophanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4f)

Using the general procedure of preparing **4a–t** from 1.03 g (3.40 mmol) Boc-Trp and 0.50 g (2.62 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 0.64 g (52%) of the title compound was obtained as yellowing powders. ESI-MS (*m/e*) 478 $[M+H]^+$; IR (cm^{-1}) 2968, 1734, 1648, 1497, 1457, 1395,1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -6.38$ (*c* = 1.0, CH_3OH);^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 10.10 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.18 (m, *J* = 6.4 Hz, 4H), 7.02 (m, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 6.4 Hz, 1H), 4.90 (d, *J* = 8.0 Hz, 1H), 4.81 (d, *J* = 5.4 Hz,1H), 4.51 (m, 2H), 3.63 (s, 3H), 3.10 (m, 4H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 135.9, 134.2, 128.4, 127.2, 126.6, 122.9, 119.0, 110.9, 79.5, 55.8, 52.0, 31.5, 44.6, 28.4, 27.0.

4.3.7. 3*S*-*N*-(Boc-L-serinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4g)

Using the general procedure of preparing **4a–t** from 1.15 g (5.65 mmol) Boc-Ser and 0.83 g (4.35 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 0.99 g (49%) of the title compound was obtained as colorless syrupy. ESI-MS (*m/e*) 469 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -7.61$ (*c* = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, *J* = 5.6 Hz, 1H), 7.02 (m, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.83 (m, *J* = 8.2 Hz, 1H), 4.63 (s, 2H), 4.51 (m, 2H), 3.86 (m, 2H), 3.63 (s, 3H), 3.29 (d, *J* = 6.5 Hz, 1H), 3.05 (d, *J* = 8.6 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 137.2, 135.9, 134.2, 128.4, 127.2, 125.6, 79.5, 74.3, 70.2, 55.8, 52.0, 50.7, 44.6, 28.4, 27.0.

4.3.8. 3*S*-*N*-(Boc-L-tyrocinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl-ester (4h)

Using the general procedure of preparing **4a–t** from 2.53 g (6.81 mmol) Boc-Tyr and 1.00 g (5.24 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 2.25 g (79%) of the title compound was obtained as colorless syrupy. ESI-MS (*m/e*) 545 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395, 1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -6.86$ (*c* = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, *J* = 7.6 Hz, 1H), 7.02 (m, *J* = 8.2 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 5.5 Hz, 2H), 5.20 (s, 1H), 4.92 (m, 1H), 4.80 (t, *J* = 6.4 Hz, 1H), 4.51 (d, *J* = 7.6 Hz, 1H), 4.41 (d, *J* = 5.4 Hz, 1H), 3.63 (d, *J* = 7.5 Hz, 3H), 3.29 (d, *J* = 6.8 Hz, 1H), 3.05 (d, *J* = 8.3 Hz, 1H), 2.92 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 157.9, 155.8, 141.2, 136.5, 134.9, 131.2, 129.0, 128.4, 127.2, 126.6, 114.2, 79.5, 70.9, 55.8, 52.9, 52.0, 44.6, 37.8, 28.4, 27.0.

4.3.9. 3*S*-*N*-(Boc-L-prolinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4i)

Using the general procedure of preparing **4a–t** from 1.46 g (6.81 mmol) of Boc-Pro and 1.00 g (5.24 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 1.73 g (85%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 389 $[M+H]^+$; IR (cm^{-1}) 3410, 2969, 1734, 1648, 1497, 1457, 1395, 1365, 1360, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -54.6$ (*c* = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 7.02 (m, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.80 (t, *J* = 8.4 Hz, 1H), 4.51 (m, 2H), 4.29 (t, *J* = 7.6 Hz, 1H), 3.63 (s, 3H), 3.20 (m, 4H), 1.71 (m, 2H), 1.60 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 135.9, 134.2, 128.4, 127.2, 126.6, 79.5, 55.8, 52.0, 47.1, 44.6, 29.7, 28.4, 27.0, 22.1.

4.3.10. 3*S*-*N*-(Boc-L-asparaginyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl-ester (4j)

Using the general procedure of preparing **4a–t** from 4.74 g (20.42 mmol) of Boc-Asn and 3.00 g (15.71 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 5.13 g (84%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 406 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395, 1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -10.4$ (*c* = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, *J* = 5.6 Hz, 1H), 7.02 (m, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.0 (s, 2H), 4.78 (m, 2H), 4.51 (d, *J* = 6.4 Hz, 1H), 4.41 (d, *J* = 5.4 Hz, 1H), 3.63 (s, 3H), 3.29 (d, *J* = 7.2 Hz, 1H), 3.05 (d, *J* = 8.6 Hz, 1H), 2.68 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 174.5, 171.6, 170.1, 155.8, 135.9, 134.2, 128.4, 127.2, 126.6, 79.5, 55.8, 52.0, 51.6, 44.6, 37.9, 28.4, 27.0.

4.3.11. 3*S*-*N*-(Boc-L-glutaminyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl-esters (4k)

Using the general procedure of preparing **4a–t** from 2.51 g (10.21 mmol) of Boc-Gln and 1.50 g (7.85 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 3.02 g (92%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 420 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395,1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -14.7$

(c = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, J = 5.6 Hz, 1H), 7.02 (m, J = 8.2 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.78 (t, J = 6.4 Hz, 1H), 4.48 (m, 3H), 3.63 (s, 3H), 3.29 (d, J = 7.2 Hz, 1H), 3.05 (d, J = 6.6 Hz, 1H), 2.18 (t, J = 8.5 Hz, 2H), 2.07 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 174.5, 171.6, 170.1, 155.8, 135.9, 134.2, 128.4, 127.2, 126.6, 79.5, 55.8, 52.0, 51.6, 44.6, 32.6, 28.4, 27.6, 27.0.

4.3.12. 3*S*-*N*-(Boc-L-histidinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl-esters (4l)

Using the general procedure of preparing **4a–t** from 3.46 g (13.61 mmol) of Boc-His and 2.00 g (10.47 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 3.23 g (72%) of the title compound was obtained as colorless powders. ESI-MS (m/e) 429 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395,1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -11.2$ (c = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 13.40 (d, J = 7.4 Hz, 1H), 8.00 (s, 1H), 7.44 (s, 1H), 7.02 (m, J = 8.2 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 6.3 Hz, 1H), 4.92 (t, J = 7.3 Hz, 1H), 4.80 (t, J = 5.4 Hz, 1H), 4.51 (d, J = 6.2 Hz, 1H), 4.41 (d, J = 8.6 Hz, 1H), 3.63 (s, 3H), 3.17 (m, 1H), 2.92 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 135.9, 134.2, 133.5, 128.4, 127.2, 126.6, 119.6, 79.5, 55.8, 52.0, 51.6, 44.6, 30.5, 28.4, 27.0.

4.3.13. 3*S*-*N*-(N^{α},N^{ω}-diBoc-L-lysinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylesters (4m)

Using the general procedure of preparing **4a–t** from 2.34 g (6.81 mmol) of Boc_2-Lys and 1.00 g (5.24 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 2.53 g (93%) of the title compound was obtained as colorless powders. ESI-MS (m/e) 520 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395,1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -9.0$ (c = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, J = 7.6 Hz, 2H), 7.02 (m, J = 8.2 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.78 (t, J = 8.4 Hz, 1H), 4.52 (m, 2H), 4.41 (d, J = 6.4 Hz, 1H), 3.63 (s, 3H), 3.29 (d, J = 5.6Hz, 1H), 3.05 (d, J = 8.5 Hz, 1H), 2.96 (m, 2H), 1.79 (m, 2H), 1.55 (m, 2H), 1.41 (s, 18H), 1.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 135.9, 134.2, 128.4, 127.2, 126.6, 79.5, 55.8, 52.0, 51.6, 44.6, 41.9, 31.9, 28.4, 27.0, 20.7.

4.3.14. 3*S*-*N*-(Boc-L-aspartyl-β-benzylester)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4n)

Using the general procedure of preparing **4a–t** from 1.16 g (3.59 mmol) of Boc-Asp(OBzl) and 0.53 g (2.85 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 0.89 g (63%) of the title compound was obtained as colorless powders. ESI-MS (m/e) 497 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395, 1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -5.70$ (c = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, J = 6.6 Hz, 1H), 7.19 (s, 5H), 7.02 (m, J = 8.2 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.34 (s, 2H), 5.17 (t, J = 7.3 Hz, 1H), 4.81 (t, J = 8.4 Hz, 1H), 4.51 (d, J = 7.3 Hz, 1H), 4.41 (d, J = 5.6 Hz, 1H), 3.63 (s, 3H), 3.29 (d, J = 6.6 Hz, 1H), 3.05 (d, J = 8.6 Hz, 1H), 2.88 (m, 1H), 2.63 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 174.5, 171.6, 170.1, 155.8, 141.2, 135.9, 134.2, 129.4, 127.2, 126.6, 79.5, 68.5, 55.8, 52.0, 51.6, 49.7, 44.6, 37.9, 28.4, 27.0.

4.3.15. 3*S*-*N*-(Boc-L-glutamoyl-γ-benzylester)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4o)

Using the general procedure of preparing **4a–t** from 2.37 g (7.04 mmol) of Boc-Glu(OBzl) and 1.19 g (6.23 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 1.59 g (50%) of the title compound was obtained as colorless powders. ESI-MS (m/e) 511 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395,1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -57.6$ (c = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, J = 6.6 Hz, 1H), 7.19 (s, 5H), 7.02 (m, J = 8.2 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.34 (s, 2H), 4.81 (t, J = 8.4 Hz, 1H), 4.53 (m, 1H), 4.51 (d, J = 5.4 Hz, 1H), 4.41 (d, J = 8.5 Hz, 1H), 3.63 (s, 3H), 3.29 (d, J = 7.6 Hz, 1H), 3.05 (d, J = 6.5 Hz, 1H), 2.21 (m, 4H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 174.5, 171.6, 170.1, 155.8, 141.2, 135.9, 134.2, 129.4, 127.2, 126.6, 79.5, 68.5, 55.8, 52.0, 51.6, 44.6, 37.9, 28.4, 27.0.

4.3.16. 3*S*-*N*-[Boc-L-(*S*-*p*-methylbenzylcysteinyl)]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4p)

Using the general procedure of preparing **4a–t** from 3.32 g (10.21 mmol) of Boc-Cys(*S*-$CH_2C_6H_4$-Me-*p*) and 1.50 g (7.85 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 3.40 g (87%) of the title compound was obtained as colorless powders. ESI-MS (m/e) 499 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, J = 6.6 Hz, 1H), 7.11 (s, 4H), 6.98 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 4.81 (t, J = 8.4 Hz, 1H), 4.53 (m, 1H), 4.51 (d, J = 5.4 Hz, 1H), 4.41 (d, J = 8.5 Hz, 1H), 3.72 (d, 2H), 3.63 (s, 3H), 3.29 (d, J = 7.6 Hz, 1H), 3.05 (d, J = 6.5 Hz, 1H), 2.82 (d, J = 9.0 Hz, 2H), 2.36 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 135.9, 134.2, 129.4, 127.2, 126.6, 125.9, 79.5, 55.8, 52.0, 51.8, 44.6, 37.9, 34.1, 28.4, 27.0, 24.3.

4.3.17. 3*S*-*N*-(Boc-L-phenylalaninyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester (4q)

Using the general procedure of preparing **4a–t** from 2.71 g (10.21 mmol) of Boc-Phe and 1.50 g (7.85 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 2.58 g (75%) of the title compound was obtained as colorless powders. ESI-MS (m/e) 439 $[M+H]^+$; IR (cm^{-1}) 2968, 1734, 1648, 1600, 1497, 1457, 1395, 1380, 1365, 1198, 1111, 750, 700, 599; $[\alpha]_D^{20} = -35.8$ (c = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, J = 6.6 Hz, 1H), 7.22 (m, J = 7.4 Hz, 2H), 7.15 (d, J = 7.2 Hz, 2H), 7.10 (d, J = 7.8 Hz, 1H), 7.02 (m, J = 8.2 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.92 (d, J = 5.2 Hz, 1H), 4.80 (d, J = 8.4 Hz, 1H), 4.51 (d, J = 7.1 Hz, 1H), 4.41 (d, J = 7.3 Hz, 1H), 3.63 (s, 3H), 3.10 (m, 4H), 1.41 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 139.5, 135.9, 134.2, 128.4, 127.2, 126.6, 79.5, 55.8, 52.0, 44.6, 37.8, 28.4, 27.0.

4.3.18. 3*S*-*N*-(Boc-L-threoninyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl-ester (4r)

Using the general procedure of preparing **4a–t** from 2.23 g (10.21 mmol) of Boc-Thr and 1.0 g (5.24 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 1.52 g (74%) of the title compound was obtained as colorless syrupy. ESI-MS (m/e) 393 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395, 1380, 1365, 1198, 1111, 750; $[\alpha]_D^{20} = -20.1$ (c = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, J = 6.6 Hz, 1H), 7.02 (m, J = 8.2 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.80 (t, J = 7.1 Hz, 1H), 4.61 (d, J = 8.2 Hz, 1H), 4.46 (m, 2H), 4.24 (m, 1H), 3.63 (s, 3H), 3.29 (d, J = 5.4 Hz, 1H), 3.05 (d, J = 6.4 Hz, 1H), 2.0 (s, 1H), 1.48 (s, 9H), 1.21 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)/ppm = 171.6, 170.1, 155.8, 135.9, 134.2, 128.4, 127.2, 126.6, 79.5, 67.8, 58.8, 55.0, 51.7, 44.6, 28.4, 27.0, 10.9.

4.3.19. 3*S*-*N*-(Boc-L-NO_2^G-argininyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylesters (4s)

Using the general procedure of preparing **4a–t** from 3.25 g (10.21 mmol) of Boc-Arg(NO_2) and 1.0 g (5.24 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 1.24 g (48%) of the title compound was obtained as colorless syrupy. ESI-MS (m/e) 494 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395,1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -2.55$ (c = 1.0, CH_3OH); ^1H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d,

J = 7.6 Hz, 2H), 7.02 (m, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.84 (m, 1H), 4.53 (m, 1H), 4.51 (d, *J* = 7.4 Hz, 1H), 4.41 (d, *J* = 8.6 Hz, 1H), 3.63 (s, 3H), 3.27 (m, 1H), 3.04 (m, 1H), 2.65 (m, 2H), 2.0 (d, *J* = 8.5 Hz, 2H), 1.79 (m, 2H), 1.55 (m, 2H), 1.41 (s, 9H); ^{13}CNMR (75 MHz, $CDCl_3$) δ/ppm = 171.8, 170.1, 158.2, 155.8, 135.9, 134.2, 129.4, 127.2, 126.6, 79.5, 71.7, 55.8, 53.8, 51.2, 44.6, 37.1, 28.4, 27.0, 24.3.

4.3.20. 3*S*-*N*-(Boc-L-methioninyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methyl-ester (4t)

Using the general procedure of preparing **4a–t** from 2.54 g (10.21 mmol) of Boc-Met and 1.0 g (5.24 mmol) of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid methylester 1.77 g (80%) of the title compound was obtained as colorless syrupy. ESI-MS (*m/e*) 423 $[M+H]^+$; IR (cm^{-1}) 3411, 2969, 1734, 1648, 1497, 1457, 1395, 1380, 1365, 1198, 1111, 750, 599; $[\alpha]_D^{20} = -17.7$ (*c* = 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ/ppm = 8.00 (d, *J* = 7.6 Hz, 1H), 7.02 (m, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.80 (t, *J* = 6.4 Hz, 1H), 4.51 (m, 3H), 3.63 (s, 3H), 3.29 (d, *J* = 5.3 Hz, 1H), 3.05 (d, *J* = 7.6 Hz, 1H), 2.44 (m, 2H), 2.16 (t, *J* = 6.6 Hz, 2H), 2.09 (s, 3H), 1.41 (s, 9H); ^{13}CNMR (75 MHz, $CDCl_3$) δ/ppm = 171.6, 170.1, 155.8, 135.9, 134.2, 128.4, 127.2, 126.6, 79.5, 55.8, 52.0, 51.6, 44.6, 31.9, 29.3, 28.4, 27.0, 17.4.

4.4. General procedure of preparing 3*S*-*N*-(Boc-aminoacyl)-1,2,3,4-tetrahydroisoquino-line-3-carboxylic acids (5a–t)

At 0 °C to the solution of 1.0 mmol of 3*S*-*N*-(Boc-aminoacyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid methylester in 5 ml of methanol 7 ml of aqueous of NaOH (2 N) 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*)-*N*-(Boc-aminoacyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic 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 **5a–t**.

4.4.1. 3*S*-*N*-(Boc-L-alaninyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5a)

Using the general procedure of preparing **5a–t** from 1.50 g (4.14 mmol) of **4a** 1.29 g (89%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 349 $[M+H]^+$.

4.4.2. 3*S*-*N*-(Boc-glycinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5b)

Using the general procedure of preparing **5a–t** from 162 mg (0.46 mmol) of **4b** 137 mg (89%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 335 $[M+H]^+$.

4.4.3. 3*S*-*N*-(Boc-L-valinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5c)

Using the general procedure of preparing **5a–t** from 0.445 g (1.14 mmol) of **4c** 0.357 g (83%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 377 $[M+H]^+$.

4.4.4. 3*S*-*N*-(Boc-L-leucinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5d)

Using the general procedure of preparing **5a–t** from 0.24 g (0.59 mmol) of **4d** 0.22 g (96%) of the title compound was obtained as colorless syrupy. ESI-MS (*m/e*) 391 $[M+H]^+$.

4.4.5. 3*S*-*N*-(Boc-L-isoleucinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5e)

Using the general procedure of preparing **5a–t** from 0.60 g (1.49 mmol) of **4e** 0.52 g (89%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 391 $[M+H]^+$.

4.4.6. 3*S*-*N*-(Boc-L-tryptophanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5f)

Using the general procedure of preparing **5a–t** from 0.61 g (1.28 mmol) of **4f** 0.56 g (95%) of the title compound was obtained as colorless syrupy. ESI-MS (*m/e*) 464 $[M+H]^+$.

4.4.7. 3*S*-*N*-(Boc-L-serinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5g)

Using the general procedure of preparing **5a–t** from 0.97 g (2.09 mmol) of **4g** 0.88 g (94%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 450 $[M+H]^+$.

4.4.8. 3*S*-*N*-(Boc-L-tyrocinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5h)

Using the general procedure of preparing **5a–t** from 1.48 g (3.73 mmol) of **4h** 1.33 g (80%) of the title compound was obtained as colorless syrupy. ESI-MS (*m/e*) 446 $[M+H]^+$.

4.4.9. 3*S*-*N*-(Boc-L-prolinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5i)

Using the general procedure of preparing **5a–t** from 0.10 g (0.26 mmol) of **4i** 0.05 g (51%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 375 $[M+H]^+$.

4.4.10. 3*S*-*N*-(Boc-L-asparaginyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5j)

Using the general procedure of preparing **5a–t** from 0.19 g (0.47 mmol) of **4j** 0.17 g (90%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 392 $[M+H]^+$.

4.4.11. 3*S*-*N*-(Boc-L-glutaminyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5k)

Using the general procedure of preparing **5a–t** from 1.33 g (3.17 mmol) of **4k** 1.26 g (98%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 406 $[M+H]^+$.

4.4.12. (3*S*)-*N*-(Boc-L-histidinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5l)

Using the general procedure of preparing **5a–t** from 0.83 g (1.93 mmol) of **4l** 0.74 g (92%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 415 $[M+H]^+$.

4.4.13. 3*S*-*N*-(N^{α},N^{ω}-diBoc-L-lysinyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5m)

Using the general procedure of preparing **5a–t** from 2.39 g (4.60 mmol) of **4m** 2.11 g (91%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 506 $[M+H]^+$.

4.4.14. 3*S*-*N*-(Boc-L-aspartyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5n)

Using the general procedure of preparing **5a–t** from 1.74 g (3.50 mmol) of **4n** 1.32 g (96%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 393 $[M+H]^+$.

4.4.15. 3*S*-*N*-(Boc-L-glutamoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5o)

Using the general procedure of preparing **5a–t** from 0.79 g (1.54 mmol) of **4o** 0.52 g (83%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 407 $[M+H]^+$.

4.4.16. 3*S*-*N*-[Boc-L-(*S*-*p*-methylbenzylcycteinyl)]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5p)

Using the general procedure of preparing **5a–t** from 1.00 g (2.01 mmol) of **4p** 0.91 g (93%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 485 $[M+H]^+$.

4.4.17. 3*S*-*N*-(Boc-L-phenylalaninyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5q)

Using the general procedure of preparing **5a–t** from 0.33 g (0.76 mmol) of **4q** 0.31 g (96%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 425 $[M+H]^+$.

4.4.18. 3*S*-*N*-(Boc-L-threoninyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5r)

Using the general procedure of preparing **5a–t** from 0.78 g (2.00 mmol) of **4r** 0.70 g (93%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 379 $[M+H]^+$.

4.4.19. 3*S*-*N*-(Boc-L-NO_2^G-argininyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5s)

Using the general procedure of preparing **5a–t** from 1.15 g (2.33 mmol) of **4s** 0.95 g (85%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 480 $[M+H]^+$.

4.4.20. 3*S*-*N*-(Boc-L-methioninyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5t)

Using the general procedure of preparing **5a–t** from 1.15 g (2.72 mmol) of **4t** 1.03 g (93%) of the title compound was obtained as colorless powders. ESI-MS (*m/e*) 409 $[M+H]^+$.

4.5. General procedure of preparing *N*-(3*S*-*N*-Boc-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)amino acid benzylesters (6a–t)

At 0 °C and with stirring to the solution of 1.0 mmol of 3*S*-*N*-(Boc-aminoacyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**5a–t**) in 30 ml of anhydrous THF 0.14 g (1.0 mmol) of HOBt was added to form reaction mixture A. The solution of 0.23 g (0.91 mmol) of AA-OBzl in 5 ml of anhydrous THF was adjusted pH 9 with triethylamine and stirred for 30 min to form mixture B. At 0 °C the mixture A and B were mixed and then 0.26 g (0.12 mmol) of DCC was added. The reaction mixture was stirred at 0 °C for 2 h, at room temperature for12 h and TLC (ethyl acetate/petroleum ether, 1:2) indicated the complete disappearance of **5a–t**. The formed precipitates of DCU were 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 **6a–t**.

4.5.1. *N*-(3*S*-*N*-Boc-L-alaninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-alanine benzylester (6a)

Using the general procedure of preparing **6a–t** from 0.505 g (1.45 mmol) of **5a** and 0.303 g (1.87 mmol) of Ala-oBzl 0.40 g (54%) of the title compound was obtained as colorless powders. Mp 100–103 °C, ESI-MS (*m/e*) 510 $[M+H]^+$. $[\alpha]_D^{20} = -25.5$ (*c* = 1.1, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.26 (d, *J* = 8.7 Hz, 2H), 7.20 (m, 5H), 7.00 (m, 4H), 5.53 (s, 2H), 4.97 (t, *J* = 5.7 Hz, 1H), 4.73 (d, *J* = 6.3 Hz, 2H), 4.61 (m, 2H), 3.32 (d, *J* = 5.5 Hz, 1H), 3.12 (d, *J* = 5.5 Hz, 1H), 1.99 (d, *J* = 7.5 Hz, 6H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.2, 172.8, 171.3, 145.1, 133.8, 133.1, 128.3, 127.9, 127.7, 127.6, 126.9, 126.2, 125.9, 81.4, 81.3, 56.4, 52.4, 47.8, 47.6, 45.2, 32.1, 30.7, 29.7, 28.4, 28.3, 19.2, 18.3. Anal. Calcd for $C_{28}H_{35}N_3O_6$: C, 65.99; H, 6.92; N, 8.25. Found: C, 65.76; H, 6.78; N, 8.00.

4.5.2. *N*-(3*S*-*N*-Boc-glycinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)glycine benzyl-ester (6b)

Using the general procedure of preparing **6a–t** from 108 mg (0.39 mmol) of **5b** and 75 mg (0.46 mmol) of Gly-oBzl 116 mg (62%) of the title compound was obtained as colorless powders. Mp 97–98 °C, ESI-MS (*m/e*) 482 $[M+H]^+$. $[\alpha]_D^{20} = -20.0$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6) δ/ppm = 8.40 (d, *J* = 4.5 Hz, 2H), 7.20 (m, 5H), 7.00 (m, 4H), 5.54 (s, 2H), 4.66 (m, 3H), 4.20 (d, *J* = 4.5 Hz, 2H), 3.82 (d, *J* = 4.5 Hz, 2H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.78 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 172.5, 170.6, 164.7, 156.2, 135.0, 133.6, 133.2, 128.7, 128.4, 127.6, 127.3, 126.0, 80.2, 67.6, 55.6, 46.3, 40.6, 31.5, 28.4, 24.3. Anal. Calcd for $C_{26}H_{31}N_3O_6$: C, 64.85; H, 6.49; N, 8.73. Found: C, 64.62; H, 6.31; N, 8.49.

4.5.3. *N*-(3*S*-*N*-Boc-L-valinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-valine benzylester (6c)

Using the general procedure of preparing **6a–t** from 1.38 g (2.86 mmol) of **5c** and 0.77 g (3.72 mmol) of Val-oBzl 1.22 g (74%) of the title compound was obtained as colorless powders. Mp 85–87 °C, ESI-MS (*m/e*) 566 $[M+H]^+$. $[\alpha]_D^{20} = -49.3$ (*c* = 1.1, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.14 (d, *J* = 9.8 Hz, 2H), 7.17 (m, *J* = 9.0 Hz, 9H), 5.15 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 3.09 (m, 1H), 2.68 (m, 1H), 1.39 (s, 9H), 0.89 (d, *J* = 3.6 Hz, 12H). ^{13} C NMR (75 MHz, DMSO-d_6): δ/ppm = 171.9, 171.6, 169.1, 155.6, 140.1, 136.9, 134.5, 129.9, 127.8, 127.5, 127.0, 125.9, 80.1, 68.5, 62.0, 57.8, 55.0, 43.8, 31.2, 30.0, 28.2, 27.5, 17.4, 17.0. Anal. Calcd for $C_{32}H_{43}N_3O_6$: C, 67.94; H, 7.66; N, 7.43. Found: C, 67.70; H, 7.51; N, 7.66.

4.5.4. *N*-(3*S*-*N*-Boc-L-leucinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-leucine benzylester (6d)

Using the general procedure of preparing **6a–t** from 1.10 g (2.86 mmol) of **5d** and 0.82 g (3.72 mmol) of Leu-OBzl 1.54 g (92%) of the title compound was obtained as colorless powders. Mp 50–52 °C, ESI-MS (*m/e*) 594 $[M+H]^+$. $[\alpha]_D^{20} = -189.7$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.14 (d, *J* = 9.8 Hz, 2H), 7.17 (m, *J* = 9.0 Hz, 9H), 5.35 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.86 (m, 2H), 1.83 (m, 2H), 1.70 (m, 2H), 1.39 (s, 9H), 0.89 (d, *J* = 3.6 Hz, 12H). ^{13} C NMR (75 MHz, DMSO-d_6): δ/ppm = 171.9, 171.6, 169.1, 155.6, 140.1, 136.9, 134.5, 129.9, 127.8, 127.5, 127.0, 125.9, 79.1, 68.0, 62.1, 55.0, 43.8, 41.2, 40.0, 28.2, 27.5, 22.9, 22.0. Anal. Calcd for $C_{34}H_{47}N_3O_6$: C, 68.78; H, 7.98; N, 7.08. Found: C, 69.01; H, 8.15; N, 7.30.

4.5.5. *N*-(3*S*-*N*-Boc-L-isoleucinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-isoleucine benzylester (6e)

Using the general procedure of preparing **6a–t** from 1.42 g (3.65 mmol) of **5e** and 1.05 g (4.74 mmol) of Ile-OBzl 1.20 g (56%) of the title compound was obtained as colorless powders. Mp 63–67 °C, ESI-MS (*m/e*) 594 $[M+H]^+$. $[\alpha]_D^{20} = -75.2$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.14 (d, *J* = 9.8 Hz, 2H), 7.17 (m, *J* = 9.0 Hz, 9H), 5.35 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.51 (m, 2H), 1.39 (s, 9H), 1.28 (m, 4H), 1.08 (d, 6H), 1.01 (t, *J* = 8.4 Hz, 6H). ^{13} C NMR (75 MHz, DMSO-d_6): δ/ppm = 171.8, 171.4, 169.0, 155.5, 140.2, 136.7, 134.6, 129.8, 127.7, 127.2, 126.8, 125.8, 79.4, 68.1, 62.5, 55.0, 53.1, 43.8, 37.2, 36.0, 28.2, 27.5, 24.9, 14.0, 10.2. Anal. Calcd for $C_{34}H_{47}N_3O_6$: C, 68.78; H, 7.98; N, 7.08. Found: C, 68.57; H, 7.81; N, 7.32.

4.5.6. *N*-(3*S*-*N*-Boc-L-tryptophanyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-tryptophan benzylester (6f)

Using the general procedure of preparing **6a–t** from 0.61 g (1.33 mmol) of **5f** and 0.51 g (1.72 mmol) of Trp-OBzl 0.84 g (85%) of the title compound was obtained as colorless powders. Mp 154–157 °C, ESI-MS (*m/e*) 740 $[M+H]^+$. $[\alpha]_D^{20} = -177.4$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 10.92 (d, *J* = 15.1 Hz, 2H), 8.52 (d, *J* = 7.5 Hz, 1H), 8.29 (d, *J* = 7.0 Hz, 1H), 7.29 (m, 13H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* =7.4 Hz, 1H), 6.86 (s, 2H), 5.33 (s, 2H), 5.03 (t, *J* = 6.1 Hz, 1H), 5.00 (m, *J* = 8.6 Hz, 2H), 4.56 (s, 2H), 3.18 (dd, *J* = 6.0 Hz, 1H), 3.03 (m, 2H), 2.95 (m, 2H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 172.7, 171.7, 155.1, 140.0, 136.8, 136.6, 136.4, 134.1, 129.6, 127.8, 127.6, 126.9, 125.8, 122.4, 120.4, 119.6, 111.9, 109.7, 79.0, 70.0, 68.4, 62.7, 54.3, 53.7, 44.4, 32.2, 30.1, 28.6, 27.5. Anal. Calcd for $C_{44}H_{45}N_5O_6$: C, 71.43; H, 6.13; N, 9.47. Found: C, 71.62; H, 6.30; N, 9.71.

4.5.7. *N*-(3*S*-*N*-Boc-L-serinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-serine benzylester (6g)

Using the general procedure of preparing **6a–t** from 99 mg (0.22 mmol) of **5g** and 57 mg (0.29 mmol) of Ser-OBzl 99 mg (85%) of the title compound was obtained as colorless powders. Mp 112–114 °C, ESI-MS (*m/e*) 542 $[M+H]^+$. $[\alpha]_D^{20} = -30.8$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.30 (d, *J* = 2.5 Hz, 2H), 7.24 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* =7.4 Hz, 1H), 5.30 (s, 2H), 4.76 (m, 5H), 4.13 (d, *J* = 8.8 Hz, 2H), 4.03 (d, *J* = 8.8 Hz, 2H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 172.0, 171.8, 170.6, 159.5, 138.2, 136.8, 134.2, 128.6, 127.5, 127.4, 127.0, 126.2, 79.0, 66.3, 61.2, 58.2, 54.2, 43.1, 28.2, 27.2. Anal. Calcd for $C_{28}H_{35}N_3O_8$: C, 62.09; H, 6.51; N, 7.76. Found: C, 62.29; H, 6.69; N, 8.00.

4.5.8. *N*-(3*S*-*N*-Boc-L-tyrocinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-tyrosine benzylester (6h)

Using the general procedure of preparing **6a–t** from 0.61 g (1.36 mmol) of **5h** and 0.48 g (1.77 mmol) of Tyr-OBzl 0.86 g (91%) of the title compound was obtained as colorless powders. Mp 141–143 °C, ESI-MS (*m/e*) 694 $[M+H]^+$. $[\alpha]_D^{20} = -20.9$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6):δ/ppm = 8.14 (d, *J* = 7.8 Hz, 2H), 7.21 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 4H), 6.80 (d, *J* = 8.1 Hz, 4H), 5.30 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.06 (m, 6H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 172.0, 171.8, 170.6, 155.5, 138.2, 136.8, 134.2, 132.1, 128.6, 127.5, 127.4, 127.0, 126.2, 115.8, 79.0, 66.3, 61.2, 53.2, 52.1, 43.1, 37.8, 37.0, 28.2, 27.2. Anal. Calcd for $C_{40}H_{43}N_3O_8$: C, 69.25; H, 6.25; N, 6.06. Found: C, 69.02; H, 6.09; N, 6.29.

4.5.9. *N*-(3*S*-*N*-Boc-L-prolinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-proline benzylester (6i)

Using the general procedure of preparing **6a–t** from 0.50 g (1.34 mmol) of **5i** and 0.35 g (1.70 mmol) of Pro-OBzl 0.50 g (67%) of the title compound was obtained as colorless powders. Mp 75–78 °C, ESI-MS (*m/e*) 562 $[M+H]^+$. $[\alpha]_D^{20} = -100.2$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 7.21 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* =7.4 Hz, 1H), 5.35 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.97 (m, 4H), 1.59 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 173.1, 171.8, 171.0, 155.6, 136.7, 135.7, 135.1, 128.8, 128.1, 127.8, 127.7, 127.5, 127.3, 127.1, 125.5, 80.0, 71.9, 61.0, 60.7, 60.2, 46.8, 44.7, 43.8, 32.4, 29.1, 29.0, 28.9, 24.5, 23.8, 21.8, 21.1. Anal. Calcd for $C_{32}H_{39}N_3O_6$: C, 68.43; H, 7.00; N, 7.48. Found: C, 68.21; H, 6.82; N, 7.23.

4.5.10. *N*-(3*S*-*N*-Boc-L-asparaginyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-asparagine benzylester (6j)

Using the general procedure of preparing **6a–t** from 102 mg (0.26 mmol) of **5j** and 73 mg (0.33 mmol) of Asn-OBzl 102 mg (66%) of the title compound was obtained as colorless powders. Mp 105–111 °C, ESI-MS (*m/e*) 596 $[M+H]^+$. $[\alpha]_D^{20} = -120.5$ (*c* = 1.1, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.19 (d, *J* = 8 Hz, 2H), 7.21 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.98 (s, 4H), 5.37 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.83 (m, 4H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.8, 171.3, 170.4, 169.6, 156.3, 140.9, 136.7, 134.3, 129.1, 127.9, 127.8, 127.7, 127.0, 125.7, 80.1, 68.1, 63.9, 50.2, 48.1, 43.4, 40.2, 39.7, 28.5, 26.8. Anal. Calcd for $C_{30}H_{37}N_5O_8$: C, 60.49; H, 6.26; N, 11.76. Found: C, 60.70; H, 6.42; N, 11.51.

4.5.11. *N*-(3*S*-*N*-Boc-L-glutaminyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-glutamine benzylester (6k)

Using the general procedure of preparing **6a–t** from 709 mg (1.75 mmol) of **5k** and 236 mg (2.25 mmol) of Gln-OBzl 502 mg (46%) of the title compound was obtained as colorless powders. Mp 65–68 °C, ESI-MS (*m/e*) 624 $[M+H]^+$. $[\alpha]_D^{20} = -4.9$ (*c* = 1.0, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.19 (d, *J* = 8.0 Hz, 2H), 7.21 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.96 (s, 4H), 5.37 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.23 (t, *J* = 8.2 Hz, 4H), 2.08 (m, 4H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 173.8, 171.3, 170.4, 169.6, 156.3, 140.9, 136.7, 134.3, 129.1, 127.9, 127.8, 127.7, 127.0, 125.7, 80.1, 68.1, 63.9, 50.2, 48.1, 43.4, 30.4, 28.5, 27.1, 26.8. Anal. Calcd for $C_{32}H_{41}N_5O_8$: C, 61.62; H, 6.63; N, 11.23. Found: C, 61.40; H, 6.47; N, 11.00.

4.5.12. *N*-(3*S*-*N*-Boc-L-histidinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-histidine benzylester (6l)

Using the general procedure of preparing **6a–t** from 1.94 g (4.69 mmol) of **5l** and 1.49 g (6.09 mmol) of His-OBzl 2.91 g (85%) of the title compound was obtained as colorless powders. Mp 204–207 °C, ESI-MS (*m/e*) 642 $[M+H]^+$. $[\alpha]_D^{20} = -3.0$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 13.5 (s, 2H), 8.19 (d, *J* = 8.0 Hz, 2H), 7.50 (s, 2H), 7.21 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.85 (s, 2H), 5.37 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.05 (m, 6H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 171.8, 170.2, 156.7, 141.3, 136.7,135.6, 134.3, 129.1, 127.9, 127.8, 127.7, 127.0, 125.7, 120.1, 80.1, 68.1, 63.9, 53.2, 51.1, 43.4, 30.4, 29.8, 28.5, 27.1. Anal. Calcd for $C_{34}H_{39}N_7O_6$: C, 63.64; H, 6.13; N, 15.28. Found: C, 63.65; H, 6.31; N, 15.52.

4.5.13. *N*-(3*S*-*N*-N^{α},N^{ω}-diBoc-L-lysinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-lysine benzylester (6m)

Using the general procedure of preparing **6a–t** from 793 mg (1.57 mmol) of **5m** and 685 mg (2.04 mmol) of Lys(Boc)-OBzl 1163 mg (90%) of the title compound was obtained as colorless powders. Mp 45–46 °C, ESI-MS (*m/e*) 824 $[M+H]^+$. $[\alpha]_D^{20} = -27.2$ (*c* = 1.3, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.19 (d, *J* = 8.0 Hz, 4H), 7.21 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* =7.4 Hz, 1H), 5.37 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.81 (t, *J* = 7.8 Hz, 4H), 1.77 (m, 8H), 1.37 (s, 27H), 1.20 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 171.8, 171.2, 170.2, 156.7, 141.3, 136.7, 134.3, 129.1,

127.9, 127.8, 127.7, 127.0, 125.7, 80.1, 68.1, 63.9, 53.2, 43.4, 41.1, 31.7, 31.0, 29.8, 28.5, 27.1, 20.6. Anal. Calcd for $C_{44}H_{65}N_5O_{10}$: C, 64.13; H, 7.95; N, 8.50. Found: C, 64.32; H, 8.10; N, 8.74.

4.5.14. *N*-(3*S*-*N*-Boc-L-aspartyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-aspartic acid dibenzylester (6n)

Using the general procedure of preparing **6a–t** from 2.08 g (5.30 mmol) of **5n** and 2.18 g (6.89 mmol) of Asp(OBzl)-OBzl 3.32 g (91%) of the title compound was obtained as colorless powders. Mp 68–70 °C, ESI-MS (*m/e*) 778 $[M+H]^+$. $[\alpha]_D^{20} = -21.3$ (*c* = 1.3, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.19 (d, *J* = 8 Hz, 2H), 7.21 (m, 15H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* =7.4 Hz, 1H), 5.37 (s, 6H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.83 (m, 4H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 177.8, 171.3, 170.4, 169.6, 156.3, 140.9, 136.7, 134.3, 129.1, 127.9, 127.8, 127.7, 127.0, 125.7, 80.1, 68.1, 63.9, 50.2, 48.1, 43.4, 40.2, 39.7, 28.5, 26.8. Anal. Calcd for $C_{44}H_{47}N_3O_{10}$: C, 67.94; H, 6.09; N, 5.40. Found: C, 67.72; H, 5.91; N, 5.63.

4.5.15. *N*-(3*S*-*N*-Boc-L-glutamoyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-glutamic acid dibenzylester (6o)

Using the general procedure of preparing **6a–t** from 0.47 g (1.15 mmol) of **5o** and 0.49 g (1.49 mmol) of Glu(OBzl)-OBzl 0.76 g (92%) of the title compound was obtained as colorless powders. Mp 66–67 °C, ESI-MS (*m/e*) 806 $[M+H]^+$. $[\alpha]_D^{20} = -30.8$ (*c* = 1.3, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.19 (d, *J* = 8.0 Hz, 2H), 7.21 (m, 15H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.37 (s, 6H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.23 (t, *J* = 8.2 Hz, 4H), 2.08 (m, 4H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 177.8, 171.3, 170.4, 169.6, 156.3, 140.9, 136.7, 134.3, 129.1, 127.9, 127.8, 127.7, 127.0, 125.7, 80.1, 68.1, 63.9, 50.2, 48.1, 43.4, 30.4, 28.5, 27.1, 26.8. Anal. Calcd for $C_{46}H_{51}N_3O_{10}$: C, 68.55; H, 6.38; N, 5.21. Found: C, 68.33; H, 6.21; N, 5.00.

4.5.16. [3*S*-*N*-Boc-L-(*S*-*p*-methylbenzylcysteinyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-L-*S*-*p*-methylbenzylcysteine benzylester (6p)

Using the general procedure of preparing **6a–t** from 0.60 g (1.24 mmol) of **5p** and 0.51 g (1.62 mmol) of Cys(S-$CH_2C_6H_4$-Me-p)-OBzl 0.75 g (83%) of the title compound was obtained as colorless powders. Mp 70–74 °C, ESI-MS (*m/e*) 782 $[M+H]^+$. $[\alpha]_D^{20} = -52.2$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHZ, DMSO-d_6):δ/ppm = 8.19 (d, *J* = 8.0 Hz, 2H), 7.21 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* =7.4 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 4H), 6.85 (d, *J* = 8.6 Hz, 4H), 5.37 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.41 (t, *J* = 7.8 Hz, 4H), 2.22 (m, 4H), 2.10 (s, 6H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 171.8, 171.2, 170.2, 158.1, 156.7, 141.3, 136.7, 134.3, 129.1, 127.9, 127.8, 127.7, 127.0, 125.7, 80.1, 68.1, 63.9, 53.2, 43.4, 31.7, 31.0, 29.8, 28.5, 27.1, 17.6. Anal. Calcd for $C_{44}H_{51}N_3O_6S_2$: C, 67.58; H, 6.57; N, 5.37. Found: C, 67.80; H, 6.73; N, 5.60.

4.5.17. *N*-(3*S*-*N*-Boc-L-phenylalaninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylalanine benzylester (6q)

Using the general procedure of preparing **6a–t** from 0.23 g (0.55 mmol) of **5q** and 0.17 g (0.71 mmol) of Phe-OBzl 0.34 g (94%) of the title compound was obtained as colorless powders. Mp 78–81 °C, ESI-MS (*m/e*) 662 $[M+H]^+$. $[\alpha]_D^{20} = -14.4$ (c = 1.1, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6):δ/ppm = 8.19 (d, *J* = 8.0 Hz, 2H), 7.21 (m, 13H), 7.10 (m, 6H), 5.37 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 3.14 (m, 4H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 171.8, 171.3, 170.4, 156.3, 140.9, 136.7, 134.3, 129.1, 128.7, 127.9, 127.8, 127.7, 127.0, 126.0, 125.7, 80.1, 68.1, 63.9, 50.2, 48.1, 43.4, 37.8, 30.4, 27.1, 26.8. Anal. Calcd for $C_{40}H_{43}N_3O_6$: C, 72.60; H, 6.55; N, 6.35. Found: C, 72.59; H, 6.40; N, 6.11.

4.5.18. *N*-(3*S*-*N*-Boc-L-threoninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-threonine benzylester (6r)

Using the general procedure of preparing **6a–t** from 1.21 g (3.21 mmol) of **5r** and 0.80 g (4.17 mmol) of Thr-OBzl 1.76 g (96%) of the title compound was obtained as colorless powders. Mp 136–138 °C, ESI-MS (*m/e*) 570 $[M+H]^+$. $[\alpha]_D^{20} = -5.5$ (*c* = 1.0, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.30 (d, *J* = 2.5 Hz, 2H), 7.24 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.30 (s, 2H), 4.76 (m, 5H), 4.30 (m, 2H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.11 (s, 2H), 1.40 (s, 9H), 1.21 (d, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 172.0, 171.8, 170.6, 159.5, 138.2, 136.8, 134.2, 128.6, 127.5, 127.4, 127.0, 126.2, 79.0, 66.3, 61.2, 58.2, 54.2, 43.1, 28.2, 27.2, 18.9. Anal. Calcd for $C_{30}H_{39}N_3O_8$: C, 63.25; H, 6.90; N, 7.38. Found: C, 63.44; H, 7.07; N, 7.14.

4.5.19. *N*-(3*S*-*N*-(Boc-L-NO_2^G-argininyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-NO_2^G-arginine benzylester (6s)

Using the general procedure of preparing **6a–t** from 0.48 g (1.00 mmol) of **5s** and 0.29 g (1.30 mmol) of Arg(NO_2)-OBzl 0.69 g (89%) of the title compound was obtained as colorless powders. Mp 109–110 °C, ESI-MS (*m/e*) 772 $[M+H]^+$. $[\alpha]_D^{20} = -19.6$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.19 (d, *J* = 8.0 Hz, 2H), 7.21 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.37 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.61 (t, *J* = 7.8 Hz, 4H), 2.02 (s, 4H), 1.77 (m, 4H), 1.54 (m, 4H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 171.8, 171.2, 170.2, 158.1, 156.7, 141.3, 136.7, 134.3, 129.1, 127.9, 127.8, 127.7, 127.0, 125.7, 80.1, 68.1, 63.9, 53.2, 43.4, 41.1, 37.2, 31.7, 31.0, 29.8, 28.5, 27.1, 24.6. Anal. Calcd for $C_{34}H_{49}N_{11}O_{10}$: C, 60.07; H, 7.27; N, 18.54. Found: C, 60.28; H, 7.45; N, 18.79.

4.5.20. *N*-(3*S*-*N*-Boc-L-methioninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-methionine benzylester (6t)

Using the general procedure of preparing **6a–t** from 0.96 g (2.36 mmol) of **5t** and 0.62 g (2.60 mmol) of Met-OBzl 0.71 g (48%) of the title compound was obtained as colorless powders. Mp 77–80 °C, ESI-MS (*m/e*) 630 $[M+H]^+$. $[\alpha]_D^{20} = -30.9$ (*c* = 1.2, CH_3OH); ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.19 (d, *J* = 8.0 Hz, 2H), 7.21 (m, 5H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.37 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.41 (t, *J* = 7.8 Hz, 4H), 2.22 (m, 4H), 2.10 (s, 6H), 1.37 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 171.8, 171.2, 170.2, 158.1, 156.7, 141.3, 136.7, 134.3, 129.1, 127.9, 127.8, 127.7, 127.0, 125.7, 80.1, 68.1, 63.9, 53.2, 43.4, 31.7, 31.0, 29.8, 28.5, 27.1, 17.6. Anal. Calcd for $C_{32}H_{43}N_3O_6S_2$: C, 61.02; H, 6.88; N, 6.67. Found: C, 61.23; H, 7.07; N, 6.91.

4.6. General procedure of preparing *N*-(3*S*-*N*-Boc-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)amino acids (7a–t)

To the suspension of 0.50 mmol of **6a–t**, 15 ml of methanol, 4 ml of water, 20 mg of Pd/C (10%) hydrogen gas was bubbled for 20 h and TLC indicates complete disappear of **6a–t**. After filtration the filtrate was evaporated under vacuum and the residue was

triturated with ether repeatedly to provide the title compound as colorless powder.

4.6.1. *N*-(3*S*-*N*-Boc-L-alaninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-alanine (7a)

Using the general procedure of preparing **7a–t** from 0.37 g (0.73 mmol) of **6a** 0.29 g (95%) of the title compound was obtained as colorless powders. Mp 155–157 °C, ESI-MS (m/e) 418 $[M-H]^-$. $[\alpha]_D^{20} = -2.1$ (c = 1.2, CH_3OH).

4.6.2. *N*-(3*S*-*N*-Boc-glycinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)glycine (7b)

Using the general procedure of preparing **7a–t** from 0.11 g (0.23 mmol) of **6b** 0.086 g (89%) of the title compound was obtained as colorless powders. Mp 142–144 °C, ESI-MS (*m/e*) 390 $[M-H]^-$. $[\alpha]_D^{20} = -10.2$ (c = 1.1, CH_3OH).

4.6.3. *N*-(3*S*-*N*-Boc-L-valinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-valine (7c)

Using the general procedure of preparing **7a–t** from 0.66 g (1.14 mmol) of **7c** 0.45 g (83%) of the title compound was obtained as colorless powders. Mp 100–103 °C, ESI-MS (*m/e*) 474 $[M-H]^-$. $[\alpha]_D^{20} = -16.2$ (c = 1.3, CH_3OH).

4.6.4. *N*-(3*S*-*N*-Boc-L-leucinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-leucine (7d)

Using the general procedure of preparing **7a–t** from 0.50 g (0.84 mmol) of **6d** 0.40 g (94%) of the title compound was obtained as colorless powders. Mp 143–147 °C, ESI-MS (*m/e*) 502 $[M-H]^-$. $[\alpha]_D^{20} = -59.2$ (c = 1.1, CH_3OH).

4.6.5. *N*-(3*S*-*N*-Boc-L-leucinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-isoleucine (7e)

Using the general procedure of preparing **7a–t** from 0.50 g (0.84 mmol) of **6e** 0.41 g (96%) of the title compound was obtained as colorless powders. Mp 77–78 °C, ESI-MS (*m/e*) 502 $[M-H]^-$. $[\alpha]_D^{20} = -59.8$ (c = 1.2, CH_3OH).

4.6.6. *N*-(3*S*-*N*-Boc-L-tryptophanyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-trypto-phan (7f)

Using the general procedure of preparing **7a–t** from 0.72 g (0.97 mmol) of **6f** 0.59 g (93%) of the title compound was obtained as colorless powders. Mp 213–215 °C, ESI-MS (*m/e*) 648 $[M-H]^-$. $[\alpha]_D^{20} = -21.2$ (c = 1.1, CH_3OH).

4.6.7. *N*-(3*S*-*N*-Boc-L-serinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-serine (7g)

Using the general procedure of preparing **7a–t** from 0.52 g (0.97 mmol) of **6g** 0.41 g (93%) of the title compound was obtained as colorless powders. Mp 213–215 °C, ESI-MS (*m/e*) 450 $[M-H]^-$. $[\alpha]_D^{20} = -21.2$ (c = 1.1, CH_3OH).

4.6.8. *N*-(3*S*-*N*-Boc-L-tyrocinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-tyrosine (7h)

Using the general procedure of preparing **7a–t** from 0.70 g (1.01 mmol) of **6h** 0.59 g (97%) of the title compound was obtained as colorless powders. Mp 251–252 °C, ESI-MS (*m/e*) 602 $[M-H]^-$. $[\alpha]_D^{20} = -6.2$ (c = 1.1, CH_3OH).

4.6.9. *N*-(3*S*-*N*-Boc-L-prolinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-proline (7i)

Using the general procedure of preparing **7a–t** from 0.56 g (0.71 mmol) of **6i** 0.31 g (94%) of the title compound was obtained as colorless powders. Mp 172–175 °C, ESI-MS (*m/e*) 470 $[M-H]^-$. $[\alpha]_D^{20} = -71.3$ (c = 1.1, CH_3OH).

4.6.10. *N*-(3*S*-*N*-Boc-L-asparaginyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-asparagine (7j)

Using the general procedure of preparing **7a–t** from 0.13 g (0.21 mmol) of **6j** 0.10 g (91%) of the title compound was obtained as colorless powders. Mp 300–303 °C, ESI-MS (*m/e*) 504 $[M-H]^-$. $[\alpha]_D^{20} = -15.7$ (c = 1.1, CH_3OH).

4.6.11. *N*-(3*S*-*N*-Boc-L-glutaminyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-glutamine (7k)

Using the general procedure of preparing **7a–t** from 0.50 g (0.80 mmol) of **6k** 0.40 g (93%) of the title compound was obtained as colorless powders. Mp 191–195 °C, ESI-MS (*m/e*) 532 $[M-H]^-$. $[\alpha]_D^{20} = -11.3$ (c = 1.2, CH_3OH).

4.6.12. *N*-(3*S*-*N*-Boc-L-histidinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-histidine (7l)

Using the general procedure of preparing **7a–t** from 0.61 g (0.83 mmol) of **6l** 0.41 g (89%) of the title compound was obtained as colorless powders. Mp 279–280 °C, ESI-MS (*m/e*) 550 $[M-H]^-$. $[\alpha]_D^{20} = -5.4$ (c = 1.0, CH_3OH).

4.6.13. *N*-(3*S*-*N*-N^{α},N^{ω}-diBoc-L-lysinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-lysine (7m)

Using the general procedure of preparing **7a–t** from 0.84 g (1.02 mmol) of **6m** 0.70 g (93%) of the title compound was obtained as colorless powders. Mp 152–154 °C, ESI-MS (*m/e*) 732 $[M-H]^-$. $[\alpha]_D^{20} = -20.7$ (c = 1.3, CH_3OH).

4.6.14. *N*-(3*S*-*N*-Boc-L-aspartyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-aspartic acid (7n)

Using the general procedure of preparing **7a–t** from 0.26 g (0.38 mmol) of **6n** 0.70 g (96%) of the title compound was obtained as colorless powders. Mp 167–168 °C, ESI-MS (*m/e*) 506 $[M-H]^-$. $[\alpha]_D^{20} = -12.1$ (c = 1.2, CH_3OH).

4.6.15. *N*-(3*S*-*N*-Boc-L-glutamoyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-glutamic acid (7o)

Using the general procedure of preparing **7a–t** from 0.26 g (0.37 mmol) of **6o** 0.18 g (90%) of the title compound was obtained as colorless powders. Mp 150–152 °C, ESI-MS (*m/e*) 534 $[M-H]^-$. $[\alpha]_D^{20} = -56.2$ (c = 1.1, CH_3OH).

4.6.16. *N*-(3*S*-Boc-L-cysteinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-cysteine (7p)

Using the general procedure of preparing **7a–t** from 0.39 g (0.50 mmol) of **6p** 0.22 g (91%) of the title compound was obtained as colorless powders. Mp 70–74 °C, ESI-MS (*m/e*) 482 $[M-H]^-$. $[\alpha]_D^{20} = -52.2$ (c = 1.2, CH_3OH).

4.6.17. *N*-(3*S*-*N*-Boc-L-phenylalaninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylalanine (7q)

Using the general procedure of preparing **7a–t** from 0.60 g (0.91 mmol) of **6q** 0.49 g (92%) of the title compound was obtained as colorless powders. Mp 113–114 °C, ESI-MS (*m/e*) 570 $[M-H]^-$. $[\alpha]_D^{20} = -19.8$ (c = 1.1, CH_3OH).

4.6.18. *N*-(3*S*-*N*-Boc-L-threoninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-threonine (7r)

Using the general procedure of preparing **7a–t** from 0.47 g (0.83 mmol) of **6r** 0.39 g (98%) of the title compound was obtained as colorless powders. Mp 98–99 °C, ESI-MS (*m/e*) 478 $[M-H]^-$. $[\alpha]_D^{20} = -2.5$ (c = 1.1, CH_3OH).

4.6.19. *N*-(3*S*-*N*-Boc-L-argininyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-arginine (7s)

Using the general procedure of preparing **7a–t** from 0.30 g (0.39 mmol) of **6s** 0.22 g (95%) of the title compound was obtained as colorless powders. Mp 215–216 °C, ESI-MS (*m/e*) 588 $[M-H]^-$. $[\alpha]_D^{20} = -15.4$ (*c* = 1.1, CH_3OH).

4.6.20. *N*-(3*S*-*N*-Boc-L-methioninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-methionine (7t)

Using the general procedure of preparing **7a–t** from 0.40 g (0.64 mmol) of **6t** 0.33 g (94%) of the title compound was obtained as colorless powders. Mp 201–204 °C, ESI-MS (*m/e*) 538 $[M-H]^-$. $[\alpha]_D^{20} = -28.4$ (*c* = 1.1, CH_3OH).

4.7. General procedure of preparing *N*-(3*S*-*N*-aminoacyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)amino acids (8a–t)

To the solution of 1 mmol of **7a–t** in 5 ml of ethyl acetate, 10 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 **7a–t**. 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 **8a–t**.

4.7.1. *N*-(3*S*-*N*-L-Alaninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-alanine (8a)

Using the general procedure of preparing **8a–t** from 0.21 g (0.50 mmol) of **7a** 0.15 g (95%) of the title compound was obtained as colorless powders. Mp 387–388 °C, ESI-MS (*m/e*) 320 $[M+H]^+$. $[\alpha]_D^{20} = -61.1$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 10.50 (s, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 7.00 (m, 4H), 4.97 (t, *J* = 5.7 Hz, 1H), 4.53 (m, 3H), 3.61 (m, 1H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.99 (s, 2H), 1.44 (d, *J* = 8.8 Hz, 3H), 1.28 (d, *J* = 8.8 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 174.2, 171.3, 170.1, 136.8, 133.1, 128.3, 127.7, 127.6, 126.9, 125.9, 52.4, 47.8, 45.2, 28.4, 19.2, 18.3. Anal. Calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found: C, 60.36; H, 6.78; N, 13.41.

4.7.2. *N*-(3*S*-*N*-Glycinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)glycine (8b)

Using the general procedure of preparing **8a–t** from 70 mg (0.18 mmol) of **7b** 49 mg (89%) of the title compound was obtained as colorless powders. Mp 380–381 °C, ESI-MS (*m/e*) 292 $[M+H]^+$. $[\alpha]_D^{20} = -12.9$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 11.09 (s, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 7.00 (m, 4H), 4.97 (t, *J* = 5.7 Hz, 1H), 4.46 (m, 2H), 4.16 (s, 2H), 3.55 (s, 2H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.99 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 173.2, 172.3, 165.1, 136.8, 133.1, 128.3, 127.7, 126.9, 125.9, 62.4, 44.8, 42.2, 28.4. Anal. Calcd for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found: C, 57.50; H, 5.71; N, 14.65.

4.7.3. *N*-(3*S*-*N*-L-Valinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-valine (8c)

Using the general procedure of preparing **8a–t** from 0.20 g (0.42 mmol) of **7c** 0.16 g (98%) of the title compound was obtained as colorless powders. Mp 112–114 °C, ESI-MS (*m/e*) 376 $[M+H]^+$. $[\alpha]_D^{20} = -32.1$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 12.09 (s, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 7.00 (m, 4H), 4.97 (t, *J* = 5.7 Hz, 1H), 4.46 (m, 3H), 3.56 (d, *J* = 8.6 Hz, 1H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.86 (m, 1H), 2.30 (m, 1H), 1.99 (s, 2H), 0.98 (d, *J* = 7.8 Hz, 12H). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 174.2, 172.3, 169.5, 136.8, 133.1, 128.3, 127.7, 126.9, 125.9, 62.4, 58.6, 57.1, 44.8, 34.1, 30.2, 28.4, 17.5. Anal. Calcd for $C_{20}H_{29}N_3O_4$: C, 63.98; H, 7.79; N, 11.19. Found: C, 64.17; H, 7.99; N, 11.00.

4.7.4. *N*-(3*S*-*N*-L-Leucinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-leucine (8d)

Using the general procedure of preparing **7a–t** from 0.20 g (0.40 mmol) of **6d** 0.15 g (94%) of the title compound was obtained as colorless powders. Mp 381–383 °C, ESI-MS (*m/e*) 404 $[M+H]^+$. $[\alpha]_D^{20} = -18.9$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 12.09 (s, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 7.00 (m, 4H), 4.97 (t, *J* = 5.7 Hz, 1H), 4.46 (m, 3H), 3.56 (d, *J* = 8.6 Hz, 1H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.99 (s, 2H), 1.83 (m, 2H), 1.74 (t, *J* = 8.0 Hz, 4H), 0.98 (d, *J* = 7.8 Hz, 12H). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 174.2, 172.3, 169.5, 136.8, 133.1, 128.3, 127.7, 126.9, 125.9, 62.4, 53.1, 48.8, 44.0, 43.6, 40.6, 28.4, 22.8. Anal. Calcd for $C_{22}H_{33}N_3O_4$: C, 65.48; H, 8.24; N, 10.41. Found: C, 65.26; H, 8.07; N, 10.66.

4.7.5. *N*-(3*S*-*N*-L-isoleucine-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-isoleucine (8e)

Using the general procedure of preparing **8a–t** from 0.20 g (0.40 mmol) of **7e** 0.14 g (87%) of the title compound was obtained as colorless powders. Mp 390–392 °C, ESI-MS (*m/e*) 404 $[M+H]^+$. $[\alpha]_D^{20} = -68.8$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 12.06 (s, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 7.00 (m, 4H), 4.97 (t, *J* = 5.7 Hz, 1H), 4.46 (m, 3H), 3.56 (d, *J* = 8.6 Hz, 1H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.61 (m, 1H), 2.12 (m, 1H), 1.99 (s, 2H), 1.30 (m, 4H), 1.02 (m, 12H). ^{13}C NMR (75 MHz, DMSO-d_6) δ/ppm = 174.2, 172.3, 169.5, 136.8, 133.1, 128.3, 127.7, 126.9, 125.9, 62.4, 58.8, 53.1, 44.0, 40.6, 36.6, 28.4, 24.6, 14.4, 10.2. Anal. Calcd for $C_{22}H_{33}N_3O_4$: C, 65.48; H, 8.24; N, 10.41. Found: C, 65.27; H, 8.08; N, 10.64.

4.7.6. *N*-(3*S*-*N*-L-Tryptophanyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-tryptophan (8f)

Using the general procedure of preparing **8a–t** from 0.25 g (0.39 mmol) of **7f** 0.20 g (93%) of the title compound was obtained as colorless powders. Mp 392–394 °C, ESI-MS (*m/e*) 550 $[M+H]^+$. $[\alpha]_D^{20} = -45.4$ (*c* = 1.2, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 10.92 (s, 1H), 10.62 (s, 2H), 8.52 (d, *J* = 7.5 Hz, 1H), 7.29 (m, 8H), 7.00 (m, 4H), 6.86 (s, 2H), 5.03 (t, *J* = 6.1 Hz, 1H), 5.00 (m, *J* = 8.6 Hz, 2H), 4.56 (s, 2H), 3.18 (dd, *J* = 6.0 Hz, 1H), 3.03 (m, 2H), 2.95 (m, 2H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.96 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.7, 171.7, 170.2, 136.8, 136.6, 136.4, 134.1, 129.6, 127.8, 126.9, 125.8, 122.4, 120.4, 119.6, 111.9, 109.7, 62.7, 54.3, 56.7, 52.7, 44.4, 34.1, 30.6, 27.5. Anal. Calcd for $C_{32}H_{31}N_5O_4$: C, 69.93; H, 5.69; N, 12.74. Found: C, 69.70; H, 5.51; N, 12.98.

4.7.7. *N*-(3*S*-*N*-L-Serinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-serine (8g)

Using the general procedure of preparing **8a–t** from 0.40 g (0.89 mmol) of **7g** 0.30 g (93%) of the title compound was obtained as colorless powders. Mp 373–375 °C, ESI-MS (*m/e*) 352 $[M+H]^+$. $[\alpha]_D^{20} = -5.8$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 12.80 (s, 1H), 8.30 (d, *J* = 2.5 Hz, 1H), 7.00 (m, 4H), 4.76 (m, 5H), 4.13 (d, *J* = 8.8 Hz, 2H), 4.03 (d, *J* = 8.8 Hz, 2H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 1.98 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.0, 171.8, 170.6, 136.8, 134.2, 128.6, 127.5, 127.4, 127.0, 66.3, 61.2, 60.9, 58.2, 57.1, 54.2, 43.1, 27.2. Anal. Calcd for $C_{16}H_{21}N_3O_6$: C, 54.69; H, 6.02; N, 11.96. Found: C, 54.90; H, 6.21; N, 12.19.

4.7.8. *N*-(3*S*-*N*-L-Tyrocinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-tyrosine (8h)

Using the general procedure of preparing **8a–t** from 0.60 g (1.00 mmol) of **7h** 0.48 g (93%) of the title compound was obtained

as colorless powders. Mp 375–376 °C, ESI-MS (*m/e*) 504 $[M+H]^+$. $[\alpha]_D^{20} = 32.7$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 11.19 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.02 (m, 4H), 6.91 (d, *J* = 8.8 Hz, 4H), 6.80 (d, *J* = 8.1 Hz, 4H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.06 (m, 6H), 1.95 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.0, 171.8, 170.6, 155.5, 138.2, 136.8, 134.2, 132.1, 128.6, 127.5, 127.4, 127.0, 126.2, 115.8, 61.2, 55.2, 52.1, 43.1, 40.8, 37.0, 27.2. Anal. Calcd for $C_{28}H_{29}N_3O_6$: C, 66.79; H, 5.80; N, 8.34. Found: C, 66.58; H, 5.64; N, 8.57.

4.7.9. *N*-(3*S*-*N*-L-Prolinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-proline (8i)

Using the general procedure of preparing **8a–t** from 0.20 g (0.42 mmol) of **7i** 0.48 g (93%) of the title compound was obtained as colorless powders. Mp 372–376 °C, ESI-MS (*m/e*) 372 $[M+H]^+$. $[\alpha]_D^{20} = -60.2$ (*c* = 1.2, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 12.08 (s, 1H), 7.01 (m, 4H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.05 (s, 1H), 1.97 (m, 4H), 1.59 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.1, 173.8, 170.0, 136.7, 134.7, 128.8, 128.1, 127.8, 127.7, 127.5, 125.5, 61.0, 60.7, 58.2, 46.8, 44.7, 43.8, 32.4, 29.1, 28.9, 27.6, 24.5, 22.8. Anal. Calcd for $C_{20}H_{25}N_3O_4$: C, 64.67; H, 6.78; N, 11.31. Found: C, 64.44; H, 6.61; N, 11.56.

4.7.10. *N*-(3*S*-*N*-L-Asparaginyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-asparagine (8j)

Using the general procedure of preparing **8a–t** from 0.20 g (0.40 mmol) of **7j** 0.15 g (95%) of the title compound was obtained as colorless powders. Mp 376–377 °C, ESI-MS (*m/e*) 406 $[M+H]^+$. $[\alpha]_D^{20} = -14.9$ (*c* = 1.2, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 11.28 (s, 1H), 8.19 (d, *J* = 8 Hz, 1H), 7.02 (m, 4H), 5.98 (s, 4H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.83 (m, 4H), 1.97 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.8, 173.3, 170.4, 169.6, 136.7, 134.3, 129.1, 127.9, 127.8, 127.7, 125.7, 59.9, 56.2, 48.1, 47.4, 43.2, 39.7, 28.5. Anal. Calcd for $C_{18}H_{23}N_5O_6$: C, 53.33; H, 5.72; N, 17.27. Found: C, 53.11; H, 5.54; N, 17.52.

4.7.11. *N*-(3*S*-*N*-L-Glutaminyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-glutamine (8k)

Using the general procedure of preparing **8a–t** from 0.30 g (0.56 mmol) of **7k** 0.23 g (96%) of the title compound was obtained as colorless powders. Mp 375–376 °C, ESI-MS (*m/e*) 434 $[M+H]^+$. $[\alpha]_D^{20} = -9.7$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 8.19 (d, *J* = 8.0 Hz, 1H), 7.02 (m, 4H), 5.96 (s, 4H), 4.91 (t, J = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.23 (t, *J* = 8.2 Hz, 4H), 2.08 (m, 4H), 1.97 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.8, 173.3, 170.4, 169.6, 136.7, 134.3, 127.9, 127.8, 127.7, 127.0, 125.7, 63.9, 54.2, 50.2, 48.1, 43.4, 32.6, 30.4, 27.1, 26.8. Anal. Calcd for $C_{20}H_{27}N_5O_6$: C, 55.42; H, 6.28; N, 16.16. Found: C, 55.61; H, 6.45; N, 16.41.

4.7.12. *N*-(3*S*-*N*-L-Histidinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-histidine (8l)

Using the general procedure of preparing **8a–t** from 0.35 g (0.64 mmol) of **7l** 0.24 g (85%) of the title compound was obtained as colorless powders. Mp 395–397 °C, ESI-MS (*m/e*) 452 $[M+H]^+$. $[\alpha]_D^{20} = -6.6$ (*c* = 1.2, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 13.50 (s, 2H), 11.05 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 2H), 7.03 (m, 4H), 6.85 (s, 2H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.05 (m, 6H), 1.97 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.9, 171.8, 170.2, 136.7, 135.6, 134.3, 129.1, 127.9, 127.7, 125.7, 120.1, 63.9, 55.2, 51.1, 43.4, 33.4, 29.8, 27.1. Anal. Calcd for $C_{22}H_{25}N_7O_4$: C, 58.53; H, 5.58; N, 21.72. Found: C, 58.72; H, 5.74; N, 21.95.

4.7.13. *N*-(3*S*-*N*-L-Lysinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-lysine (8m)

Using the general procedure of preparing **8a–t** from 0.55 g (0.75 mmol) of **7m** 0.24 g (90%) of the title compound was obtained as colorless powders. Mp 299–303 °C, ESI-MS (*m/e*) 434 $[M+H]^+$. $[\alpha]_D^{20} = -5.5$ (*c* = 1.3, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 11.02 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.03 (m, 4H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.81 (t, *J* = 7.8 Hz, 4H), 1.77 (m, 8H), 1.97 (s, 6H), 1.20 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.8, 171.2, 170.2, 136.7, 134.3, 129.1, 127.9, 127.8, 127.7, 125.7, 63.9, 55.2, 51.4, 43.1, 41.7, 34.0, 32.1, 29.8, 27.1, 20.6. Anal. Calcd for $C_{22}H_{35}N_5O_4$: C, 60.95; H, 8.14; N, 16.15. Found: C, 60.76; H, 8.29; N, 16.36.

4.7.14. *N*-(3*S*-*N*-L-Aspartyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-aspartic acid (8n)

Using the general procedure of preparing **8a–t** from 0.20 g (0.39 mmol) of **7n** 0.15 g (94%) of the title compound was obtained as colorless powders. Mp 376–377 °C, ESI-MS (*m/e*) 408 $[M+H]^+$. $[\alpha]_D^{20} = -10.3$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 12.01 (s, 1H), 11.20 (s, 2H), 8.19 (d, *J* = 8 Hz, 1H), 7.02 (m, 4H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.83 (m, 4H), 1.98 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 177.8, 174.3, 170.4, 169.6, 136.7, 134.3, 129.1, 127.9, 127.7, 125.7, 63.9, 50.2, 48.1, 47.2, 43.4, 39.7, 26.8. Anal. Calcd for $C_{18}H_{21}N_3O_8$: C, 53.07; H, 5.20; N, 10.31. Found: C, 52.84; H, 5.03; N, 10.55.

4.7.15. *N*-(3*S*-*N*-L-Glutamoyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-glutamic acid (8o)

Using the general procedure of preparing **8a–t** from 0.15 g (0.28 mmol) of **7o** 0.11 g (92%) of the title compound was obtained as colorless powders. Mp 291–293 °C, ESI-MS (*m/e*) 436 $[M+H]^+$. $[\alpha]_D^{20} = -40.7$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-*d6*): δ/ppm = 11.13 (s, 3H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.03 (m, 4H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.23 (t, *J* = 8.2 Hz, 4H), 2.08 (m, 4H), 1.99 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 177.8, 174.3, 171.3, 169.6, 136.7, 134.3, 129.1, 127.9, 127.0, 125.7, 63.9, 54.2, 51.1, 43.4, 30.4, 28.5, 27.1, 26.8. Anal. Calcd for $C_{20}H_{25}N_3O_8$: C, 55.17; H, 5.79; N, 9.65. Found: C, 55.38; H, 5.95; N, 9.89.

4.7.16. *N*-(3*S*-L-Cysteinyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-cysteine (8p)

Using the general procedure of preparing **8a–t** from 68 mg (0.14 mmol) of **7p** 49 mg (92%) of the title compound was obtained as colorless powders. Mp 291–293 °C, ESI-MS (*m/e*) 384 $[M+H]^+$. $[\alpha]_D^{20} = -18.1$ (*c* = 1.1, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 11.02 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.05 (m, 4H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.41 (t, *J* = 7.8 Hz, 4H), 1.96 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.8, 171.2, 170.2, 136.7, 134.3, 129.1, 127.9, 127.8, 127.0, 125.7, 63.9, 57.8, 53.2, 43.4, 31.0, 28.5, 27.1. Anal. Calcd for $C_{16}H_{21}N_3O_4S_2$: C, 50.11; H, 5.52; N, 10.96. Found: C, 50.33; H, 5.69; N, 10.71.

4.7.17. *N*-(3*S*-*N*-L-Phenylalaninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-phenylala-nine (8q)

Using the general procedure of preparing **8a–t** from 0.41 g (0.70 mmol) of **7q** 0.31 g (95%) of the title compound was obtained as colorless powders. Mp 291–293 °C, ESI-MS (*m/e*) 472 $[M+H]^+$. $[\alpha]_D^{20} = -34.5$ (*c* = 1.2, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 12.07 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.10 (m, 14H), 4.91 (t, *J* = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, *J* = 6.0 Hz, 1H), 3.14 (m, 4H), 2.91 (dd, *J* = 6.0 Hz, 1H), 2.01 (s, 2H). ^{13}C NMR (75 MHz,

DMSO-d_6): δ/ppm = 174.8, 171.3, 170.4, 140.9, 136.7, 134.3, 129.1, 128.7, 127.9, 127.8, 127.0, 126.0, 125.7, 63.9, 55.1, 51.2, 48.1, 43.4, 40.4, 37.1, 26.8. Anal. Calcd for $C_{28}H_{29}N_3O_4$: C, 71.32; H, 6.20; N, 8.91. Found: C, 71.51; H, 6.38; N, 8.70.

4.7.18. *N*-(3*S*-*N*-L-Threoninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-threonine (8r)

Using the general procedure of preparing **8a–t** from 0.40 g (0.84 mmol) of **7r** 0.31 g (96%) of the title compound was obtained as colorless powders. Mp 329–330 °C, ESI-MS (*m/e*) 380 $[M+H]^+$. $[\alpha]_D^{20} = -12.9$ (c = 1.2, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 12.05 (s, 1H), 8.30 (d, J = 2.5 Hz, 1H), 7.04 (m, 4H), 4.76 (m, 5H), 4.30 (m, 2H), 3.18 (dd, J = 6.0 Hz, 1H), 2.91 (dd, J = 6.0 Hz, 1H), 2.11 (s, 2H), 1.98 (s, 2H), 1.21 (d, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 175.0, 171.8, 170.6, 136.8, 134.2, 128.6, 127.5, 127.0, 126.2, 70.0, 66.3, 63.2, 62.8, 61.2, 43.1, 27.2, 18.9. Anal. Calcd for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.64; N, 11.08. Found: C, 56.77; H, 6.50; N, 10.84.

4.7.19. *N*-(3*S*-*N*-L-Argininyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-arginine (8s)

Using the general procedure of preparing **8a–t** from 0.25 g (0.43 mmol) of **7s** 0.19 g (90%) of the title compound was obtained as colorless powders. Mp 391–393 °C, ESI-MS (*m/e*) 490 $[M+H]^+$. $[\alpha]_D^{20} = -4.5$ (c = 1.2, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 12.09 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.02 (m, 4H), 4.91 (t, J = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, J = 6.0 Hz, 1H), 2.91 (dd, J = 6.0 Hz, 1H), 2.61 (t, J = 7.8 Hz, 4H), 2.02 (s, 4H), 1.77 (m, 4H), 1.54 (m, 4H), 1.98 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.8, 171.2, 170.2, 158.1, 136.7, 134.3, 129.1, 127.9, 127.8, 127.0, 125.7, 63.9, 54.2, 51.8, 43.4, 37.2, 31.7, 28.2, 27.1, 24.6. Anal. Calcd for $C_{22}H_{35}N_9O_4$: C, 53.97; H, 7.21; N, 25.75. Found: C, 53.75; H, 7.03; N, 25.51.

4.7.20. *N*-(3*S*-*N*-L-Methioninyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-L-methionine (8t)

Using the general procedure of preparing **8a–t** from 0.40 g (0.74 mmol) of **7s** 0.30 g (91%) of the title compound was obtained as colorless powders. Mp 391–393 °C, ESI-MS (*m/e*) 440 $[M+H]^+$. $[\alpha]_D^{20} = -34.6$ (c = 1.2, H_2O). ^1H NMR (300 MHz, DMSO-d_6): δ/ppm = 11.13 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.02 (m, 4H), 4.91 (t, J = 8.2 Hz, 1H), 4.46 (m, 4H), 3.18 (dd, J = 6.0 Hz, 1H), 2.91 (dd, J = 6.0 Hz, 1H), 2.41 (t, J = 7.8 Hz, 4H), 2.22 (m, 4H), 2.10 (s, 6H), 1.99 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ/ppm = 174.8, 171.2, 170.2, 136.7, 134.3, 129.1, 127.9, 127.8, 127.0, 125.7, 63.9, 53.2, 50.3, 43.4, 34.7, 31.0, 29.8, 27.1, 17.6. Anal. Calcd for $C_{20}H_{29}N_3O_4S_2$: C, 54.64; H, 6.65; N, 9.56. Found: C, 54.83; H, 6.82; N, 9.79.

4.8. 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 1000*g* for 10 min and the platelet rich plasma (PRP) was removed. The remaining blood was centrifuged for an additional 10 min at 1500*g* 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 **8a–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 **8a–t**)] ÷ (A_m% of NS), where A_m% of NS = 50.16 ± 3.65%. The concentration versus inhibition rate curve is plotted to determine the IC_{50} values via GWBASIC.EXE program.

4.9. In vivo anti-thrombotic assay of intravenously injection of 8a–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 Wister 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, ip) 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 **8a–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.

4.10. 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). Thirty 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.

Acknowledgments

This work was finished in the Beijing Area Major Laboratory of Peptide and Small Molecular Drugs, supported by PHR (IHLB, KZ200910025010), Special Project (2008ZX09401–002) and the National Natural Science Foundation of China (30672513 and 20772082).

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