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Toward breast cancer resistance protein (BCRP) inhibitors: design, synthesis of a series of new simplified fumitremorgin C analogues

Guofeng Wu,[a] Jiawang Liu,[a] Lanrong Bi,[b] Ming Zhao,[b,*] Chao Wang,[a] Michèle Baudy-Floc'h,[d] Jingfang Ju[c,*] and Shiqi Peng[b,*]

[a]*College of Pharmaceutical Sciences, Peking University, Beijing 100083, PR China*
[b]*College of Pharmaceutical Sciences, Capital Medical University, Beijing 100069, PR China*
[c]*Mitchell Cancer Institute, University of South Alabama, 307 N. University Blvd, Mobile, AL 36688-0002, USA*
[d]*UMR 6226 CNRS, Groupe 'Ciblage et Autoassemblages Fonctionnels', Université de Rennes I, 263 Av. du Général Leclerc, F-35042 Rennes Cedex, France*

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Abstract—In this study, we report the design and synthesis of a series of new simplified fumitremorgin C analogues. The preliminary biological study indicated some of these simplified fumitremorgin C might be developed into breast cancer resistance inhibitors.

1. Introduction

Chemoresistance is one of the major obstacles in cancer chemotherapy due to intrinsic or acquired drug resistance. A broad-spectrum resistance to structurally and mechanistically diverse antitumor agents is known as multidrug resistance (MDR). The multidrug resistance phenotype is often associated with overexpression of members of the ATP-binding cassette (ABC) transporter family proteins. They are plasma membrane proteins that can actively extrude a wide variety of structurally diverse xenobiotic agents, thereby reducing intracellular drug concentrations.[1] P-glycoprotein (Pgp) and multidrug resistance-associated protein (MRP) are two of the most extensively studied ABC transporters. Breast cancer resistance protein (BCRP) is an additional member of the ABC transporter family. BCRP has been shown to have a well-defined role in the transport of clinically relevant drugs and mediate cellular resistance to these drugs in vitro.[2] Similar to Pgp, BCRP localizes primarily on the plasma membrane, in accordance with its capacity to efficiently efflux drug substrates from the cell.[3] Furthermore, the substrate specificity of BCRP overlaps considerably with that of Pgp, suggesting that BCRP has a similar role to Pgp in the pharmacokinetics of substrate drugs.[4] BCRP is able to transport Pgp substrates and is not inhibited by Pgp chemosensitizers such as calcium channel blockers, cardiovascular drugs, and immunosuppressors. Besides an overlap in substrate specificity, there may also be an overlap in modulating activity, illustrated, for example, by 'dual specificity inhibitor' GF 120918.[5] In addition, BCRP is able to efflux a broad range of anti-cancer drugs through cellular membrane, thus limiting their anti-proliferative effects.[6,7]

More recently, it has become apparent that the BCRP is potentially an important mediator of multidrug resistance.[8] Inhibitors of BCRP could be used not only to reverse MDR mediated by this transporter but also to alter the pharmacokinetics of BCRP substrate drugs, including their intestinal absorption, biliary excretion, and brain penetration, causing either beneficial or adverse drug interactions.[9] In this context and in order to overcome BCRP-mediated multidrug resistance, BCRP-specific inhibitors are highly desired.[10,11]

Several BCRP-specific inhibitors have been reported in the past decade. Such inhibitors include the antifungal agent, fumitremorgin C (FTC), GF120918, imatinib mesylate (Gleevec), Ko132, Ko134, and so on (Fig. 1). FTC, a member of a group of indole alkaloids, is a selective inhibitor of the breast cancer resistance protein (BCRP/ABCG2).[12–14] However, this natural product of fungal origin also has

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* Corresponding authors. Mitchell Cancer Institute, University of South Alabama, 307 N. University Blvd, Mobile, AL 36688-0002, USA. Tel.: +1 251 460 7393; fax: +1 251 460 6994 (J.J.); tel./fax: +86 10 8280 2482 (M.Z.); tel./fax: +86 10 8391 1528 (S.P.); e-mail addresses: jju@usouthal.edu; sqpeng@bjmu.edu.cn

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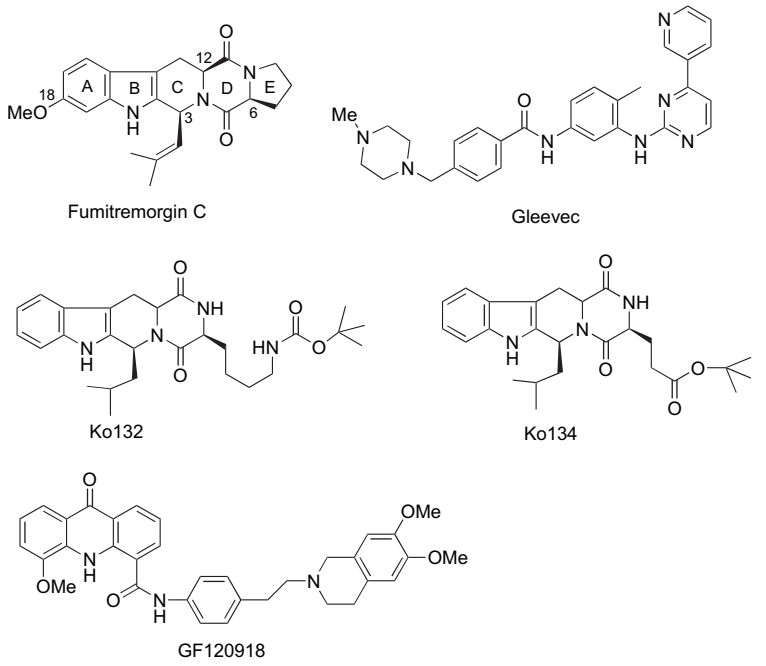


Figure 1. Structure of some known BCRP inhibitors.

tumor-inducing activity and causes cell cycle arrest at the G2/M transition.[15,16] To improve the specificity and selectivity of FTC while eliminating the potential for toxicity, we have designed and synthesized a new class of FTC simplified structural analogues. Compared with the native pentacyclic FTC, the new simplified FTC analogues developed in this study retain the tetracyclic core of FTC. This is similar to the other FTC analogues, i.e., Ko132 and Ko134, all lack the E ring derived from L-proline. In addition, the methoxy group at C-18 in the indole moiety was omitted.

It was reported that the replacement of the proline moiety (E ring) by acyclic substituent might allow the adjacent diketopiperazine ring to assume a different conformation that renders the analogues less neurotoxic than native FTC.[16] Therefore, our efforts in this study are mainly focused on exploring the influence of C-6 substituents on their biological activities. Herein, we report the synthesis of these simplified FTC analogues in a concise and efficient method and some preliminary biological results.

2. Results and discussion

A large number of synthetic fumitremorgin analogues are marked as racemic mixtures. Since it is nearly always the case that only one enantiomer has the desired effect, the elimination of the other enantiomer with undesirable effects has a number of clinical advantages including improvement in pharmacological profile and simplified pharmacokinetics. The lack of an efficient stereoselective synthetic route to fumitremorgin analogues is one of the main reasons that most of biological studies are usually carried out with diastereomeric mixtures of fumitremorgin analogues. For instance, Koomen et al. reported the BCRP inhibitory assay using a panel of 42 diastereomeric mixtures of fumitremorgin analogues[17]. More specifically, Koomen et al. previously reported the preparation of fumitremorgina analogues using a solid phase synthesis.[18] This approach inevitably led to the compounds formed as a mixture of four diastereoisomers, which is due to the fact that two diastereoisomers are formed in the Pictet–Spengler condensation and that racemization of the stereogenic center of the finally introduced building block did occur during the coupling of the activated Fmoc-amino acid. A simple and efficient route toward diastereopure fumitremorgin analogues is of great importance for construction of the molecular libraries. Through the screening of these new diastereopure fumitremorgin analogues, we will further investigate the accurate structure–activity relationship information to facilitate the discovery of effective BCRP inhibitors. In this study, we report a concise and efficient synthetic route to generate a series of new diastereopure FTC simplified structural analogues and some preliminary biological study result.

Fumitremorgin analogues belong to the class of indolyl diketopiperazine alkaloids, which contains the 1,4-dioxo-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indoles skeleton (Fig. 2). One of the most straightforward ways for construction of the key skeleton is based on the Pictet–Spengler reaction, which involves the acid-catalyzed intramolecular condensation between an iminium ion and an aromatic C-nucleophile. The main advantage of this reaction is the formation of a product with a stable C–C bond in a single step.

Starting from optically pure L-tryptophan, compound **1** was readily obtained by treating it with formaldehyde using 5% TFA as catalyst (75% yield). With the available tetrahydro-β-carboline derivative **1**, we next constructed the diketopiperazine ring of fumitremorgin analogues, which can be created from the amino acid coupling followed by intramolecular cyclization. Apparently, the chiral amino acid side chains can be installed from either the C-terminal or the

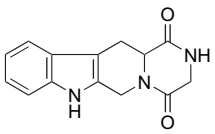
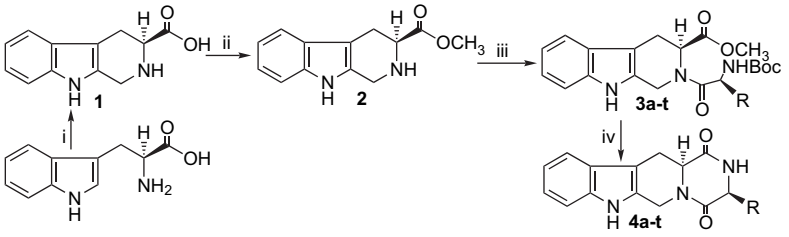


Figure 2. The skeleton of 1,4-dioxo-2,3,6,7,12,12a-hexahydropyrazino-[1′,2′:1,6]pyrido[3,4-*b*]indoles.

N-terminal. We therefore investigated two different synthetic routes to discover the optimal conditions. In the first approach (Scheme 1), compound **1** was easily transformed into its methylester **2** (92% yield) under the treatment of $SOCl_2$/MeOH at the room temperature. However, subsequent coupling of the resulting **2** with protected amino acids remained elusive under various conditions, despite the use of PyBrop,[19] PyBrop/HOAt,[20] and HATU,[21] particularly effective reagents for the coupling of sterically demanding components. These reagents resulted in high racemization during coupling and with very low yield, probably due to severe steric restrictions, acylation of the secondary amine of tetrahydro-β-carbolines obtained from Pictet–Spengler reaction remained difficult. More favorable condition for the hindered secondary amide bond formation was [2-bromopyridinium salt (1.1 equiv)/DIEA (3.2 equiv)/CH_2Cl_2 (3–5 ml/mmol)], stirred for 1 min at 0 °C and then for 1 h at room temperature.[22] Moreover, we further tested the generality of the pyridinium-type coupling methodology. When different amino acid side chains were introduced to tetrahydro-β-carboline system, the key intermediates corresponding to products **3a–t** (84–88% yield) were obtained with excellent purity and diastereoselectivity, suggesting that the coupling methodology is applicable to a range of natural amino acid residues at this sterically demanding position.

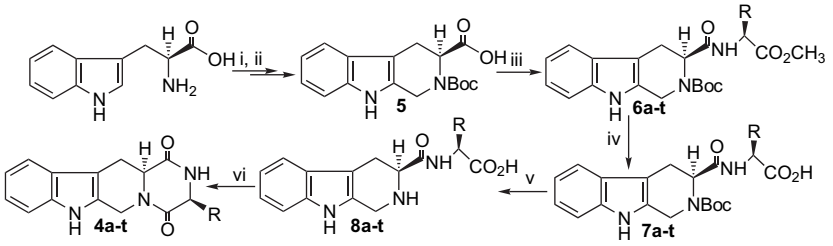
Next, Boc deprotection and subsequent intramolecular cyclization of **3a–t** were carried out in a one-pot reaction at room temperature. Reaction times for this step depend on the amino acid residues being attached on the diketopiperazine unit. After chromatography purification, the desired products **4a–t** were obtained in good yields and high diastereopurity.

An alternative coupling approach was also investigated. As shown in Scheme 2, tetrahydro-β-carboline derivative **2**



No	**3** (% Yield)	**4** (% Yield)
a	93	96
b	93	96
c	87	92
d	93	89
e	90	96
f	87	91
g	92	90
h	93	91
i	91	90
j	91	85
k	92	93
l	92	91
m	89	90
n	88	90
o	95	95
p	92	87
q	86	93
r	91	91
s	87	87
t	88	98

Scheme 1. Synthetic route to **4a–t** via approach A. Reagents: (i) formaldehyde and TFA, 75% yield; (ii) methanol and thionyl chloride, rt, 92% yield; (iii) Boc-L-amino acid, BEP, DIEA; (iv) HCl in ethyl acetate (4 mol/l); **3a** and **4a** R=CH_3; **3b** and **4b** R=$CH_2C_6H_5$; **3c** and **4c** R=$CH(CH_3)_2$; **3d** and **4d** R=CH_2OH; **3e** and **4e** R=$CH(OH)CH_3$; **3f** and **4f** R=$CH_2C_6H_4$–OH-*p*; **3g** and **4g** R=tetrahydropyrrol-2-yl; **3h** and **4h** R=CH_2SH; **3i** and **4i** R=$CH_2CH_2SCH_3$; **3j** R=$CH_2CH_2CO_2CH_3$, **4j** R=$CH_2CH_2CO_2H$; **3k** R=$CH_2CO_2CH_3$, **4k** R=CH_2CO_2H; **3l** and **4l** R=1,3-imidazol-5-methylene; **3m** and **4m** R=indol-3-methylene; **3n** and **4n** R=$CH_2(CH_2)_2NHC(NH_2)$=NH, **3o** and **4o** R=H; **3p** R=$CH_2(CH_2)_3NHZ$, **4p** R=$CH_2(CH_2)_3NH_2$; (After cyclization a colorless powder of 922 mg (2.0 mmol) of the product was mixed with 50 mg of Pd/C (5%) and 25 ml of formic acid in methanol (4.4%), and agitated with hydrogen at room temperature for 24 h. The reaction mixture was filtrated and evaporated to give **4p** as colorless powder.) **3q** and **4q** R=$CH_2CH_2CONH_2$; **3r** and **4r** R=CH_2CONH_2; **3s** and **4s** R=$CH_2CH(CH_3)_2$; **3t** and **4t** R=$CH(CH_3)CH_2CH_3$.



No	6 (% Yield)	7 (% Yield)	8 (% Yield)	4 (% Yield)
a	96	79	94	90
b	98	94	95	95
c	95	71	95	85
d	92	84	89	85
e	92	78	88	92
f	93	67	89	90
g	97	83	94	87
h	92	78	92	86
i	97	72	90	85
j	93	76	92	85
k	90	72	92	85
l	93	76	92	86
m	93	70	90	89
n	88	81	91	87
o	97	95	94	92
p	90	92	90	83
q	90	90	92	93
r	92	92	94	87
s	95	95	92	88
t	92	96	95	87

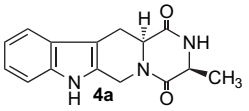
Scheme 2. Synthetic route to **4a**–**t** via approach B. Reagents: (i) formaldehyde and TFA; (ii) Boc-N_3 and triethylamine; (iii) L-amino acid methylester and DCC; (iv) aqueous NaOH (2 mol/l); (v) hydrogen chloride in ethyl acetate (4 mol/l); (vi) DCC/HOBt. In **6a**, **7a**, **8a**, and **4a** R=CH_3; **6b**, **7b**, **8b**, and **4b** R=$CH_2C_6H_5$; **6c**, **7c**, **8c**, and **4c** R=$CH(CH_3)_2$; **6d**, **7d**, **8d**, and **4d** R=CH_2OH; **6e**, **7e**, **8e**, and **4e** R=$CH(OH)CH_3$; **6f**, **7f**, **8f**, and **4f** R=$CH_2C_6H_4$–OH-*p*; **6g**, **7g**, **8g**, and **4g** R=tetrahydropyrrol-2-yl; **6h**, **7h**, **8h**, and **4h** R=CH_2SH; **6i**, **7i**, **8i**, and **4i** R=$CH_2CH_2SCH_3$; **6j** R=$CH_2CH_2COOCH_3$, **7j**, **8j**, and **4j** R=CH_2CH_2COOH; **6k** R=CH_2COOCH_3, **7k**, **8k**, and **4k** R=CH_2COOH; **6l**, **7l**, **8l**, and **4l** R=1,3-imidazol-5-methylene; **6m**, **7m**, **8m**, and **4m** R=indol-3-methylene; **6n**, **7n**, **8n**, and **4n** R=$CH_2(CH_2)_2NHC(NH_2)$=NH, **6o**, **7o**, **8o**, and **4o** R=H; **6p**, **7p**, and **8p** R=$CH_2(CH_2)_3NHZ$; **4p** R=$CH_2(CH_2)_3NH_2$; (After cyclization, a colorless powder of 922 mg (2.0 mmol) of the product was mixed with 50 mg of Pd/C (5%) and 25 ml of formic acid in methanol (4.4%), and agitated with hydrogen at room temperature for 24 h. The reaction mixture was filtrated and evaporated to give **4p** as colorless powder.) **6q**, **7q**, **8q**, and **4q** R=$CH_2CH_2CONH_2$; **6r**, **7r**, **8r**, and **4r** R=CH_2CONH_2; **6s**, **7s**, **8s**, and **4s** R=$CH_2CH(CH_3)_2$; **6t**, **7t**, **8t**, and **4t** R=$CH(CH_3)CH_2CH_3$.

was selectively protected with Boc-N_3 to yield compound **5** (76% yield), which was then subjected to the coupling reaction with a series of amino acid methylesters in the presence of DCC and HOBt. Compounds **6a**–**t** were prepared with high yield (90–98% yield). After saponification, the resulting **7a**–**t** were easily obtained in high yield. The fourth ring was then furnished by the following two steps: deprotection of *tert*-butoxycarbonyl group and intramolecular cyclization under classical HOBT/DCC conditions. Finally, the desired compounds **4a**–**t** were generated in high diastereopurity and good yield. Compared to the second approach, the first approach provides a simpler (four step) and practical route to synthesize a plurality of structurally varied FTC analogues in almost diastereomerically pure form.

To determine if any racemization of the preexisting stereogenic center had occurred during the course of the synthesis, upon removal of the solvent and volatile side products, the crude products **4a**–**t** were then directly analyzed by HPLC. In all cases, the diastereopurity of compounds **4a**–**t** was found to be higher than 98%. The optical rotations of **4a**–**t** are listed in Table 1.

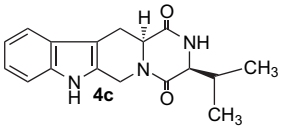
The impact of these new compounds on doxorubicin (a known BCRP substrate) chemosensitivity was examined in the BCRP-overexpressing MES-SA/Dx5 cells and the data were listed in Table 2. It seems that different amino acid residues influence their biological activities. Compared with doxorubicin alone (IC_{50}: 1.55±0.26 μmol/l, resistance index: 4.47), compounds **4c**,**e**,**g**,**l**,**r** significantly reversed BCRP-mediated resistance of MES-SA/Dx5 cells to doxorubicin. In the presence of 0.1 μmol of **4c**,**e**,**g**,**l**,**r** the IC_{50} values of doxorubicin for MES-SA/Dx5 cells were 0.86±0.06, 0.75±0.08, 0.80±0.05, 0.82±0.06, and 0.66±0.04 μmol/l (resistance index: 2.48, 2.16, 2.31, 2.37, 1.89), respectively. Whereas other compounds (i.e., **4h**,**i**) showed a weak action (IC_{50}: 1.30±0.12; 1.14±0.30 μmol/l; resistance index: 3.75; 3.29). The preliminary biological study suggested that C-6 substitution might be important to the potency of this class

Table 1



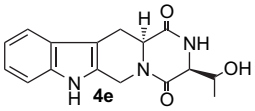
4a

$[\alpha]_D^{20}$ −150 (*c* 1.0, CH_3OH)



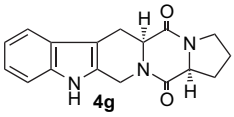
4c

$[\alpha]_D^{20}$ −84 (*c* 1.0, CH_3OH)



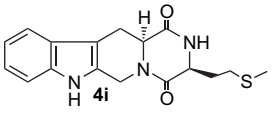
4e

$[\alpha]_D^{20}$ −109 (*c* 1.0, CH_3OH)



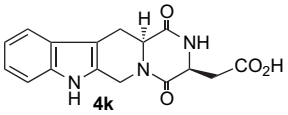
4g

$[\alpha]_D^{20}$ −89 (*c* 1.0, CH_3OH)



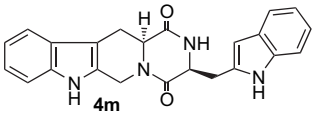
4i

$[\alpha]_D^{20}$ −65 (*c* 1.0, CH_3OH)



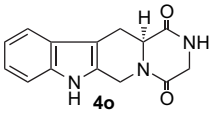
4k

$[\alpha]_D^{20}$ −70 (*c* 1.0, CH_3OH)



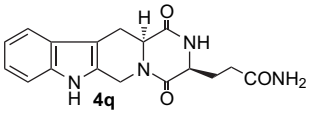
4m

$[\alpha]_D^{20}$ −182 (*c* 0.34, $CHCl_3/CH_3OH$, 1:1, v/v)



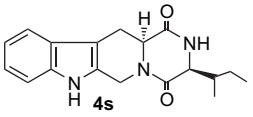
4o

$[\alpha]_D^{20}$ −135 (*c* 1.0, CH_3OH)



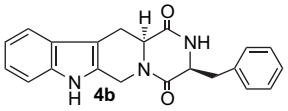
4q

$[\alpha]_D^{20}$ −62 (*c* 1.0, CH_3OH)



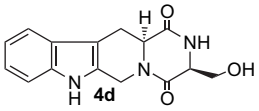
4s

$[\alpha]_D^{20}$ −52 (*c* 1.0, CH_3OH)



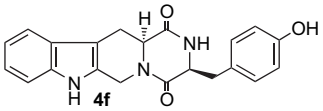
4b

$[\alpha]_D^{20}$ −53 (*c* 1.0, CH_3OH)



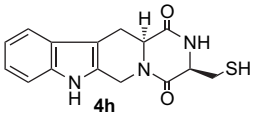
4d

$[\alpha]_D^{20}$ −141 (*c* 1.0, CH_3OH)



4f

$[\alpha]_D^{20}$ −122 (*c* 1.0, CH_3OH)



4h

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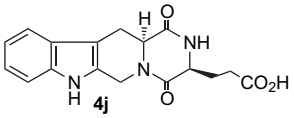
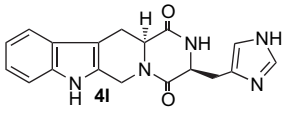


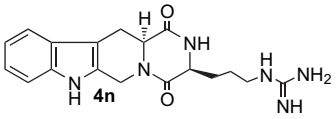
4j

$[\alpha]_D^{20}$ −109 (*c* 1.0, CH_3OH)



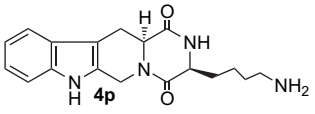
4l

$[\alpha]_D^{20}$ −88 (*c* 1.0, CH_3OH)



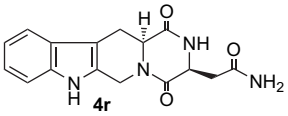
4n

$[\alpha]_D^{20}$ −91 (*c* 1.0, CH_3OH)



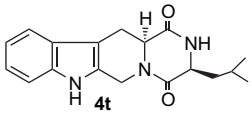
4p

$[\alpha]_D^{20}$ −48 (*c* 1.0, CH_3OH)



4r

$[\alpha]_D^{20}$ −45 (*c* 1.0, CH_3OH)



4t

$[\alpha]_D^{20}$ −74 (*c* 1.0, CH_3OH)

Table 2. The $^{Dx}IC_{50}$ values of doxorubicin for MES-SA/Dx5 cells in the presence of **4a–t** (0.1 μmol)

AA residue	IC_{50} (μmol/l)	Resistance index
Doxorubicin alone	1.55±0.26	4.47
Doxorubicin plus **4a**	1.56±0.21	4.50
Doxorubicin plus **4b**	1.55±0.28	4.47
Doxorubicin plus **4c**	0.86±0.06	2.48
Doxorubicin plus **4d**	1.54±0.28	4.44
Doxorubicin plus **4e**	0.75±0.08	2.16
Doxorubicin plus **4f**	1.54±0.22	4.44
Doxorubicin plus **4g**	0.80±0.05	2.31
Doxorubicin plus **4h**	1.30±0.12	3.75
Doxorubicin plus **4i**	1.14±0.30	3.29
Doxorubicin plus **4j**	1.49±0.25	4.29
Doxorubicin plus **4k**	1.55±0.24	4.47
Doxorubicin plus **4l**	0.82±0.06	2.37
Doxorubicin plus **4m**	1.55±0.26	4.47
Doxorubicin plus **4n**	1.61±0.23	4.64
Doxorubicin plus **4o**	1.55±0.32	4.47
Doxorubicin plus **4p**	1.61±0.23	4.64
Doxorubicin plus **4q**	1.53±0.28	4.41
Doxorubicin plus **4r**	0.66±0.04	1.89
Doxorubicin plus **4s**	1.55±0.26	4.47
Doxorubicin plus **4t**	1.55±0.26	4.47

MES-SA/Dx5 cells were exposed to doxorubicin in the presence of 1 μM **4a–t** for 48 h and IC50 was determined by MTT assay. Values are mean±SD of three experiments. IC_{50} for MES-SA and MES-SA/Dx5 were calculated to be 0.347 and 1.55 μmol/l, respectively. Resistance index of doxorubicine alone=4.47.

of compounds to inhibit BCRP. The detailed in vitro and in vivo biological activity data will be reported elsewhere.

In summary, we have developed a straightforward and efficient method to give a series of new FTC analogues in four steps with high diastereopurity and good yields. This method was easily scaled up to yield gram scale quantity of this new class compounds.

3. Experimental

3.1. General

The protected amino acids with L-configuration were purchased from Sigma Chemical Co. All of the coupling and deprotective reactions were carried out under anhydrous conditions. Chromatography was performed on Qingdao silica gel H. The purities of the intermediates and the products were confirmed by TLC (Merck silica gel plates of type 60 F_{254}, 0.25 mm layer thickness) and HPLC (Waters, C_{18} column 4.6×150 mm). The amino acid analysis was determined with a Hitachi 835-50 instrument. FABMS was determined by VG-ZAB-MS high resolution GC/MS/DS and HP ES-5989x. Optical rotations were determined with a Schmidt+Haensch Polartromic D instrument. The statistical analysis of all the biological data was performed by ANOVA test with $p<0.05$ cut-off.

3.1.1. (3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid (1). To a mixture of 5.0 g (24.5 mmol) of L-tryptophane in 50 ml of dichloromethane, 25 ml of 5% TFA and 8 ml of formaldehyde (36–38%) were added. The reaction mixture was stirred at room temperature for 2 h, and pH was adjusted to pH 6–7 with concentrated ammonia liquor. The mixture was kept at 0 °C for 12 h and precipitates were collected by filtration. After recrystallization, 3.97 g (75%) of the title compound was obtained as a colorless powder. Mp 280–282 °C; EIMS: 217 $[M+H]^+$; IR (KBr): 3450, 3200, 3000, 2950, 2850, 1700, 1601, 1452, 1070, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.99 (s, 1H), 9.89 (s, 1H), 7.30 (t, J=7.5 Hz, 1H), 7.22 (t, J=8.0 Hz, 1H), 7.01 (d, J=8.0 Hz, 1H), 6.81 (d, J=7.5 Hz, 1H), 4.01 (t, J=4.8 Hz, 1H), 3.75 (dd, J=10.5, 5.0 Hz, 1H), 3.64 (dd, J=10.5, 2.4 Hz, 1H), 2.91 (d, J=10.5 Hz, 2H), 2.86 (s, 1H). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.45; H, 5.72; N, 12.79.

3.1.2. (3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylic acid methylester (2). At 0 °C, 10 ml of thionyl chloride was added dropwise to 50 ml of methanol, after which 5.0 g (23.1 mmol) of 3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid was added. The reaction mixture was stirred at room temperature for 15 h and then TLC (ethyl acetate/petroleum, 5:12) was used to indicate the completion of the reaction. The excess methanol and thionyl chloride were removed by evaporation. The residue was dissolved in 30 ml of ethyl acetate and washed successively with saturated $NaCO_3$ in water (3×30 ml), saturated NaCl in water (30 ml×3), and $KHSO_4$ in water (5%, 3×30 ml). The separated ethyl acetate layer was dried with anhydrous $MgSO_4$, evaporated, and purified with flash chromatography ($CHCl_3$/CH_3OH, 30:1) to provide 4.9 g (92%) of the title compound as a colorless powder. Mp 143–145 °C; FABMS: 231 $[M+H]^+$; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.79 (s, 1H), 7.28 (t, J=7.5 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.01 (t, J=7.5 Hz, 1H), 6.99 (t, J=7.5 Hz, 1H), 4.22 (d, J=4.8 Hz, 2H), 3.69 (dd, J=10.5, 5.0 Hz, 1H), 3.56 (s, 3H), 3.14 (dd, J=10.5, 2.4 Hz, 1H), 2.83 (ddd, J=10.5, 5.0, 2.4 Hz, 1H), 2.66 (s, 1H). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.98; H, 6.04; N, 12.30.

3.1.3. 2-Bromo-1-ethyl pyridinium tetrafluoroborate (BEP).[22] To a 10 ml solution of triethyloxonium tetrafluoroborate (10 mmol) in $ClCH_2CH_2Cl$, 2-bromopyridine (10 mmol) was added slowly under the argon atmosphere. After stirring at room temperature for 1 h and heating to 50 °C for additional 30 min, the reaction mixture was cooled. After dilution with anhydrous ether, it was filtered and washed again with ether. The crude product was crystallized from acetone/ether to give the corresponding pyridinium-type reagents as colorless crystals.

3.2. General procedure for the preparation of (3*S*)-*N*-(Boc-aminoacyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3a–t)

To a solution of Boc-L-amino acids (2.2 mmol), 500 mg (2.17 mmol) of 3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester, BEP (0.603 g, 2.2 mmol) in 3 ml CH_2Cl_2, and DIEA (1.1 ml, 6.4 mmol) were added. The reaction mixture was stirred at 0 °C for 1 min and then room temperature for 1 h. The crude product was purified with flash chromatography ($CHCl_3$/CH_3OH, 30:1) to yield the title compound as colorless powder.

3.2.1. (3*S*)-*N*-(Boc-L-alanyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3a). Yield 93%. Mp 148–150 °C; FABMS: 403 $[M+H]^+$; IR (KBr): 3340, 3006,

2953, 2840, 1748, 1642, 1605, 1450, 1391, 1072, 902 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.93 (s, 1H), 8.03 (s, 1H), 7.28 (t, J=7.5 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 6.97 (t, J=7.5 Hz, 1H), 6.94 (t, J=7.5 Hz, 1H), 4.76 (t, J=5.8 Hz, 1H), 4.66 (m, J=5.3 Hz, 1H), 3.84 (s, 2H), 3.62 (dd, J=10.2, 5.2 Hz, 1H), 3.61 (s, 3H), 3.20 (dd, J=10.2, 2.8 Hz, 1H), 1.48 (d, J=5.3 Hz, 3H), 1.45 (s, 9H). $[\alpha]_D^{20}$ −131 (*c* 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.66; H, 6.61; N 10.29.

3.2.2. (3*S*)-*N*-(Boc-L-phenylalanyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3b). Yield 93%. Mp 147–149 °C; FABMS: 478 $[M+H]^+$; IR (KBr): 3338, 3010, 2943, 2840, 1752, 1640, 1602, 1458, 1390, 1070, 902 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.97 (s, 1H), 7.89 (s, 1H), 7.27 (t, J=7.4 Hz, 1H), 7.20 (t, J=7.8 Hz, 2H), 7.16 (t, J=7.4 Hz, 1H), 7.11 (d, J=7.8 Hz, 2H), 7.07 (t, J=7.8 Hz, 1H), 6.99 (t, J=7.4 Hz, 1H), 6.95 (t, J=7.4 Hz, 1H), 5.01 (t, J=5.6 Hz, 1H), 4.79 (t, J=5.6 Hz, 1H), 3.88 (s, 2H), 3.64 (dd, J=10.0, 5.1 Hz, 1H), 3.63 (s, 3H), 3.26 (dd, J=10.0, 2.9 Hz, 1H), 3.06 (d, J=5.6 Hz, 2H), 1.46 (s, 9H). $[\alpha]_D^{20}$ −89 (*c* 0.37, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.73; H, 6.70; N, 9.00.

3.2.3. (3*S*)-*N*-(Boc-L-valinyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3c). Yield 87%. Mp 137–139 °C; FABMS: 430 $[M+H]^+$; IR (KBr): 3343, 3000, 2952, 2845, 1743, 1640, 1605, 1455, 1391, 1375, 1070, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.92 (s, 1H), 8.00 (s, 1H), 7.25 (t, J=7.2 Hz, 1H), 7.13 (t, J=7.2 Hz, 1H), 6.95 (t, J=7.2 Hz, 1H), 6.91 (t, J=7.2 Hz, 1H), 4.73 (t, J=5.6 Hz, 1H), 4.52 (d, J=5.2 Hz, 1H), 3.86 (s, 2H), 3.62 (dd, J=10.3, 5.1 Hz, 1H), 3.64 (s, 3H), 3.22 (dd, J=10.3, 3.2 Hz, 1H), 2.66 (m, J=5.2 Hz, 1H), 1.45 (s, 9H), 1.03 (d, J=5.4 Hz, 6H). $[\alpha]_D^{20}$ −46 (*c* 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{23}H_{31}N_3O_5$: C, 64.32; H, 7.27; N, 9.78. Found: C, 64.16; H, 7.20; N, 9.92.

3.2.4. (3*S*)-*N*-(Boc-L-serinyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3d). Yield 93%. Mp 155–157 °C; FABMS: 418 $[M+H]^+$; IR (KBr): 3339, 3006, 2945, 2842, 1750, 1643, 1605, 1459, 1391, 1072, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.01 (s, 1H), 8.03 (s, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 7.02 (t, J=7.6 Hz, 1H), 6.90 (t, J=7.6 Hz, 1H), 4.78 (t, J=5.7 Hz, 1H), 4.65 (t, J=5.5 Hz, 1H), 4.05 (d, J=5.5 Hz, 1H), 3.91 (s, 2H), 3.62 (dd, J=10.1, 5.0 Hz, 1H), 3.60 (s, 3H), 3.28 (dd, J=10.1, 2.7 Hz, 1H), 3.08 (d, J=5.5 Hz, 2H), 1.48 (s, 9H). $[\alpha]_D^{20}$ −77 (*c* 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.60; H, 6.71; N, 9.88.

3.2.5. (3*S*)-*N*-(Boc-L-threoninyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3e). Yield 90%. Mp 128–130 °C; ESIMS: 432 $[M+H]^+$; IR (KBr): 3433, 3205, 3000, 2955, 2841, 1730, 1643, 1605, 1452, 1390, 1372, 1060, 904 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.02 (s, 1H), 7.89 (s, 1H), 7.30 (t, J=7.3 Hz, 1H), 7.22 (t, J=7.3 Hz, 1H), 6.90 (d, J=7.4 Hz, 1H), 6.70 (d, J=7.3 Hz, 1H), 4.82 (t, J=5.3 Hz, 1H), 4.63 (m, J=5.3 Hz, 1H), 4.44 (t, J=5.3 Hz, 1H), 4.03 (m, J=5.2 Hz, 2H), 3.62 (s, 3H), 2.95 (d, J=5.4 Hz, 2H), 2.21 (d, J=3.6 Hz, 1H), 1.45 (s, 9H), 1.21 (d, J=5.6 Hz, 3H). Anal. Calcd for $C_{22}H_{29}N_3O_6$: C, 61.24; H, 6.77; N, 9.74. Found: C, 61.11; H, 6.65; N, 9.89.

3.2.6. (3*S*)-*N*-(Boc-L-Tyrosinyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3f). Yield 87%. Mp 145–147 °C; FABMS: 494 $[M+H]^+$; IR (KBr): 3337, 3004, 2945, 2845, 1752, 1641, 1600, 1452, 1390, 1070, 903 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.02 (s, 1H), 8.00 (s, 1H), 7.27 (t, J=7.5 Hz, 1H), 7.19 (t, J=7.5 Hz, 1H), 6.96 (d, J=7.6 Hz, 2H), 6.89 (d, J=7.5 Hz, 1H), 6.88 (d, J=7.5 Hz, 1H), 6.68 (d, J=7.6 Hz, 2H), 5.02 (s, 1H), 4.94 (t, J=5.4 Hz, 1H), 4.83 (t, J=5.4 Hz, 1H), 3.93 (s, 2H), 3.64 (dd, J=10.0, 5.1 Hz, 1H), 3.63 (s, 3H), 3.31 (dd, J=10.0, 2.7 Hz, 1H), 3.07 (d, J=5.4 Hz, 2H), 1.46 (s, 9H). $[\alpha]_D^{20}$ −26 (*c* 0.36, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{27}H_{31}N_3O_6$: C, 65.71; H, 6.33; N, 8.51. Found: C, 65.54; H, 6.46; N, 8.70.

3.2.7. (3*S*)-*N*-(Boc-prolinyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3g). Yield 92%. Mp 118–120 °C; ESIMS: 428 $[M+H]^+$; IR (KBr): 3431, 3206, 3003, 2954, 2842, 1730, 1643, 1605, 1456, 1394, 1370, 1065, 904 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.97 (s, 1H), 7.32 (t, J=7.2 Hz, 1H), 7.22 (t, J=7.4 Hz, 1H), 7.03 (d, J=7.4 Hz, 1H), 6.93 (d, J=7.2 Hz, 1H), 4.85 (t, J=5.3 Hz, 1H), 4.31 (t, J=5.5 Hz, 1H), 4.25 (d, J=5.4 Hz, 2H), 3.62 (s, 3H), 3.44 (t, J=5.5 Hz, 2H), 2.97 (d, J=5.5 Hz, 2H), 2.25 (d, J=5.4 Hz, 2H), 1.95 (t, J=5.1 Hz, 2H), 1.47 (s, 9H). Anal. Calcd for $C_{23}H_{29}N_3O_5$: C, 64.62; H, 6.84; N, 9.83. Found: C, 64.75; H, 6.92; N, 9.97.

3.2.8. (3*S*)-*N*-(Boc-cysteinyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3h). Yield 93%. Mp 133–135 °C; ESIMS: 434 $[M+H]^+$; IR (KBr): 3441, 3205, 3004, 2940, 2842, 1734, 1640, 1605, 1450, 1392, 1370, 1064, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.02 (s, 1H), 7.99 (s, 1H), 7.30 (t, J=7.3 Hz, 1H), 7.20 (t, J=7.5 Hz, 1H), 7.03 (d, J=7.5 Hz, 1H), 6.85 (d, J=7.3 Hz, 1H), 4.90 (t, J=5.1 Hz, 1H), 4.73 (t, J=5.3 Hz, 1H), 4.23 (d, J=5.4 Hz, 2H), 3.63 (s, 3H), 3.13 (d, J=5.2 Hz, 2H), 2.99 (d, J=5.3 Hz, 2H), 1.47 (s, 9H), 1.64 (s, 1H). Anal. Calcd for $C_{21}H_{27}N_3O_5S$: C, 58.18; H, 6.28; N, 9.69. Found: C, 58.25; H, 6.38; N, 9.86.

3.2.9. (3*S*)-*N*-(Boc-methioninyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3i). Yield 91%. Mp 133–135 °C; ESIMS: 462 $[M+H]^+$; IR (KBr): 3443, 3205, 3007, 2950, 2844, 1730, 1645, 1602, 1455, 1392, 1375, 1064, 902 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.01 (s, 1H), 7.99 (s, 1H), 7.30 (t, J=7.3 Hz, 1H), 7.20 (t, J=7.5 Hz, 1H), 6.97 (d, J=7.5 Hz, 1H), 6.83 (d, J=7.3 Hz, 1H), 4.83 (t, J=5.2 Hz, 1H), 4.47 (t, J=5.3 Hz, 1H), 4.27 (d, J=5.3 Hz, 2H), 3.66 (s, 3H), 2.95 (d, J=5.4 Hz, 2H), 2.45 (t, J=5.3 Hz, 2H), 2.25 (d, J=5.3 Hz, 2H), 2.11 (s, 3H), 1.47 (s, 9H). Anal. Calcd for $C_{23}H_{31}N_3O_5S$: C, 59.85; H, 6.77; N, 9.10. Found: C, 59.69; H, 6.85; N, 9.26.

3.2.10. (3*S*)-*N*-[Boc-glutamyl(OMe)]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3j). Yield

91%. Mp 122–124 °C; ESIMS: 474 $[M+H]^+$; IR (KBr): 3443, 3205, 3004, 2940, 2834, 1735, 1642, 1601, 1452, 1395, 1370, 1063, 901 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.92 (s, 1H), 8.01 (s, 1H), 7.35 (t, J=7.2 Hz, 1H), 7.26 (t, J=7.2 Hz, 1H), 7.00 (d, J=7.5 Hz, 1H), 6.86 (d, J=7.3 Hz, 1H), 4.87 (d, J=5.3 Hz, 1H), 4.45 (t, J=5.5 Hz, 1H), 4.24 (d, J=5.4 Hz, 2H), 3.67 (s, 3H), 3.65 (s, 3H), 2.97 (d, J=5.3 Hz, 2H), 2.29 (t, J=5.4 Hz, 2H), 2.23 (t, J=5.5 Hz, 2H), 1.47 (s, 9H). Anal. Calcd for $C_{24}H_{31}N_3O_7$: C, 60.88; H, 6.60; N, 8.87. Found: C, 60.75; H, 6.47; N, 9.05.

3.2.11. (3*S*)-*N*-[Boc-L-aspartyl(OBzl)]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3k). Yield 92%. Mp 144–146 °C; FABMS: 536 $[M+H]^+$; IR (KBr): 3340, 3004, 2948, 2845, 1748, 1642, 1600, 1455, 1391, 1072, 904 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.95 (s, 1H), 8.02 (s, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.22 (t, J=7.2 Hz, 2H), 7.20 (d, J=7.2 Hz, 2H), 7.18 (t, J=7.5 Hz, 1H), 7.16 (t, J=7.2 Hz, 1H), 6.97 (t, J=7.5 Hz, 1H), 6.93 (t, J=7.5 Hz, 1H), 5.36 (s, 2H), 5.14 (t, J=5.5 Hz, 1H), 4.77 (t, J=5.7 Hz, 1H), 3.62 (dd, J=10.2, 5.1 Hz, 1H), 3.64 (s, 3H), 3.24 (dd, J=10.2, 2.7 Hz, 1H), 3.06 (d, J=5.6 Hz, 2H), 2.75 (d, J=5.5 Hz, 2H), 1.46 (s, 9H). $[\alpha]_D^{20}$ −61 (c 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{29}H_{33}N_3O_7$: C, 65.03; H, 6.21; N, 7.85. Found: C, 65.18; H, 6.06; N, 7.99.

3.2.12. (3*S*)-*N*-(Boc-L-histidinyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3l). Yield 92%. Mp 140–142 °C; ESIMS: 468 $[M+H]^+$; IR (KBr): 3445, 3203, 3005, 2944, 2837, 1731, 1645, 1602, 1451, 1393, 1370, 1060, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=12.95 (s, 1H), 9.98 (s, 1H), 8.02 (s, 1H), 7.45 (s, 1H), 7.32 (t, J=7.2 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.18 (d, J=7.5 Hz, 1H), 6.99 (t, J=7.2 Hz, 1H), 6.87 (s, 1H), 4.94 (t, J=5.1 Hz, 1H), 4.81 (t, J=5.3 Hz, 1H), 4.23 (d, J=5.1 Hz, 2H), 3.67 (s, 3H), 3.17 (d, J=5.2 Hz, 2H), 2.95 (d, J=5.1 Hz, 2H), 1.47 (s, 9H). Anal. Calcd for $C_{24}H_{29}N_5O_5$: C, 61.66; H, 6.25; N, 14.98. Found: C, 61.79; H, 6.34; N, 14.82.

3.2.13. (3*S*)-*N*-(Boc-L-tryptophanyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3m). Yield 89%. Mp 126–128 °C; FABMS: 517 $[M+H]^+$; IR (KBr): 3335, 3009, 2942, 2842, 1750, 1643, 1604, 1453, 1391, 1072, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.99 (s, 1H), 9.96 (s, 1H), 8.02 (s, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.21 (t, J=7.4 Hz, 1H), 7.19 (t, J=7.4 Hz, 1H), 7.18 (t, J=7.4 Hz, 1H), 7.17 (t, J=7.4 Hz, 1H), 7.16 (t, J=7.6 Hz, 1H), 7.01 (t, J=7.6 Hz, 1H), 6.89 (t, J=7.6 Hz, 1H), 6.82 (s, 1H), 4.90 (t, J=5.5 Hz, 1H), 4.85 (t, J=5.4 Hz, 1H), 3.92 (s, 2H), 3.62 (dd, J=10.1, 5.0 Hz, 1H), 3.65 (s, 3H), 3.32 (dd, J=10.1, 2.9 Hz, 1H), 2.92 (t, J=5.5 Hz, 2H), 1.48 (s, 9H). $[\alpha]_D^{20}$ −97 (c 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{29}H_{32}N_4O_5$: C, 67.43; H, 6.24; N, 10.85. Found: C, 67.59; H, 6.40; N, 10.72.

3.2.14. (3*S*)-*N*-(Boc-L-argininyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3n). Yield 88%. Mp 137–139 °C; ESIMS: 487 $[M+H]^+$; IR (KBr): 3445, 3209, 3004, 2945, 2840, 1733, 1642, 1600, 1451, 1392, 1370, 1064, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.20 (s, 1H), 8.43 (s, 2H), 8.25 (s, 1H), 8.20 (s, 1H), 8.03 (s, 1H), 7.27 (t, J=7.4 Hz, 1H), 7.17 (t, J=7.5 Hz, 1H), 7.01 (d, J=7.5 Hz, 1H), 6.93 (d, J=7.4 Hz, 1H), 4.91 (d, J=5.1 Hz, 1H), 4.40 (t, J=4.3 Hz, 1H), 4.27 (d, J=5.1 Hz, 2H), 3.67 (s, 3H), 2.92 (d, J=4.3 Hz, 2H), 2.66 (t, J=5.5 Hz, 2H), 1.93 (m, J=5.3 Hz, 2H), 1.57 (m, J=5.4 Hz, 2H), 1.55 (s, 9H). Anal. Calcd for $C_{24}H_{34}N_6O_5$: C, 59.24; H, 7.04; N, 17.27. Found: C, 59.10; H, 6.95; N, 17.40.

3.2.15. (3*S*)-*N*-(Boc-glycyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3o). Yield 95%. Mp 150–152 °C; FABMS: 388 $[M+H]^+$; IR (KBr): 3342, 3003, 2950, 2844, 1745, 1645, 1603, 1452, 1390, 1070, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.91 (s, 1H), 8.11 (s, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.16 (t, J=7.6 Hz, 1H), 7.00 (t, J=7.6 Hz, 1H), 6.97 (t, J=7.6 Hz, 1H), 4.76 (t, J=5.6 Hz, 2H), 4.52 (d, J=4.9 Hz, 2H), 3.87 (s, 2H), 3.65 (dd, J=10.5, 5.0 Hz, 1H), 3.58 (s, 3H), 3.17 (dd, J=10.5, 2.4 Hz, 1H), 1.44 (s, 9H). $[\alpha]_D^{20}$ −100 (c 0.34, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 62.18; H, 6.34; N, 10.67.

3.2.16. (3*S*)-*N*-[Boc-L-lysinyl(*Z*)]-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3p). Yield 92%. Mp 95–97 °C; FABMS: 593 $[M+H]^+$; IR (KBr): 3342, 3003, 2940, 2845, 1752, 1641, 1602, 1456, 1390, 1070, 902 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.97 (s, 1H), 8.05 (s, 1H), 8.00 (s, 1H), 7.27 (t, J=7.5 Hz, 1H), 7.22 (t, J=7.2 Hz, 1H), 7.17 (t, J=7.5 Hz, 1H), 7.15 (d, J=7.2 Hz, 2H), 7.13 (t, J=7.2 Hz, 2H), 7.00 (t, J=7.5 Hz, 1H), 6.88 (t, J=7.5 Hz, 1H), 5.36 (s, 2H), 4.76 (t, J=5.6 Hz, 1H), 4.55 (t, J=5.6 Hz, 1H), 3.63 (dd, J=10.2, 5.1 Hz, 1H), 3.64 (s, 3H), 3.30 (dd, J=10.1, 2.7 Hz, 1H), 3.08 (d, J=5.5 Hz, 2H), 2.95 (t, J=5.4 Hz, 2H), 1.75 (t, J=5.5 Hz, 2H), 1.58 (t, J=5.3 Hz, 2H), 1.48 (s, 9H), 1.27 (m, J=5.6 Hz, 2H). $[\alpha]_D^{20}$ −29 (c 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{32}H_{40}N_4O_7$: C, 64.85; H, 6.80; N, 9.45. Found: C, 64.69; H, 6.71; N, 9.62.

3.2.17. (3*S*)-*N*-(Boc-L-glutaminyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3q). Yield 86%. Mp 145–147 °C; FABMS: 459 $[M+H]^+$; IR (KBr): 3342, 3011, 2949, 2844, 1750, 1640, 1603, 1456, 1391, 1072, 905 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.00 (s, 1H), 8.02 (s, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.17 (t, J=7.6 Hz, 1H), 6.86 (d, J=7.6 Hz, 1H), 6.83 (d, J=7.6 Hz, 1H), 6.12 (s, 2H), 4.90 (t, J=5.4 Hz, 1H), 4.55 (t, J=5.4 Hz, 1H), 3.95 (s, 2H), 3.62 (dd, J=10.2, 5.0 Hz, 1H), 3.60 (s, 3H), 3.32 (dd, J=10.1, 2.9 Hz, 1H), 2.19 (t, J=4.9 Hz, 2H), 2.01 (m, J=4.9 Hz, 2H), 1.42 (s, 9H). $[\alpha]_D^{20}$ −27 (c 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{23}H_{30}N_4O_6$: C, 60.25; H, 6.59; N, 12.22. Found: C, 60.38; H, 6.77; N, 12.37.

3.2.18. (3*S*)-*N*-(Boc-L-asparaginyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3r). Yield 91%. Mp 137–139 °C; ESIMS: 445 $[M+H]^+$; IR (KBr): 3443, 3205, 3001, 2932, 2833, 1734, 1630, 1604, 1457, 1391, 1370, 1061, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.97 (s, 1H), 8.01 (s, 1H), 7.22 (t, J=7.3 Hz, 1H), 7.14 (t, J=7.1 Hz, 1H), 7.01 (d, J=7.3 Hz, 1H), 6.85 (d, J=7.3 Hz, 1H), 6.03 (s, 2H), 4.91 (d, J=5.3 Hz, 1H), 4.41 (t, J=5.3 Hz, 1H), 4.24 (d, J=5.3 Hz, 2H), 3.65 (s, 3H), 2.92 (d, J=5.1 Hz, 2H), 2.55 (t, J=5.3 Hz, 2H), 1.49 (s, 9H). $[\alpha]_D^{20}$ −38 (c 0.30, $CHCl_3/CH_3OH$, 1:1, v/v). Anal.

Calcd for $C_{22}H_{28}N_4O_6$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.62; H, 6.44; N, 12.43.

3.2.19. (3*S*)-*N*-(Boc-L-leucyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3s). Yield 87%. Mp 135–137 °C; FABMS: 444 $[M+H]^+$; IR (KBr): 3344, 3002, 2950, 2842, 1745, 1640, 1603, 1452, 1390, 1070, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.87 (s, 1H), 8.00 (s, 1H), 7.27 (t, J=7.4 Hz, 1H), 7.15 (t, J=7.4 Hz, 1H), 6.99 (t, J=7.4 Hz, 1H), 6.96 (t, J=7.4 Hz, 1H), 4.75 (t, J=5.9 Hz, 1H), 4.55 (d, J=5.4 Hz, 1H), 3.88 (s, 2H), 3.60 (dd, J=10.0, 5.0 Hz, 1H), 3.62 (s, 3H), 3.22 (dd, J=10.0, 2.9 Hz, 1H), 1.88 (m, J=5.4 Hz, 1H), 1.78 (t, J=5.0 Hz, 2H), 1.46 (s, 9H), 1.03 (d, J=5.4 Hz, 6H). $[\alpha]_D^{20}$ −52 (c 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{24}H_{33}N_3O_5$: C, 64.99; H, 7.50; N, 9.47. Found: C, 65.16; H, 7.63; N, 9.32.

3.2.20. (3*S*)-*N*-(Boc-L-isoleucyl)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid methylester (3t). Yield 88%. Mp 130–132 °C; FABMS: 444 $[M+H]^+$; IR (KBr): 3344, 3002, 2950, 2842, 1745, 1640, 1603, 1452, 1390, 1070, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.89 (s, 1H), 8.03 (s, 1H), 7.27 (t, J=7.4 Hz, 1H), 7.15 (t, J=7.4 Hz, 1H), 6.99 (t, J=7.4 Hz, 1H), 6.96 (t, J=7.4 Hz, 1H), 4.75 (t, J=5.9 Hz, 1H), 4.55 (d, J=5.4 Hz, 1H), 3.88 (s, 2H), 3.60 (dd, J=10.0, 5.0 Hz, 1H), 3.62 (s, 3H), 3.22 (dd, J=10.0, 2.9 Hz, 1H), 2.48 (m, J=5.4 Hz, 1H), 1.33 (m, J=5.0 Hz, 2H), 1.46 (s, 9H), 1.06 (d, J=5.4 Hz, 3H), 1.00 (t, J=5.0 Hz, 3H). $[\alpha]_D^{20}$ −40 (c 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{24}H_{33}N_3O_5$: C, 64.99; H, 7.50; N, 9.47. Found: C, 65.16; H, 7.63; N, 9.32.

3.3. (3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (5)

The suspension of 1.08 g (5.0 mmol) of compound **1** in 15 ml of DMF and 1.4 ml of triethylamine was vigorously stirred at room temperature, to which 1.62 g (7.5 mmol) of Boc-N_3 was added in 30 min. The reaction mixture was stirred at room temperature for 24 h and at 40 °C for 80 h. Five milliliters of citrate solution (20%) was added to the reaction mixture, and the solution was extracted with ethyl acetate (3×30 ml). The separated ethyl acetate layer was dried with anhydrous $MgSO_4$. After removal of $MgSO_4$ by filtration the filtrate was evaporated to dryness. The residue obtained was crystallized in $CHCl_3$ to give 1.20 g (76%) of the title compound. Mp 165–170 °C; ESIMS: 317 $[M+H]^+$; IR (KBr): 3452, 3205, 3001, 2952, 2848, 1705, 1645, 1600, 1450, 1072, 901 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.87 (s, 1H), 9.86 (s, 1H), 7.32 (t, J=7.6 Hz, 1H), 7.21 (t, J=7.9 Hz, 1H), 7.00 (d, J=7.9 Hz, 1H), 6.84 (t, J=7.6 Hz, 1H), 4.84 (t, J=5.0 Hz, 1H), 4.20 (dd, J=10.2, 4.8 Hz, 1H), 3.98 (dd, J=10.2, 3.2 Hz, 1H), 2.93 (d, J=10.2 Hz, 2H), 1.46 (s, 9H). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.41; H, 6.25; N, 8.74.

3.4. General procedure for the preparation of *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-amino acid methylesters (6a–t)

At 0 °C, to the solution of 2.0 g (6.33 mmol) *N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid in 30 ml of anhydrous THF, 1.2 g (8.9 mmol) of HOBt was added, and 10 min later 1.75 g (8.5 mmol) of DCC was added. The suspension of 6.96 mmol of HCl·L-AA-OMe in 3 ml of anhydrous THF was adjusted pH to 8–9 with *N*-methyl morpholine and stirred at room temperature for 20 min. This suspension was then added to the solution of *N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid and the reaction mixture was stirred at 0 °C for 2 h and at room temperature for 16 h. On evaporation, the residue was dissolved in 30 ml of ethyl acetate. The solution was washed successively with 5% sodium bicarbonate, 5% citric acid, and saturated sodium chloride and the organic phase was separated and dried over anhydrous sodium sulfate. After filtration and evaporation under reduced pressure, the title compound was obtained as powder.

3.4.1. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-alanine methylester (6a). Yield 96%. Mp 144–146 °C; ESIMS: 402 $[M+H]^+$; IR (KBr): 3451, 3011, 2949, 2847, 1730, 1604, 1450, 1392, 1370, 1066, 897 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.89 (s, 1H), 7.98 (s, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.23 (t, J=7.8 Hz, 1H), 6.97 (d, J=7.8 Hz, 1H), 6.81 (d, J=7.5 Hz, 1H), 4.88 (d, J=5.2 Hz, 1H), 4.59 (m, J=5.5 Hz, 1H), 4.25 (dd, J=10.0, 4.7 Hz, 1H), 4.17 (dd, J=10.1, 3.5 Hz, 1H), 3.64 (s, 3H), 2.94 (d, J=10.1 Hz, 2H), 1.55 (d, J=5.2 Hz, 3H), 1.43 (s, 9H). Anal. Calcd for $C_{21}H_{27}N_3O_5$: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.92; H, 6.74; N, 10.30.

3.4.2. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-phenylalanine methylester (6b). Yield 98%. Mp 150–152 °C; ESIMS: 478 $[M+H]^+$; IR (KBr): 3446, 3205, 3006, 2948, 2847, 1731, 1645, 1603, 1451, 1392, 1370, 1069, 904 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.92 (s, 1H), 7.97 (s, 1H), 7.31 (t, J=7.5 Hz, 1H), 7.28 (t, J=7.9 Hz, 2H), 7.19 (t, J=7.6 Hz, 1H), 7.14 (d, J=7.6 Hz, 2H), 7.02 (t, J=7.6 Hz, 1H), 6.96 (d, J=7.8 Hz, 1H), 6.80 (d, J=7.6 Hz, 1H), 4.93 (d, J=5.4 Hz, 1H), 4.82 (t, J=5.4 Hz, 1H), 4.27 (dd, J=10.2, 4.5 Hz, 1H), 4.18 (dd, J=10.2, 3.4 Hz, 1H), 3.62 (s, 3H), 3.17 (d, J=5.4 Hz, 2H), 2.93 (d, J=10.2 Hz, 2H), 1.48 (s, 9H). Anal. Calcd for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.72; H, 6.62; N, 8.67.

3.4.3. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-valine methylester (6c). Yield 95%. Mp 138–140 °C; ESIMS: 430 $[M+H]^+$; IR (KBr): 3443, 3202, 3001, 2951, 2845, 1729, 1648, 1602, 1450, 1392, 1370, 1067, 902 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.04 (s, 1H), 7.96 (s, 1H), 7.29 (t, J=7.4 Hz, 1H), 7.21 (t, J=7.7 Hz, 1H), 7.00 (d, J=7.7 Hz, 1H), 6.89 (d, J=7.4 Hz, 1H), 4.84 (t, J=5.4 Hz, 1H), 4.42 (d, J=5.4 Hz, 1H), 4.22 (dd, J=10.2, 4.5 Hz, 1H), 4.03 (dd, J=10.2, 3.7 Hz, 1H), 3.62 (s, 3H), 3.10 (m, J=5.4 Hz, 1H), 2.95 (d, J=6.7 Hz, 2H), 1.47 (s, 9H), 1.05 (d, J=5.4 Hz, 6H). Anal. Calcd for $C_{23}H_{31}N_3O_5$: C, 64.32; H, 7.27; N, 9.78. Found: C, 64.43; H, 7.09; N, 9.67.

3.4.4. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-serine methylester (6d). Yield 92%. Mp 139–141 °C; ESIMS: 418 $[M+H]^+$; IR (KBr): 3442, 3200, 3001, 2952, 2845, 1730, 1644, 1606, 1455, 1392, 1370, 1067, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.95 (s, 1H), 7.97 (s, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.22

(t, J=7.9 Hz, 1H), 6.99 (d, J=7.9 Hz, 1H), 6.83 (t, J=7.6 Hz, 1H), 4.87 (d, J=5.4 Hz, 1H), 4.52 (t, J=5.6 Hz, 1H), 4.19 (d, J=5.2 Hz, 2H), 4.13 (d, J=5.6 Hz, 2H), 3.63 (s, 3H), 2.95 (d, J=5.6 Hz, 1H), 2.92 (d, J=5.6 Hz, 1H), 2.28 (s, 1H), 1.45 (s, 9H). Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.31; H, 6.36; N, 10.24.

3.4.5. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-threonine methylester (6e). Yield 92%. Mp 140–142 °C; ESIMS: 432 $[M+H]^+$; IR (KBr): 3437, 3200, 3002, 2951, 2844, 1735, 1649, 1600, 1450, 1392, 1370, 1065, 901 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.98 (s, 1H), 7.87 (s, 1H), 7.34 (t, J=7.4 Hz, 1H), 7.25 (t, J=7.6 Hz, 1H), 6.95 (d, J=7.6 Hz, 1H), 6.72 (d, J=7.4 Hz, 1H), 4.87 (t, J=5.4 Hz, 1H), 4.67 (m, J=5.6 Hz, 1H), 4.48 (t, J=5.6 Hz, 1H), 3.99 (m, J=5.2 Hz, 2H), 3.65 (s, 3H), 2.97 (d, J=5.7 Hz, 2H), 2.19 (d, J=3.7 Hz, 1H), 1.47 (s, 9H), 1.19 (d, J=5.6 Hz, 3H). Anal. Calcd for $C_{22}H_{29}N_3O_6$: C, 61.24; H, 6.77; N, 9.74. Found: C, 61.40; H, 6.91; N, 9.55.

3.4.6. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-tyrosine methylester (6f). Yield 93%. Mp 143–145 °C; ESIMS: 494 $[M+H]^+$; IR (KBr): 3439, 3203, 3001, 2955, 2847, 1732, 1644, 1601, 1453, 1391, 1372, 1062, 903 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.99 (s, 1H), 8.02 (s, 1H), 7.37 (t, J=7.6 Hz, 1H), 7.22 (t, J=7.7 Hz, 1H), 7.15 (d, J=7.5 Hz, 2H), 7.02 (d, J=7.5 Hz, 1H), 6.96 (d, J=7.7 Hz, 1H), 6.91 (d, J=7.5 Hz, 2H), 4.98 (s, 1H), 4.93 (d, J=5.4 Hz, 1H), 4.80 (t, J=5.6 Hz, 1H), 4.29 (m, J=5.2 Hz, 2H), 3.64 (s, 3H), 3.15 (d, J=5.2 Hz, 2H), 2.97 (d, J=5.0 Hz, 2H), 1.49 (s, 9H). Anal. Calcd for $C_{27}H_{31}N_3O_6$: C, 65.71; H, 6.33; N, 8.51. Found: C, 65.67; H, 6.50; N, 8.67.

3.4.7. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-proline methylester (6g). Yield 97%. Mp 139–141 °C; ESIMS: 428 $[M+H]^+$; IR (KBr): 3435, 3202, 3000, 2950, 2846, 1732, 1645, 1602, 1454, 1390, 1371, 1063, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.01 (s, 1H), 7.35 (t, J=7.4 Hz, 1H), 7.20 (t, J=7.7 Hz, 1H), 7.07 (d, J=7.7 Hz, 1H), 6.91 (d, J=7.4 Hz, 1H), 4.88 (t, J=5.4 Hz, 1H), 4.35 (t, J=5.6 Hz, 1H), 4.22 (d, J=5.3 Hz, 2H), 3.59 (s, 3H), 3.47 (t, J=5.6 Hz, 2H), 2.95 (d, J=5.6 Hz, 2H), 2.29 (d, J=5.6 Hz, 2H), 1.97 (t, J=4.9 Hz, 2H), 1.45 (s, 9H). Anal. Calcd for $C_{23}H_{29}N_3O_5$: C, 64.62; H, 6.84; N, 9.83. Found: C, 64.57; H, 6.90; N, 9.67.

3.4.8. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-cysteine methylester (6h). Yield 92%. Mp 151–153 °C; ESIMS: 434 $[M+H]^+$; IR (KBr): 3445, 3203, 3000, 2944, 2840, 1731, 1643, 1601, 1453, 1390, 1372, 1061, 898 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.93 (s, 1H), 7.97 (s, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.22 (t, J=7.8 Hz, 1H), 7.00 (d, J=7.8 Hz, 1H), 6.88 (d, J=7.5 Hz, 1H), 4.93 (t, J=5.3 Hz, 1H), 4.72 (t, J=5.5 Hz, 1H), 4.21 (d, J=5.3 Hz, 2H), 3.68 (s, 3H), 3.16 (d, J=5.5 Hz, 2H), 3.01 (d, J=5.6 Hz, 2H), 1.45 (s, 9H), 1.62 (s, 1H). Anal. Calcd for $C_{21}H_{27}N_3O_5S$: C, 58.18; H, 6.28; N, 9.69. Found: C, 58.27; H, 6.33; N, 9.57.

3.4.9. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-methionine methylester (6i). Yield 97%. Mp 159–161 °C; ESIMS: 462 $[M+H]^+$; IR (KBr): 3441, 3203, 3004, 2953, 2847, 1732, 1641, 1603, 1454, 1390, 1372, 1061, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.04 (s, 1H), 7.97 (s, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.22 (t, J=7.8 Hz, 1H), 6.99 (d, J=7.8 Hz, 1H), 6.81 (d, J=7.5 Hz, 1H), 4.86 (t, J=5.3 Hz, 1H), 4.45 (t, J=5.5 Hz, 1H), 4.28 (d, J=5.1 Hz, 2H), 3.68 (s, 3H), 2.93 (d, J=5.3 Hz, 2H), 2.42 (t, J=5.4 Hz, 2H), 2.28 (d, J=5.6 Hz, 2H), 2.10 (s, 3H), 1.44 (s, 9H). Anal. Calcd for $C_{23}H_{31}N_3O_5S$: C, 59.85; H, 6.77; N, 9.10. Found: C, 59.67; H, 6.59; N, 9.04.

3.4.10. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-glutamic acid dimethylester (6j). Yield 93%. Mp 154–156 °C; ESIMS: 474 $[M+H]^+$; IR (KBr): 3441, 3203, 3000, 2944, 2831, 1731, 1645, 1604, 1455, 1390, 1372, 1067, 903 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.89 (s, 1H), 8.04 (s, 1H), 7.39 (t, J=7.6 Hz, 1H), 7.28 (t, J=7.6 Hz, 1H), 7.01 (d, J=7.7 Hz, 1H), 6.84 (d, J=7.6 Hz, 1H), 4.90 (d, J=5.4 Hz, 1H), 4.43 (t, J=5.6 Hz, 1H), 4.22 (d, J=5.5 Hz, 2H), 3.66 (s, 3H), 3.64 (s, 3H), 2.96 (d, J=5.4 Hz, 2H), 2.28 (t, J=5.6 Hz, 2H), 2.24 (t, J=5.7 Hz, 2H), 1.43 (s, 9H). Anal. Calcd for $C_{24}H_{31}N_3O_7$: C, 60.88; H, 6.60; N, 8.87. Found: C, 60.73; H, 6.49; N, 8.69.

3.4.11. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-aspartic acid dimethylester (6k). Yield 90%. Mp 158–160 °C; ESIMS: 460 $[M+H]^+$; IR (KBr): 3441, 3210, 3004, 2955, 2841, 1732, 1643, 1604, 1453, 1390, 1371, 1061, 903 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.05 (s, 1H), 8.05 (s, 1H), 7.37 (t, J=7.4 Hz, 1H), 7.25 (t, J=7.4 Hz, 1H), 7.00 (d, J=7.6 Hz, 1H), 6.95 (d, J=7.4 Hz, 1H), 4.92 (d, J=5.5 Hz, 1H), 4.77 (t, J=5.5 Hz, 1H), 4.24 (d, J=5.6 Hz, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 2.91 (d, J=5.2 Hz, 2H), 2.85 (d, J=5.4 Hz, 2H), 1.49 (s, 9H). Anal. Calcd for $C_{23}H_{29}N_3O_7$: C, 60.12; H, 6.36; N, 9.14. Found: C, 60.03; H, 6.49; N, 8.99.

3.4.12. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-histidine methylester (6l). Yield 93%. Mp 162–164 °C; ESIMS: 468 $[M+H]^+$; IR (KBr): 3442, 3206, 3004, 2949, 2839, 1730, 1643, 1601, 1454, 1391, 1368, 1062, 902 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=12.98 (s, 1H), 9.96 (s, 1H), 8.05 (s, 1H), 7.47 (s, 1H), 7.36 (t, J=7.4 Hz, 1H), 7.20 (t, J=7.7 Hz, 1H), 7.16 (d, J=7.7 Hz, 1H), 6.98 (t, J=7.4 Hz, 1H), 6.85 (s, 1H), 4.93 (t, J=5.3 Hz, 1H), 4.83 (t, J=5.4 Hz, 1H), 4.26 (d, J=5.2 Hz, 2H), 3.64 (s, 3H), 3.19 (d, J=5.4 Hz, 2H), 2.92 (d, J=5.2 Hz, 2H), 1.49 (s, 9H). Anal. Calcd for $C_{24}H_{29}N_5O_5$: C, 61.66; H, 6.25; N, 14.98. Found: C, 61.52; H, 6.38; N, 14.79.

3.4.13. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-tryptophan methylester (6m). Yield 93%. Mp 161–163 °C; ESIMS: 517 $[M+H]^+$; IR (KBr): 3442, 3204, 3000, 2948, 2839, 1729, 1642, 1604, 1448, 1391, 1372, 1062, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.87 (s, 1H), 9.86 (s, 1H), 8.09 (s, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.30 (t, J=7.4 Hz, 1H), 7.12 (d, J=7.8 Hz, 1H), 7.11 (t, J=7.8 Hz, 1H), 7.10 (d, J=7.6 Hz, 1H), 7.09 (t, J=7.8 Hz, 1H), 7.04 (d, J=7.6 Hz, 1H), 6.98 (d, J=7.5 Hz, 1H), 6.83 (s, 1H), 4.94 (d, J=5.4 Hz, 1H), 4.76 (t, J=5.3 Hz, 1H), 4.29 (d, J=5.2 Hz, 2H), 3.64 (s, 3H),

3.19 (d, J=5.4 Hz, 2H), 2.95 (d, J=6.4 Hz, 2H), 1.49 (s, 9H). Anal. Calcd for $C_{29}H_{32}N_4O_5$: C, 67.43; H, 6.24; N, 10.85. Found: C, 67.55; H, 6.34; N, 10.72.

3.4.14. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-arginine methylester (6n). Yield 88%. Mp 168–170 °C; ESIMS: 487 $[M+H]^+$; IR (KBr): 3443, 3207, 3001, 2948, 2842, 1731, 1645, 1602, 1453, 1390, 1372, 1061, 904 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.22 (s, 1H), 8.45 (s, 2H), 8.27 (s, 1H), 8.22 (s, 1H), 8.01 (s, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.18 (t, J=7.7 Hz, 1H), 7.04 (d, J=7.7 Hz, 1H), 6.96 (d, J=7.6 Hz, 1H), 4.90 (d, J=5.3 Hz, 1H), 4.42 (t, J=4.2 Hz, 1H), 4.25 (d, J=5.0 Hz, 2H), 3.65 (s, 3H), 2.94 (d, J=4.1 Hz, 2H), 2.68 (t, J=5.4 Hz, 2H), 1.92 (m, J=5.5 Hz, 2H), 1.58 (m, J=5.5 Hz, 2H), 1.57 (s, 9H). Anal. Calcd for $C_{24}H_{34}N_6O_5$: C, 59.24; H, 7.04; N, 17.27. Found: C, 59.38; H, 7.19; N, 17.31.

3.4.15. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-glycine methylester (6o). Yield 97%. Mp 133–135 °C; ESIMS: 388 $[M+H]^+$; IR (KBr): 3448, 3010, 2945, 2843, 1732, 1600, 1453, 1390, 1371, 1062, 899 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.93 (s, 1H), 8.02 (s, 1H), 7.30 (t, J=7.5 Hz, 1H), 7.20 (t, J=7.6 Hz, 1H), 6.95 (d, J=7.6 Hz, 1H), 6.83 (d, J=7.6 Hz, 1H), 4.89 (d, J=5.4 Hz, 1H), 4.22 (dd, J=10.2, 4.5 Hz, 1H), 4.18 (s, 2H), 4.19 (dd, J=10.2, 3.7 Hz, 1H), 3.66 (s, 3H), 2.95 (d, J=10.1 Hz, 2H), 1.45 (s, 9H). $[\alpha]_D^{20}$ −101 (c 0.36, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 62.15; H, 6.68; N, 10.68.

3.4.16. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-(*Z*)lysine methylester (6p). Yield 90%. Mp 134–136 °C; ESIMS: 593 $[M+H]^+$; IR (KBr): 3442, 3007, 2940, 2848, 1730, 1605, 1455, 1391, 1370, 1066, 897 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.95 (s, 1H), 8.03 (s, 1H), 7.96 (s, 1H), 7.28 (t, J=7.6 Hz, 1H), 7.22 (t, J=7.2 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 7.17 (d, J=7.2 Hz, 2H), 7.15 (t, J=7.2 Hz, 2H), 6.96 (d, J=7.6 Hz, 1H), 6.85 (d, J=7.6 Hz, 1H), 5.36 (s, 2H), 4.90 (d, J=5.5 Hz, 1H), 4.41 (t, J=4.4 Hz, 1H), 4.20 (dd, J=10.0, 4.5 Hz, 1H), 4.18 (dd, J=10.0, 3.7 Hz, 1H), 3.64 (s, 3H), 2.98 (t, J=4.4 Hz, 2H), 2.93 (d, J=10.0 Hz, 2H), 1.91 (m, J=4.4 Hz, 2H), 1.55 (m, J=4.4 Hz, 2H), 1.46 (s, 9H), 1.29 (m, J=4.4 Hz, 2H). $[\alpha]_D^{20}$ −22 (c 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{32}H_{40}N_4O_7$: C, 64.85; H, 6.80; N, 9.45. Found: C, 64.98; H, 6.69; N, 9.62.

3.4.17. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-glutamine methylester (6q). Yield 90%. Mp 122–124 °C; ESIMS: 459 $[M+H]^+$; IR (KBr): 3445, 3200, 3001, 2940, 2835, 1733, 1640, 1602, 1452, 1391, 1370, 1065, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.91 (s, 1H), 8.00 (s, 1H), 7.29 (t, J=7.4 Hz, 1H), 7.20 (t, J=7.4 Hz, 1H), 7.00 (d, J=7.4 Hz, 1H), 6.80 (d, J=7.4 Hz, 1H), 6.05 (s, 2H), 4.92 (d, J=5.5 Hz, 1H), 4.41 (t, J=5.5 Hz, 1H), 4.24 (d, J=5.6 Hz, 2H), 3.67 (s, 3H), 2.94 (d, J=5.4 Hz, 2H), 2.18 (t, J=5.5 Hz, 2H), 2.14 (t, J=5.5 Hz, 2H), 1.46 (s, 9H). $[\alpha]_D^{20}$ −56 (c 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{23}H_{30}N_4O_6$: C, 60.25; H, 6.59; N, 12.22. Found: C, 60.73; H, 6.49; N, 8.69.

3.4.18. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-asparagine methylester (6r). Yield 92%. Mp 129–131 °C; ESIMS: 445 $[M+H]^+$; IR (KBr): 3440, 3203, 3005, 2936, 2830, 1730, 1632, 1600, 1455, 1394, 1372, 1062, 903 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.94 (s, 1H), 8.03 (s, 1H), 7.25 (t, J=7.2 Hz, 1H), 7.17 (t, J=7.2 Hz, 1H), 7.04 (d, J=7.2 Hz, 1H), 6.82 (d, J=7.2 Hz, 1H), 6.01 (s, 2H), 4.95 (d, J=5.4 Hz, 1H), 4.43 (t, J=5.4 Hz, 1H), 4.26 (d, J=5.4 Hz, 2H), 3.63 (s, 3H), 2.90 (d, J=5.2 Hz, 2H), 2.15 (t, J=5.3 Hz, 2H), 1.49 (s, 9H). $[\alpha]_D^{20}$ −50 (c 0.30, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{22}H_{28}N_4O_6$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.28; H, 6.26; N, 12.77.

3.4.19. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-leucine methylester (6s). Yield 95%. Mp 131–133 °C; ESIMS: 444 $[M+H]^+$; IR (KBr): 3442, 3203, 3001, 2955, 2840, 1731, 1640, 1600, 1451, 1390, 1375, 1063, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.90 (s, 1H), 8.03 (s, 1H), 7.25 (t, J=7.2 Hz, 1H), 7.19 (t, J=7.2 Hz, 1H), 7.00 (d, J=7.2 Hz, 1H), 6.84 (d, J=7.2 Hz, 1H), 4.95 (t, J=5.3 Hz, 1H), 4.44 (t, J=5.3 Hz, 1H), 4.25 (dd, J=10.1, 4.4 Hz, 1H), 4.06 (dd, J=10.1, 3.6 Hz, 1H), 3.64 (s, 3H), 2.93 (d, J=6.4 Hz, 2H), 2.85 (d, J=5.0 Hz, 2H), 1.51 (s, 9H), 1.36 (m, J=5.0 Hz, 1H), 1.09 (d, J=5.2 Hz, 6H). $[\alpha]_D^{20}$ −41 (c 0.31, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{24}H_{33}N_3O_5$: C, 64.99; H, 7.50; N, 9.47. Found: C, 65.16; H, 7.61; N, 9.30.

3.4.20. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-isoleucine methylester (6t). Yield 92%. Mp 122–125 °C; ESIMS: 444 $[M+H]^+$; IR (KBr): 3440, 3205, 3006, 2952, 2844, 1736, 1645, 1603, 1454, 1380, 1390, 1060, 905 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.93 (s, 1H), 8.02 (s, 1H), 7.29 (t, J=7.3 Hz, 1H), 7.22 (t, J=7.3 Hz, 1H), 7.02 (d, J=7.3 Hz, 1H), 6.89 (d, J=7.3 Hz, 1H), 4.97 (t, J=5.2 Hz, 1H), 4.40 (t, J=5.2 Hz, 1H), 4.22 (dd, J=10.0, 4.2 Hz, 1H), 4.01 (dd, J=10.0, 3.4 Hz, 1H), 3.69 (s, 3H), 2.96 (d, J=6.2 Hz, 2H), 2.93 (m, J=5.4 Hz, 1H), 1.49 (s, 9H), 1.33 (m, J=5.5 Hz, 2H), 1.07 (d, J=5.1 Hz, 3H), 0.97 (t, J=5.5 Hz, 3H). $[\alpha]_D^{20}$ −49 (c 0.37, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{24}H_{33}N_3O_5$: C, 64.99; H, 7.50; N, 9.47. Found: C, 64.80; H, 7.39; N, 9.62.

3.5. General procedure for the preparation of *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-amino acids (7a–t)

At 0 °C, to the solution of 2.5 mmol of **6a–t** in 4 ml of methanol and 2 ml of chloroform, 0.45 g (11.34 mmol) of NaOH was added. The reaction mixture was stirred at 0 °C for 70 min and TLC analysis (chloroform/methanol, 30:1) indicated complete disappearance of **3a–t**. On evaporation, the residue was dissolved in 30 ml of water and extracted with ethyl acetate (3×20 ml). The organic phase was washed successively with 5% sodium bicarbonate, 5% citric acid, and saturated sodium chloride and then dried over anhydrous sodium sulfate. After filtration and evaporation under reduced pressure, the title compound was obtained as powder.

3.5.1. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-alanine (7a). Yield 79%. Mp 169–171 °C;

ESIMS: 388 $[M+H]^+$; IR (KBr): 3439, 3234, 3215, 3000, 2952, 2847, 1732, 1645, 1602, 1453, 1390, 1373, 1061, 904 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.02 (s, 1H), 9.95 (s, 1H), 7.98 (s, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.17 (t, J=7.9 Hz, 1H), 7.03 (d, J=7.9 Hz, 1H), 6.94 (d, J=7.6 Hz, 1H), 4.93 (d, J=5.4 Hz, 1H), 4.66 (m, J=5.4 Hz, 1H), 4.27 (d, J=6.3 Hz, 2H), 2.97 (d, J=9.5 Hz, 2H), 1.48 (d, J=5.4 Hz, 3H), 1.45 (s, 9H). $[\alpha]_D^{20}$ −46 (c 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{20}H_{25}N_3O_5$: C, 62.00; H, 6.50; N, 10.85. Found: C, 62.18; H, 6.39; N, 10.71.

3.5.2. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-phenylalanine (7b). Yield 94%. Mp 129–131 °C; ESIMS: 464 $[M+H]^+$; IR (KBr): 3446, 3205, 3006, 2948, 2847, 1731, 1645, 1603, 1451, 1392, 1370, 1069, 904 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.94 (s, 1H), 9.93 (s, 1H), 7.97 (s, 1H), 7.30 (t, J=7.3 Hz, 1H), 7.26 (t, J=7.4 Hz, 2H), 7.17 (t, J=7.6 Hz, 1H), 7.15 (d, J=7.4 Hz, 2H), 7.10 (t, J=7.4 Hz, 1H), 7.02 (t, J=7.4 Hz, 1H), 6.97 (d, J=7.4 Hz, 1H), 4.93 (d, J=5.2 Hz, 1H), 4.78 (t, J=5.2 Hz, 1H), 4.27 (d, J=5.2 Hz, 2H), 3.07 (d, J=4.5 Hz, 2H), 2.98 (d, J=5.2 Hz, 2H), 1.49 (s, 9H). $[\alpha]_D^{20}$ −30 (c 0.36, $CHCl_3/CH_3OH$, 1:1, v/v); $[\alpha]_D^{20}$ −66 (c 0.36, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{26}H_{29}N_3O_5$: C, 67.37; H, 6.31; N, 9.07. Found: C, 67.22; H, 6.39; N, 10.21.

3.5.3. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-valine (7c). Yield 71%. Mp 148–150 °C; ESIMS: 416 $[M+H]^+$; IR (KBr): 3441, 3236, 3212, 3002, 2951, 2845, 1731, 1643, 1600, 1450, 1392, 1374, 1060, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.94 (s, 1H), 9.23 (s, 1H), 7.96 (s, 1H), 7.29 (t, J=7.5 Hz, 1H), 7.18 (t, J=7.6 Hz, 1H), 7.06 (d, J=7.4 Hz, 1H), 6.97 (d, J=7.5 Hz, 1H), 4.95 (d, J=5.2 Hz, 1H), 4.48 (d, J=5.2 Hz, 1H), 4.27 (d, J=5.1 Hz, 2H), 2.92 (d, J=5.5 Hz, 2H), 2.78 (m, J=4.5 Hz, 1H), 1.49 (s, 9H), 1.25 (d, J=5.6 Hz, 6H). $[\alpha]_D^{20}$ −72 (c 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{22}H_{29}N_3O_5$: C, 63.60; H, 7.04; N, 10.11. Found: C, 63.42; H, 7.19; N, 10.21.

3.5.4. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-serine (7d). Yield 84%. Mp 136–138 °C; ESIMS: 390 $[M+H]^+$; IR (KBr): 3437, 3236, 3213, 3005, 2950, 2846, 1730, 1641, 1600, 1451, 1392, 1370, 1058, 897 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.92 (s, 1H), 9.93 (s, 1H), 7.97 (s, 1H), 7.30 (t, J=7.3 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 7.06 (d, J=7.6 Hz, 1H), 6.98 (d, J=7.3 Hz, 1H), 4.92 (d, J=5.5 Hz, 1H), 4.46 (t, J=5.2 Hz, 1H), 4.27 (d, J=5.0 Hz, 2H), 4.06 (d, J=5.1 Hz, 2H), 2.93 (d, J=5.4 Hz, 2H), 2.07 (s, 1H), 1.51 (s, 9H). $[\alpha]_D^{20}$ −70 (c 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{20}H_{25}N_3O_6$: C, 59.54; H, 6.25; N, 10.42. Found: C, 59.42; H, 6.19; N, 10.29.

3.5.5. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-threonine (7e). Yield 78%. Mp 143–145 °C; ESIMS: 405 $[M+H]^+$; IR (KBr): 3444, 3235, 3217, 3005, 2950, 2843, 1730, 1641, 1600, 1450, 1389, 1370, 1055, 896 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.97 (s, 1H), 8.92 (s, 1H), 7.95 (s, 1H), 7.29 (t, J=7.2 Hz, 1H), 7.15 (t, J=7.4 Hz, 1H), 7.05 (d, J=7.4 Hz, 1H), 6.98 (d, J=7.2 Hz, 1H), 4.89 (d, J=5.3 Hz, 1H), 4.46 (d, J=5.4 Hz, 1H), 4.37 (m, J=5.1 Hz, 1H), 4.27 (d, J=4.8 Hz, 2H), 2.95 (d, J=5.5 Hz, 2H), 2.16 (s, 1H), 1.48 (s, 9H), 1.26 (d, J=5.2 Hz, 3H). $[\alpha]_D^{20}$ −49 (c 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.28; H, 6.39; N, 10.16.

3.5.6. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-tyrosine (7f). Yield 67%. Mp 147–149 °C; ESIMS: 480 $[M+H]^+$; IR (KBr): 3441, 3236, 3217, 3004, 2955, 2846, 1731, 1647, 1600, 1450, 1392, 1371, 1058, 899 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.97 (s, 1H), 9.60 (s, 1H), 8.15 (s, 1H), 7.32 (t, J=7.2 Hz, 1H), 7.14 (t, J=7.4 Hz, 1H), 7.01 (d, J=7.2 Hz, 1H), 6.96 (d, J=7.2 Hz, 1H), 6.94 (d, J=7.5 Hz, 2H), 6.88 (d, J=7.2 Hz, 2H), 5.03 (s, 1H), 4.94 (d, J=5.2 Hz, 1H), 4.84 (d, J=5.3 Hz, 1H), 4.27 (d, J=5.2 Hz, 2H), 3.07 (m, J=3.4 Hz, 2H), 2.92 (d, J=4.5 Hz, 2H), 1.48 (s, 9H). $[\alpha]_D^{20}$ −61 (c 0.36, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{26}H_{29}N_3O_6$: C, 65.12; H, 6.10; N, 8.76. Found: C, 65.28; H, 6.17; N, 8.59.

3.5.7. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-proline (7g). Yield 83%. Mp 136–138 °C; ESIMS: 414 $[M+H]^+$; IR (KBr): 3440, 3236, 3217, 3004, 2956, 2841, 1735, 1641, 1605, 1450, 1392, 1370, 1044, 897 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.95 (s, 1H), 9.70 (s, 1H), 7.32 (t, J=7.2 Hz, 1H), 7.14 (t, J=7.5 Hz, 1H), 7.08 (d, J=7.5 Hz, 1H), 6.96 (d, J=7.2 Hz, 1H), 4.92 (d, J=5.1 Hz, 1H), 4.32 (t, J=5.3 Hz, 1H), 4.22 (m, J=5.3 Hz, 2H), 3.47 (t, J=5.2 Hz, 2H), 2.95 (d, J=5.2 Hz, 2H), 2.17 (dd, J=5.2, 3.4 Hz, 2H), 1.94 (t, J=4.5 Hz, 2H), 1.47 (s, 9H). $[\alpha]_D^{20}$ −49 (c 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16. Found: C, 64.14; H, 6.47; N, 10.32.

3.5.8. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-cysteine (7h). Yield 78%. Mp 150–152 °C; ESIMS: 420 $[M+H]^+$; IR (KBr): 3436, 3232, 3217, 3004, 2950, 2844, 1731, 1647, 1600, 1455, 1392, 1375, 1058, 902 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.89 (s, 1H), 9.95 (s, 1H), 7.99 (s, 1H), 7.27 (t, J=7.3 Hz, 1H), 7.15 (t, J=7.6 Hz, 1H), 7.05 (d, J=7.6 Hz, 1H), 6.95 (t, J=7.2 Hz, 1H), 4.91 (t, J=5.0 Hz, 1H), 4.75 (t, J=5.2 Hz, 1H), 4.24 (m, J=5.0 Hz, 2H), 3.06 (d, J=5.0 Hz, 2H), 2.89 (d, J=4.5 Hz, 2H), 1.55 (s, 1H), 1.52 (s, 9H). $[\alpha]_D^{20}$ −45 (c 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{20}H_{25}N_3O_5S$: C, 57.26; H, 6.01; N, 10.02. Found: C, 57.19; H, 6.13; N, 10.12.

3.5.9. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-methionine (7i). Yield 72%. Mp 148–150 °C; ESIMS: 448 $[M+H]^+$; IR (KBr): 3436, 3232, 3213, 3007, 2953, 2849, 1735, 1648, 1600, 1450, 1393, 1375, 1055, 897 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.01 (s, 1H), 9.97 (s, 1H), 8.01 (s, 1H), 7.33 (t, J=7.0 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.05 (d, J=7.5 Hz, 1H), 6.95 (t, J=7.0 Hz, 1H), 4.44 (t, J=5.5 Hz, 1H), 4.25 (m, J=5.2 Hz, 1H), 4.23 (m, J=5.0 Hz, 2H), 2.89 (d, J=4.4 Hz, 2H), 2.46 (t, J=5.4 Hz, 2H), 2.16 (m, J=5.6 Hz, 2H), 2.09 (s, 3H), 1.50 (s, 9H). $[\alpha]_D^{20}$ −38 (c 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{22}H_{29}N_3O_5S$: C, 59.04; H, 6.53; N, 9.39. Found: C, 59.20; H, 6.44; N, 9.22.

3.5.10. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-glutamic acid (7j). Yield 76%. Mp 160–162 °C; ESIMS: 446 $[M+H]^+$; IR (KBr): 3444, 3231, 3212, 3008, 2954, 2843, 1730, 1642, 1600, 1450, 1391, 1371, 1058, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.02 (s, 2H), 9.87 (s, 1H), 8.11 (s, 1H), 7.28 (t, *J*=7.2 Hz, 1H), 7.14 (t, *J*=7.2 Hz, 1H), 7.06 (d, *J*=7.4 Hz, 1H), 6.97 (t, *J*=7.2 Hz, 1H), 4.90 (t, *J*=5.1 Hz, 1H), 4.42 (t, *J*=5.4 Hz, 1H), 4.21 (d, *J*=5.1 Hz, 2H), 2.87 (d, *J*=5.3 Hz, 2H), 2.22 (t, *J*=5.2 Hz, 2H), 2.08 (t, *J*=5.2 Hz, 2H), 1.47 (s, 9H). $[\alpha]_D^{20}$ −51 (*c* 0.33, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{22}H_{27}N_3O_7$: C, 59.32; H, 6.11; N, 9.43. Found: C, 59.24; H, 6.01; N, 9.29.

3.5.11. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-aspartic acid (7k). Yield 72%. Mp 141–143 °C; ESIMS: 432 $[M+H]^+$; IR (KBr): 3442, 3236, 3217, 3005, 2950, 2843, 1728, 1642, 1600, 1450, 1392, 1370, 1058, 896 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.99 (s, 2H), 9.94 (s, 1H), 7.98 (s, 1H), 7.26 (t, *J*=7.1 Hz, 1H), 7.11 (t, *J*=7.1 Hz, 1H), 7.05 (d, *J*=7.2 Hz, 1H), 6.94 (d, *J*=7.2 Hz, 1H), 4.87 (t, *J*=5.2 Hz, 1H), 4.76 (t, *J*=5.3 Hz, 1H), 4.20 (m, *J*=4.8 Hz, 2H), 2.89 (d, *J*=5.2 Hz, 2H), 2.66 (d, *J*=5.2 Hz, 2H), 1.47 (s, 9H). $[\alpha]_D^{20}$ −47 (*c* 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{21}H_{25}N_3O_7$: C, 58.46; H, 5.84; N, 9.74. Found: C, 58.55; H, 6.02; N, 9.91.

3.5.12. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-histidine (7l). Yield 76%. Mp 156–158 °C; ESIMS: 454 $[M+H]^+$; IR (KBr): 3445, 3231, 3212, 3007, 2947, 2842, 1730, 1642, 1600, 1450, 1388, 1370, 1059, 899 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.85 (s, 1H), 11.62 (s, 1H), 9.94 (s, 1H), 7.89 (s, 1H), 7.45 (s, 1H), 7.29 (t, *J*=7.2 Hz, 1H), 7.15 (t, *J*=7.5 Hz, 1H), 7.06 (d, *J*=7.5 Hz, 1H), 6.98 (d, *J*=7.2 Hz, 1H), 6.82 (s, 1H), 4.89 (t, *J*=5.0 Hz, 1H), 4.82 (t, *J*=5.1 Hz, 1H), 4.20 (m, *J*=5.1 Hz, 2H), 3.02 (d, *J*=5.0 Hz, 2H), 2.92 (d, *J*=5.2 Hz, 2H), 1.50 (s, 9H). $[\alpha]_D^{20}$ −50 (*c* 0.36, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{23}H_{27}N_5O_5$: C, 60.92; H, 6.00; N, 15.44. Found: C, 61.05; H, 6.09; N, 15.26.

3.5.13. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-tryptophan (7m). Yield 70%. Mp 158–160 °C; ESIMS: 503 $[M+H]^+$; IR (KBr): 3445, 3238, 3217, 3008, 2951, 2842, 1728, 1641, 1600, 1450, 1393, 1370, 1058, 897 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.98 (s, 1H), 9.87 (s, 1H), 9.84 (s, 1H), 8.01 (s, 1H), 7.30 (t, *J*=7.1 Hz, 1H), 7.16 (t, *J*=7.1 Hz, 1H), 7.14 (t, *J*=7.4 Hz, 1H), 7.12 (t, *J*=7.2 Hz, 1H), 7.06 (d, *J*=7.4 Hz, 1H), 7.05 (d, *J*=7.2 Hz, 1H), 6.99 (d, *J*=7.1 Hz, 1H), 6.96 (d, *J*=7.1 Hz, 1H), 6.82 (s, 1H), 4.89 (t, *J*=5.2 Hz, 1H), 4.84 (t, *J*=5.1 Hz, 1H), 4.25 (m, *J*=5.0 Hz, 2H), 2.91 (d, *J*=5.0 Hz, 2H), 2.88 (d, *J*=5.1 Hz, 2H), 1.53 (s, 9H). $[\alpha]_D^{20}$ −47 (*c* 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{28}H_{30}N_4O_5$: C, 66.92; H, 6.02; N, 11.15. Found: C, 66.79; H, 5.94; N, 11.27.

3.5.14. *N*-(*N*-Boc-3*S*-1,2,3,4-tetrahydro-β-carboline-3-carboxyl)-L-arginine (7n). Yield 81%. Mp 144–146 °C; ESIMS: 473 $[M+H]^+$; IR (KBr): 3441, 3230, 3212, 3007, 2950, 2844, 1730, 1640, 1600, 1450, 1392, 1375, 1057, 896 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.94 (s, 1H), 8.55 (s, 2H), 8.31 (s, 2H), 8.23 (s, 1H), 7.98 (s, 1H), 7.29 (t, *J*=7.5 Hz, 1H), 7.11 (t, *J*=7.6 Hz, 1H), 7.02 (d, *J*=7.6 Hz, 1H), 6.98 (d, *J*=7.5 Hz, 1H), 4.87 (t, *J*=5.4 Hz, 1H), 4.41 (t, *J*=4.3 Hz, 1H), 4.25 (d, *J*=4.8 Hz, 2H), 2.89 (d, *J*=4.9 Hz, 2H), 2.66 (t, *J*=5.2 Hz, 2H), 1.81 (m, *J*=5.1 Hz, 2H), 1.59 (m, *J*=5.3 Hz, 2H), 1.56 (s, 9H). $[\alpha]_D^{20}$ −66 (*c* 0.37, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{23}H_{32}N_6O_5$: C, 58.46; H, 6.83; N, 17.78. Found: C, 58.38; H, 6.96; N, 17.57.

3.5.15. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-glycine (7o). Yield 95%. Mp 148–150 °C; ESIMS: 374 $[M+H]^+$; IR (KBr): 3444, 3230, 3008, 2942, 2841, 1730, 1602, 1455, 1391, 1370, 1064, 898 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.03 (s, 1H), 9.98 (s, 1H), 8.01 (s, 1H), 7.29 (t, *J*=7.5 Hz, 1H), 7.18 (t, *J*=7.6 Hz, 1H), 6.97 (d, *J*=7.6 Hz, 1H), 6.85 (d, *J*=7.6 Hz, 1H), 4.90 (d, *J*=5.4 Hz, 1H), 4.24 (dd, *J*=10.2, 4.5 Hz, 1H), 4.17 (s, 2H), 4.16 (dd, *J*=10.2, 3.7 Hz, 1H), 2.93 (d, *J*=10.0 Hz, 2H), 1.46 (s, 9H). $[\alpha]_D^{20}$ −98 (*c* 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{19}H_{23}N_3O_5$: C, 61.11; H, 6.21; N, 11.25. Found: C, 61.30; H, 6.40; N, 11.09.

3.5.16. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-lys(*Z*)-OH (7p). Yield 92%. Mp 155–157 °C; ESIMS: 579 $[M+H]^+$; IR (KBr): 3438, 3234, 3215, 3009, 2944, 2845, 1733, 1602, 1453, 1390, 1372, 1064, 899 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.88 (s, 1H), 9.97 (s, 1H), 8.01 (s, 1H), 7.98 (s, 1H), 7.29 (t, *J*=7.5 Hz, 1H), 7.21 (t, *J*=7.3 Hz, 1H), 7.18 (t, *J*=7.5 Hz, 1H), 7.17 (d, *J*=7.3 Hz, 2H), 7.16 (t, *J*=7.3 Hz, 2H), 6.98 (d, *J*=7.5 Hz, 1H), 6.88 (d, *J*=7.5 Hz, 1H), 5.33 (s, 2H), 4.92 (d, *J*=5.6 Hz, 1H), 4.45 (t, *J*=4.6 Hz, 1H), 4.23 (dd, *J*=10.0, 4.5 Hz, 1H), 4.19 (dd, *J*=10.0, 3.7 Hz, 1H), 2.94 (t, *J*=4.6 Hz, 2H), 2.95 (d, *J*=10.0 Hz, 2H), 1.84 (m, *J*=4.6 Hz, 2H), 1.54 (m, *J*=4.6 Hz, 2H), 1.46 (s, 9H), 1.29 (m, *J*=4.6 Hz, 2H). $[\alpha]_D^{20}$ −34 (*c* 0.36, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{31}H_{38}N_4O_7$: C, 64.34; H, 6.62; N, 9.68. Found: C, 64.18; H, 6.44; N, 9.83.

3.5.17. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-glutamine (7q). Yield 90%. Mp 129–131 °C; ESIMS: 445 $[M+H]^+$; IR (KBr): 3448, 3230, 3215, 3005, 2942, 2833, 1738, 1642, 1604, 1450, 1390, 1372, 1063, 901 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.96 (s, 1H), 9.88 (s, 1H), 8.02 (s, 1H), 7.28 (t, *J*=7.5 Hz, 1H), 7.21 (t, *J*=7.5 Hz, 1H), 7.01 (d, *J*=7.5 Hz, 1H), 6.82 (d, *J*=7.5 Hz, 1H), 6.02 (s, 2H), 4.90 (d, *J*=5.6 Hz, 1H), 4.45 (t, *J*=5.4 Hz, 1H), 4.25 (d, *J*=5.5 Hz, 2H), 2.92 (d, *J*=5.5 Hz, 2H), 2.17 (t, *J*=5.5 Hz, 2H), 2.07 (t, *J*=5.5 Hz, 2H), 1.42 (s, 9H). $[\alpha]_D^{20}$ −54 (*c* 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{22}H_{28}N_4O_6$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.63; H, 6.20; N, 12.79.

3.5.18. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-asparagine (7r). Yield 92%. Mp 155–157 °C; ESIMS: 431 $[M+H]^+$; IR (KBr): 3445, 3225, 3008, 2939, 2834, 1735, 1639, 1602, 1452, 1391, 1370, 1060, 905 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.92 (s, 1H), 9.86 (s, 1H), 8.00 (s, 1H), 7.27 (t, *J*=7.3 Hz, 1H), 7.19 (t, *J*=7.3 Hz, 1H), 7.02 (d, *J*=7.3 Hz, 1H), 6.80 (d, *J*=7.3 Hz, 1H), 6.04 (s, 2H), 4.92 (d, *J*=5.5 Hz, 1H), 4.46 (t, *J*=5.5 Hz, 1H), 4.23 (d, *J*=5.5 Hz, 2H), 2.94 (d,

J=5.5 Hz, 2H), 2.18 (t, J=5.5 Hz, 2H), 1.52 (s, 9H). $[\alpha]_D^{20}$ −44 (c 0.33, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{21}H_{26}N_4O_6$: C, 58.59; H, 6.09; N, 13.02. Found: C, 58.42; H, 6.00; N, 13.22.

3.5.19. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-leucine (7s). Yield 95%. Mp 144–146 °C; ESIMS: 430 $[M+H]^+$; IR (KBr): 3441, 3233, 3207, 3010, 2950, 2840, 1731, 1642, 1600, 1455, 1390, 1375, 1060, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.96 (s, 1H), 9.90 (s, 1H), 8.02 (s, 1H), 7.22 (t, J=7.3 Hz, 1H), 7.17 (t, J=7.3 Hz, 1H), 6.91 (d, J=7.3 Hz, 1H), 6.82 (d, J=7.3 Hz, 1H), 4.93 (t, J=5.5 Hz, 1H), 4.40 (t, J=5.5 Hz, 1H), 4.17 (dd, J=10.0, 4.5 Hz, 1H), 4.00 (dd, J=10.0, 3.8 Hz, 1H), 2.94 (d, J=5.4 Hz, 2H), 2.80 (d, J=5.4 Hz, 2H), 1.45 (s, 9H), 1.39 (m, J=5.4 Hz, 1H), 1.11 (d, J=5.4 Hz, 6H). $[\alpha]_D^{20}$ −39 (c 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{23}H_{31}N_3O_5$: C, 64.32; H, 7.27; N, 9.78. Found: C, 64.48; H, 7.37; N, 9.64.

3.5.20. *N*-[(3*S*)-*N*-Boc-1,2,3,4-tetrahydro-β-carboline-3-carboxyl]-L-isoleucine (7t). Yield 96%. Mp 144–146 °C; ESIMS: 430 $[M+H]^+$; IR (KBr): 3445, 3237, 3212, 3003, 2955, 2844, 1734, 1645, 1602, 1457, 1382, 1062, 904 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.98 (s, 1H), 9.93 (s, 1H), 8.04 (s, 1H), 7.26 (t, J=7.3 Hz, 1H), 7.21 (t, J=7.3 Hz, 1H), 6.94 (d, J=7.3 Hz, 1H), 6.85 (d, J=7.3 Hz, 1H), 4.97 (t, J=5.4 Hz, 1H), 4.43 (t, J=5.4 Hz, 1H), 4.20 (dd, J=10.2, 4.3 Hz, 1H), 4.02 (dd, J=10.2, 3.9 Hz, 1H), 2.96 (d, J=5.3 Hz, 2H), 1.82 (m, J=5.3 Hz, 1H), 1.47 (s, 9H), 1.30 (m, J=5.3 Hz, 2H), 1.09 (d, J=5.2 Hz, 3H), 0.95 (t, J=5.2 Hz, 3H). $[\alpha]_D^{20}$ −57 (c 0.37, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{23}H_{31}N_3O_5$: C, 64.32; H, 7.27; N, 9.78. Found: C, 4.16; H, 7.09; N, 9.62.

3.6. General procedure for the preparation of *N*-[(3*S*)-1,2,3,4-tetrahydro-β-carboline- 3-carboxyl]amino acids 8a–t from 7a–t

At 0 °C, to the solution of 2.5 mmol of **7a–t** in 4 ml of methanol and 2 ml of chloroform, 450 mg (11.34 mmol) of NaOH was added. The reaction mixture was stirred at 0 °C for 70 min and TLC (chloroform/methanol, 30:1) indicated the completion of the reaction. The reaction mixture was adjusted to pH 2 with hydrochloric acid (2 mol/l). Upon evaporation, the residue was dissolved in 30 ml of ethyl acetate. The organic phase was washed with saturated aqueous sodium chloride and then dried over anhydrous sodium sulfate. After filtration, the title compound was obtained as pale yellow powder upon evaporation under reduced pressure and purified with flash chromatography.

3.6.1. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-alanine (8a). Yield 94%. Mp 177–179 °C; ESIMS: 288 $[M+H]^+$; IR (KBr): 3439, 3234, 3215, 3000, 2952, 2847, 1732, 1645, 1602, 1453, 1061, 904 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=11.06 (s, 1H), 10.01 (s, 1H), 9.97 (s, 1H), 8.01 (s, 1H), 7.29 (t, J=6.5 Hz, 1H), 7.18 (t, J=7.8 Hz, 1H), 6.84 (d, J=7.8 Hz, 1H), 6.80 (d, J=7.6 Hz, 1H), 4.64 (m, J=5.4 Hz, 1H), 3.96 (m, J=5.5 Hz, 1H), 3.86 (d, J=5.3 Hz, 2H), 2.83 (d, J=5.4 Hz, 2H), 1.45 (d, J=5.4 Hz, 3H). $[\alpha]_D^{20}$ −80 (c 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.55; H, 5.79; N, 14.55.

3.6.2. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-phenylalanine (8b). Yield 95%. ESIMS: 364 $[M+H]^+$; IR (KBr): 3435, 3231, 3213, 3003, 2950, 2844, 1730, 1642, 1600, 1450, 1060, 901 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=11.33 (s, 1H), 10.05 (s, 1H), 9.93 (s, 1H), 8.01 (s, 1H), 7.33 (t, J=6.8 Hz, 1H), 7.30 (t, J=6.4 Hz, 2H), 7.20 (t, J=7.6 Hz, 1H), 7.17 (d, J=7.8 Hz, 2H), 7.10 (t, J=6.8 Hz, 1H), 7.02 (d, J=7.6 Hz, 1H), 6.89 (d, J=7.4 Hz, 1H), 4.86 (t, J=5.4 Hz, 1H), 4.00 (m, J=5.4 Hz, 1H), 3.88 (d, J=6.2 Hz, 2H), 3.07 (d, J=6.5 Hz, 2H), 2.81 (d, J=6.2 Hz, 2H). $[\alpha]_D^{20}$ −30 (c 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.56; H, 5.75; N, 11.34.

3.6.3. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-valine (8c). Yield 95%. ESIMS: 316 $[M+H]^+$; IR (KBr): 3441, 3236, 3212, 3002, 2951, 2845, 1731, 1643, 1600, 1450, 1060, 900 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=11.68 (s, 1H), 10.19 (s, 1H), 9.88 (s, 1H), 8.03 (s, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.17 (t, J=7.8 Hz, 1H), 7.05 (d, J=7.4 Hz, 1H), 6.98 (d, J=7.4 Hz, 1H), 4.48 (t, J=5.2 Hz, 1H), 3.94 (t, J=5.2 Hz, 1H), 3.90 (d, J=5.2 Hz, 2H), 2.82 (d, J=5.4 Hz, 2H), 2.80 (m, J=6.9 Hz, 1H), 1.06 (d, J=6.9 Hz, 6H). $[\alpha]_D^{20}$ −70 (c 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.89; H, 6.85; N, 13.44.

3.6.4. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-serine (8d). Yield 89%. ESIMS: 304 $[M+H]^+$; IR (KBr): 3437, 3236, 3213, 3005, 2950, 2846, 1730, 1641, 1600, 1451, 1058, 897 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=11.50 (s, 1H), 10.19 (s, 1H), 9.96 (s, 1H), 8.10 (s, 1H), 7.31 (t, J=7.5 Hz, 1H), 7.18 (t, J=7.8 Hz, 1H), 7.09 (d, J=7.8 Hz, 1H), 6.89 (d, J=7.5 Hz, 1H), 4.59 (t, J=5.1 Hz, 1H), 4.04 (d, J=5.1 Hz, 2H), 3.96 (t, J=5.1 Hz, 1H), 3.81 (d, J=5.9 Hz, 2H), 2.78 (d, J=5.5 Hz, 2H), 2.30 (s, 1H). $[\alpha]_D^{20}$ −70 (c 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.56; H, 5.81; N, 13.79.

3.6.5. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-threonine (8e). Yield 88%. ESIMS: 318 $[M+H]^+$; IR (KBr): 3446, 3238, 3213, 3007, 2952, 2840, 1732, 1645, 1602, 1455, 1372, 1051, 895 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.99 (s, 1H), 8.90 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.27 (t, J=7.0 Hz, 1H), 7.13 (t, J=7.2 Hz, 1H), 7.02 (d, J=7.2 Hz, 1H), 6.96 (d, J=7.0 Hz, 1H), 4.87 (d, J=5.2 Hz, 1H), 4.44 (d, J=5.2 Hz, 1H), 4.35 (m, J=5.2 Hz, 1H), 4.23 (d, J=4.7 Hz, 2H), 2.97 (d, J=5.4 Hz, 2H), 2.14 (s, 1H), 1.25 (d, J=5.1 Hz, 3H). $[\alpha]_D^{20}$ −62 (c 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.40; H, 6.12; N, 13.41.

3.6.6. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-tyrosine (8f). Yield 89%. ESIMS: 380 $[M+H]^+$; IR (KBr): 3443, 3234, 3215, 3002, 2950, 2842, 1735, 1643, 1602, 1453, 1372, 1055, 896 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.05 (s, 1H), 8.98 (s, 1H), 8.17 (s, 1H), 8.03 (s, 1H), 7.30 (t, J=7.0 Hz, 1H), 7.10 (t, J=7.2 Hz, 1H), 7.00 (d, J=7.0 Hz, 1H), 6.97 (d, J=7.0 Hz, 1H), 6.90

(d, J=7.2 Hz, 2H), 6.85 (d, J=7.0 Hz, 2H), 5.00 (s, 1H), 4.92 (d, J=5.0 Hz, 1H), 4.80 (d, J=5.1 Hz, 1H), 4.25 (d, J=5.0 Hz, 2H), 3.05 (m, J=3.5 Hz, 2H), 2.90 (d, J=4.4 Hz, 2H). $[\alpha]_D^{20}$ −69 (*c* 0.36, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.62; H, 6.67; N, 11.24.

3.6.7. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-proline (8g). Yield 94%. ESIMS: 314 $[M+H]^+$; IR (KBr): 3443, 3232, 3215, 3000, 2951, 2845, 1730, 1644, 1603, 1452, 1046, 899 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.98 (s, 1H), 8.96 (s, 1H), 8.13 (s, 1H), 7.30 (t, J=7.0 Hz, 1H), 7.12 (t, J=7.2 Hz, 1H), 7.02 (d, J=7.2 Hz, 1H), 6.94 (d, J=7.0 Hz, 1H), 4.94 (d, J=5.2 Hz, 1H), 4.35 (t, J=5.1 Hz, 1H), 4.28 (m, J=5.1 Hz, 2H), 3.44 (t, J=5.3 Hz, 2H), 2.92 (d, J=5.1 Hz, 2H), 2.13 (dd, J=5.0, 3.5 Hz, 2H), 1.92 (t, J=4.4 Hz, 2H). $[\alpha]_D^{20}$ −60 (*c* 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41. Found: C, 65.01; H, 6.03; N, 13.58.

3.6.8. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-cysteine (8h). Yield 92%. ESIMS: 320 $[M+H]^+$; IR (KBr): 3439, 3235, 3212, 3005, 2953, 2840, 1734, 1644, 1603, 1450, 1055, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.99 (s, 1H), 8.98 (s, 1H), 8.10 (s, 1H), 8.01 (s, 1H), 7.25 (t, J=7.1 Hz, 1H), 7.13 (t, J=7.2 Hz, 1H), 7.02 (d, J=7.2 Hz, 1H), 6.98 (t, J=7.0 Hz, 1H), 4.93 (t, J=5.0 Hz, 1H), 4.77 (t, J=5.1 Hz, 1H), 4.21 (m, J=5.1 Hz, 2H), 3.09 (d, J=5.1 Hz, 2H), 2.92 (d, J=4.6 Hz, 2H), 1.53 (s, 1H). $[\alpha]_D^{20}$ −57 (*c* 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{15}H_{17}N_3O_3S$: C, 56.41; H, 5.37; N, 13.16. Found: C, 56.58; H, 5.44; N, 113.33.

3.6.9. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-methionine (8i). Yield 90%. ESIMS: 348 $[M+H]^+$; IR (KBr): 3441, 3236, 3215, 3002, 2950, 2843, 1732, 1645, 1604, 1452, 1052, 899 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.03 (s, 1H), 8.97 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.29 (t, J=7.1 Hz, 1H), 7.15 (t, J=7.2 Hz, 1H), 7.02 (d, J=7.2 Hz, 1H), 6.93 (t, J=7.1 Hz, 1H), 4.42 (t, J=5.4 Hz, 1H), 4.25 (m, J=5.1 Hz, 1H), 4.20 (m, J=5.1 Hz, 2H), 2.92 (d, J=4.6 Hz, 2H), 2.42 (t, J=5.2 Hz, 2H), 2.13 (m, J=5.4 Hz, 2H), 2.07 (s, 3H). $[\alpha]_D^{20}$ −46 (*c* 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{17}H_{21}N_3O_3S$: C, 58.77; H, 6.09; N, 12.09. Found: C, 58.61; H, 6.00; N, 12.26.

3.6.10. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-glutamic acid (8j). Yield 92%. ESIMS: 346 $[M+H]^+$; IR (KBr): 3445, 3234, 3210, 3002, 2951, 2840, 1734, 1645, 1602, 1453, 1052, 903 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.00 (s, 2H), 8.97 (s, 1H), 8.10 (s, 1H), 8.00 (s, 1H), 7.25 (t, J=7.0 Hz, 1H), 7.11 (t, J=7.0 Hz, 1H), 7.02 (d, J=7.2 Hz, 1H), 6.95 (t, J=7.0 Hz, 1H), 4.92 (t, J=5.2 Hz, 1H), 4.40 (t, J=5.2 Hz, 1H), 4.23 (d, J=5.2 Hz, 2H), 2.85 (d, J=5.1 Hz, 2H), 2.20 (t, J=5.3 Hz, 2H), 2.06 (t, J=5.1 Hz, 2H). $[\alpha]_D^{20}$ −57 (*c* 0.33, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{17}H_{19}N_3O_5$: C, 59.12; H, 5.55; N, 12.17. Found: C, 59.28; H, 5.64; N, 12.35.

3.6.11. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-aspartic acid (8k). Yield 92%. ESIMS: 332 $[M+H]^+$; IR (KBr): 3442, 3236, 3217, 3005, 2950, 2843, 1728, 1642, 1600, 1450, 1392, 1370, 1058, 896 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.99 (s, 2H), 9.94 (s, 1H), 7.98 (s, 1H), 7.26 (t, J=7.1 Hz, 1H), 7.11 (t, J=7.1 Hz, 1H), 7.05 (d, J=7.2 Hz, 1H), 6.94 (d, J=7.2 Hz, 1H), 4.87 (t, J=5.2 Hz, 1H), 4.76 (t, J=5.3 Hz, 1H), 4.20 (m, J=4.8 Hz, 2H), 2.89 (d, J=5.2 Hz, 2H), 2.66 (d, J=5.2 Hz, 2H), 1.47 (s, 9H). $[\alpha]_D^{20}$ −47 (*c* 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{21}H_{25}N_3O_7$: C, 58.46; H, 5.84; N, 9.74. Found: C, 58.55; H, 6.02; N, 9.91.

3.6.12. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-histidine (8l). Yield 92%. ESIMS: 354 $[M+H]^+$; IR (KBr): 3442, 3236, 3210, 3002, 2945, 2840, 1733, 1645, 1602, 1451, 1055, 901 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.92 (s, 1H), 11.02 (s, 1H), 9.90 (s, 1H), 8.00 (s, 1H), 7.85 (s, 1H), 7.47 (s, 1H), 7.27 (t, J=7.0 Hz, 1H), 7.13 (t, J=7.2 Hz, 1H), 7.02 (d, J=7.2 Hz, 1H), 6.95 (d, J=7.0 Hz, 1H), 6.84 (s, 1H), 4.85 (t, J=5.1 Hz, 1H), 4.80 (t, J=5.2 Hz, 1H), 4.23 (m, J=5.0 Hz, 2H), 3.05 (d, J=5.1 Hz, 2H), 2.93 (d, J=5.2 Hz, 2H). $[\alpha]_D^{20}$ −59 (*c* 0.36, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 61.35; H, 5.51; N, 19.67.

3.6.13. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-tryptophan (8m). Yield 90%. Mp 159–161 °C; ESIMS: 403 $[M+H]^+$; IR (KBr): 3445, 3238, 3217, 3008, 2951, 2842, 1728, 1641, 1600, 1450, 1058, 897 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=11.52 (s, 1H), 11.15 (s, 1H), 10.97 (s, 1H), 10.21 (s, 1H), 8.02 (s, 1H), 7.31 (t, J=7.2 Hz, 1H), 7.18 (t, J=7.3 Hz, 1H), 7.14 (t, J=7.5 Hz, 1H), 7.12 (t, J=7.5 Hz, 1H), 7.12 (d, J=7.5 Hz, 1H), 7.10 (d, J=7.5 Hz, 1H), 7.04 (d, J=7.5 Hz, 1H), 6.98 (d, J=7.2 Hz, 1H), 6.85 (s, 1H), 4.87 (t, J=5.5 Hz, 1H), 3.95 (t, J=5.5 Hz, 1H), 3.86 (d, J=5.4 Hz, 2H), 2.94 (d, J=5.4 Hz, 2H), 2.79 (d, J=5.5 Hz, 2H). $[\alpha]_D^{20}$ −64 (*c* 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{23}H_{22}N_4O_3$: C, 68.64; H, 5.51; N, 13.92. Found: C, 68.55; H, 5.43; N, 13.79.

3.6.14. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-arginine (8n). Yield 91%. ESIMS: 373 $[M+H]^+$; IR (KBr): 3443, 3235, 3214, 3002, 2953, 2840, 1732, 1644, 1602, 1454, 1052, 901 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.04 (s, 1H), 10.00 (s, 1H), 8.51 (s, 2H), 8.27 (s, 2H), 8.11 (s, 1H), 8.01 (s, 1H), 7.27 (t, J=7.2 Hz, 1H), 7.08 (t, J=7.2 Hz, 1H), 7.00 (d, J=7.3 Hz, 1H), 6.95 (d, J=7.2 Hz, 1H), 4.85 (t, J=5.3 Hz, 1H), 4.43 (t, J=4.2 Hz, 1H), 4.22 (d, J=4.6 Hz, 2H), 2.91 (d, J=4.8 Hz, 2H), 2.69 (t, J=5.1 Hz, 2H), 1.83 (m, J=5.1 Hz, 2H), 1.55 (m, J=5.1 Hz, 2H). $[\alpha]_D^{20}$ −57 (*c* 0.37, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{18}H_{24}N_6O_3$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.22; H, 6.61; N, 22.31.

3.6.15. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]glycine (8o). Yield 94%. Mp 181–183 °C; ESIMS: 274 $[M+H]^+$; IR (KBr): 3434, 3230, 3213, 3004, 2950, 2844, 1730, 1646, 1601, 1455, 1062, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.05 (s, 1H), 9.94 (s, 1H), 8.00 (s, 1H), 7.27 (t, J=7.6 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 6.95 (d, J=7.6 Hz, 1H), 6.87 (d, J=7.6 Hz, 1H), 4.16 (s, 2H), 4.08 (dd, J=5.4, 4.5 Hz, 1H), 3.89 (d, J=5.3 Hz, 2H), 2.83 (d, J=5.4 Hz, 2H), 2.05 (s, 1H). $[\alpha]_D^{20}$ −104 (*c* 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for

$C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.38; H, 5.38; N, 15.51.

3.6.16. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-Lys(*Z*)-OH (8p). Yield 90%. ESIMS: 479 $[M+H]^+$; IR (KBr): 3440, 3236, 3217, 3004, 2940, 2846, 1736, 1604, 1455, 1062, 898 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.92 (s, 1H), 9.95 (s, 1H), 8.03 (s, 1H), 8.00 (s, 1H), 7.27 (t, *J*=7.5 Hz, 1H), 7.20 (t, *J*=7.3 Hz, 1H), 7.19 (t, *J*=7.5 Hz, 1H), 7.17 (d, *J*=7.3 Hz, 2H), 7.14 (t, *J*=7.3 Hz, 2H), 6.96 (d, *J*=7.5 Hz, 1H), 6.89 (d, *J*=7.5 Hz, 1H), 5.35 (s, 2H), 4.46 (t, *J*=4.6 Hz, 1H), 3.99 (d, *J*=5.6 Hz, 1H), 3.88 (dd, *J*=10.0, 4.5 Hz, 1H), 3.86 (dd, *J*=10.0, 3.7 Hz, 1H), 2.96 (t, *J*=4.6 Hz, 2H), 2.83 (d, *J*=10.0 Hz, 2H), 1.80 (m, *J*=4.6 Hz, 2H), 2.10 (s, 1H), 1.56 (m, *J*=4.6 Hz, 2H), 1.29 (m, *J*=4.6 Hz, 2H). $[\alpha]_D^{20}$ −39 (*c* 0.38, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{26}H_{30}N_4O_5$: C, 65.26; H, 6.32; N, 11.71. Found: C, 65.41; H, 6.49; N, 11.53.

3.6.17. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-glutamine (8q). Yield 92%. ESIMS: 345 $[M+H]^+$; IR (KBr): 3443, 3236, 3219, 3001, 2945, 2830, 1733, 1645, 1601, 1452, 1065, 900 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.01 (s, 1H), 9.98 (s, 1H), 8.09 (s, 1H), 8.00 (s, 1H), 7.25 (t, *J*=7.2 Hz, 1H), 7.18 (t, *J*=7.2 Hz, 1H), 7.03 (d, *J*=7.2 Hz, 1H), 6.85 (d, *J*=7.2 Hz, 1H), 6.05 (s, 2H), 4.93 (d, *J*=5.5 Hz, 1H), 4.42 (t, *J*=5.2 Hz, 1H), 4.23 (d, *J*=5.3 Hz, 2H), 2.90 (d, *J*=5.3 Hz, 2H), 2.15 (t, *J*=5.3 Hz, 2H), 2.03 (t, *J*=5.2 Hz, 2H). $[\alpha]_D^{20}$ −63 (*c* 0.39, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 59.12; H, 5.77; N, 16.43.

3.6.18. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-asparagine (8r). Yield 94%. ESIMS: 331 $[M+H]^+$; IR (KBr): 3443, 3231, 3002, 2935, 2838, 1730, 1634, 1600, 1450, 1062, 901 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.03 (s, 1H), 9.98 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.25 (t, *J*=7.1 Hz, 1H), 7.15 (t, *J*=7.1 Hz, 1H), 7.00 (d, *J*=7.1 Hz, 1H), 6.83 (d, *J*=7.1 Hz, 1H), 6.06 (s, 2H), 4.91 (d, *J*=5.6 Hz, 1H), 4.42 (t, *J*=5.6 Hz, 1H), 4.25 (d, *J*=5.6 Hz, 2H), 2.92 (d, *J*=5.5 Hz, 2H), 2.15 (t, *J*=5.6 Hz, 2H). $[\alpha]_D^{20}$ −57 (*c* 0.33, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.34; H, 5.40; N, 16.80.

3.6.19. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-leucine (8s). Yield 92%. ESIMS: 330 $[M+H]^+$; IR (KBr): 3445, 3239, 3202, 3003, 2952, 2844, 1734, 1645, 1603, 1450, 1062, 901 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=11.03 (s, 1H), 9.99 (s, 1H), 8.10 (s, 1H), 8.00 (s, 1H), 7.25 (t, *J*=7.1 Hz, 1H), 7.15 (t, *J*=7.1 Hz, 1H), 6.93 (d, *J*=7.1 Hz, 1H), 6.80 (d, *J*=7.1 Hz, 1H), 4.91 (t, *J*=5.4 Hz, 1H), 4.43 (t, *J*=5.4 Hz, 1H), 4.15 (dd, *J*=10.1, 4.4 Hz, 1H), 4.02 (dd, *J*=10.1, 3.9 Hz, 1H), 2.92 (d, *J*=5.3 Hz, 2H), 2.83 (d, *J*=5.3 Hz, 2H), 1.35 (m, *J*=5.2 Hz, 1H), 1.13 (d, *J*=5.5 Hz, 6H). $[\alpha]_D^{20}$ −55 (*c* 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.78; H, 7.14; N, 12.61.

3.6.20. *N*-[(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxyl]-L-isoleucine (8t). Yield 95%. Mp 169–171 °C; ESIMS: 330 $[M+H]^+$; IR (KBr): 3436, 3232, 3217, 3008, 2950, 2840, 1730, 1645, 1602, 1453, 1382, 1065, 904 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.95 (s, 1H), 9.83 (s, 1H), 8.02 (s, 1H), 7.26 (t, *J*=7.3 Hz, 1H), 7.18 (t, *J*=7.3 Hz, 1H), 6.98 (d, *J*=7.3 Hz, 1H), 6.89 (d, *J*=7.3 Hz, 1H), 4.48 (t, *J*=5.2 Hz, 1H), 3.95 (t, *J*=5.3 Hz, 1H), 3.94 (d, *J*=5.2 Hz, 2H), 2.92 (d, *J*=5.3 Hz, 2H), 1.83 (m, *J*=5.3 Hz, 1H), 1.49 (s, 9H), 1.32 (m, *J*=5.2 Hz, 2H), 1.10 (d, *J*=5.2 Hz, 3H), 0.93 (t, *J*=5.2 Hz, 3H). $[\alpha]_D^{20}$ −67 (*c* 0.35, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.46; H, 7.15; N, 12.63.

3.7. General procedure for the preparation of (12a*S*)-3-substituted-1,4-dioxo-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]-pyrido-[3,4-b]indole (4a–t)

(A) While stirring at 0 °C, 2.0 mmol of compound **3** was dissolved in 10 ml of hydrogen chloride/ethyl acetate (5 mol/l). The reaction mixture was stirred at 0 °C for 10 min and at room temperature for 1 h and TLC (ethyl acetate/petroleum, 5:12) indicated the completion of the reaction. The reaction mixture was evaporated. After evaporation, the residue was diluted in 10 ml of ethyl acetate and then evaporated to dryness, and this procedure was repeated three times. The residue was dissolved in 20 ml of methanol, to which 2 ml of triethylamine was added. The solution was stirred at room temperature for 1 h and evaporated to give the title compounds as colorless powder. (B) At 0 °C, to the solution of 2.0 mmol of **8**, 297 mg (2.0 mmol) of HOBt and 515 mg (2.5 mmol) of DCC in 30 ml of anhydrous THF were added and stirred at pH 8–9 with *N*-methyl morpholine. The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 16 h, and TLC (ethyl acetate/petroleum, 5:12) indicated the completion of the reaction. Upon evaporation, the residue was dissolved in 30 ml of ethyl acetate. The solution was washed successively with 5% sodium bicarbonate, 5% citric acid, and saturated sodium chloride and the organic phase was separated and dried over anhydrous sodium sulfate. After filtration and evaporation under reduced pressure, the title compounds were obtained as pale yellow powder after purification with flash chromatography ($CHCl_3/CH_3OH$, 30:1).

3.7.1. (3*S*,12a*S*)-3-Methyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dion (4a). (A) Yield 96%, (B) yield 90%. Mp 233–235 °C, ESIMS: (*m*/*z*) 270 $[M+H]^+$; IR (KBr): 3337, 2926, 1678, 1455, 1326, 744 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ=10.97 (s, 1H), 8.46 (d, *J*=2.1 Hz, 1H), 7.46 (d, *J*=7.5 Hz, 1H), 7.35 (t, *J*=7.5 Hz, 1H), 7.07 (t, *J*=7.5 Hz, 1H), 6.96 (t, *J*=7.5 Hz, 1H), 5.33 (d, *J*=16.8 Hz, lH), 4.73 (m, *J*=6.9 Hz, 1H), 4.28 (dd, *J*=4.2, 11.7 Hz, 1H), 4.20 (d, *J*=16.5 Hz, 1H), 3.26 (dd, *J*=4.2, 15.0 Hz, 1H), 2.80 (t, *J*=4.8 Hz, 1H), 1.35 (d, *J*=6.9 Hz, 3H). ^{13}C NMR (DMSO-d_6, 300 MHz): δ=167.21, 166.82, 136.02, 134.55, 131.00, 126.26, 121.36, 120.12, 119.15, 111.09, 59.80, 52.98, 42.87, 24.75, 17.31. $[\alpha]_D^{20}$ −150 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.70; H, 5.41; N, 15.81.

3.7.2. (3*S*,12a*S*)-3-Benzyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4b). (A)

Yield 96%, (B) yield 95%. Mp 242–245 °C; EIMS: (*m/z*) 346 $[M+H]^+$; IR (KBr): 3328, 2936, 1669, 1455, 1328, 744 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ=10.81 (s, 1H), 8.46 (d, *J*=1.8 Hz, 1H), 7.42 (d, *J*=7.5 Hz, 1H), 7.31 (t, *J*=7.5 Hz, 1H), 7.22 (t, *J*=7.2 Hz, 2H), 7.14 (d, *J*=7.2 Hz, 2H), 7.06 (t, *J*=7.2 Hz, 1H), 7.02 (t, *J*=7.5 Hz, 1H), 6.93 (t, *J*=7.5 Hz, 1H), 5.32 (d, *J*=16.5 Hz, 1H), 4.37 (s, 2H), 4.07 (d, *J*=16.8 Hz, 1H), 3.98 (dd, *J*=11.7, 4.5 Hz, 1H), 3.17 (dd, *J*=13.2, 3.3 Hz, 1H), 2.88 (dd, *J*=13.5, 5.1 Hz, 1H), 2.64 (dd, *J*=14.7, 3.6 Hz, 1H). $[\alpha]_D^{20}$ −53 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 73.30; H, 5.76; N, 12.01.

3.7.3. (3*S*,12a*S*)-3-(Isopropyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4c). (A) Yield 92%, (B) yield 86%. Mp 216–218 °C, ESIMS: (*m/z*) 298 $[M+H]^+$; IR (KBr): 3331, 2939, 1662, 1457, 1384, 1365, 746 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ=10.82 (s, 1H), 8.60 (d, *J*=2.7 Hz, 1H), 7.36 (d, *J*=7.1 Hz, 1H), 7.25 (t, *J*=7.1 Hz, 1H), 7.02 (t, *J*=7.1 Hz, 1H), 6.93 (t, *J*=7.1 Hz, 1H), 5.22 (d, *J*=15.2 Hz, 1H), 4.21 (dd, *J*=11.3, 4.2 Hz, 1H), 4.19 (d, *J*=17.0 Hz, 1H), 3.27 (dd, *J*=14.6, 3.7 Hz, 1H), 2.99 (m, *J*=13.3 Hz, 1H), 2.89 (t, *J*=13.3 Hz, 1H), 2.74 (m, *J*=6.2 Hz, 1H), 1.07 (d, *J*=6.2 Hz, 6H). ^{13}C NMR (DMSO-d_6, 300 MHz): δ=169.05, 168.48, 135.09, 133.71, 130.93, 122.59, 121.47, 118.99, 113.44, 111.27, 66.99, 63.10, 41.72, 28.75, 24.38, 16.82. $[\alpha]_D^{20}$ −84 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.50; H, 6.27; N, 14.00.

3.7.4. (3*S*,12a*S*)-3-Hydroxymethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4d). (A) Yield 89%, (B) yield 85%. Mp 264–267 °C, ESIMS (*m/z*) 286 $[M+H]^+$; IR (KBr): 3344, 2926, 1683, 1642, 1463, 1334, 744 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ=10.92 (s, 1H), 8.24 (d, *J*=2.4 Hz, 1H), 7.43 (d, *J*=7.5 Hz, 1H), 7.32 (t, *J*=7.5 Hz, 1H), 7.04 (t, *J*=7.5 Hz, 1H), 6.93 (t, *J*=7.5 Hz, 1H), 5.42 (d, *J*=16.5 Hz, 1H), 5.23 (t, *J*=4.8 Hz, 1H), 4.25 (dd, *J*=11.4, 4.2 Hz, 1H), 4.15 (d, *J*=16.5 Hz, 1H), 4.05 (d, *J*=4.8 Hz, 1H), 3.94 (s, 1H), 3.17 (dd, *J*=15.0, 3.6 Hz, 1H), 2.98 (t, *J*=13.5 Hz, 2H). ^{13}C NMR (DMSO-d_6, 300 MHz): δ=166.88, 163.82, 135.86, 129.77, 126.33, 120.86, 118.56, 117.46, 110.96, 105.82, 62.66, 57.37, 55.82, 27.00. $[\alpha]_D^{20}$ −141 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.48; H, 5.52; N, 14.54.

3.7.5. (3*S*,12a*S*)-3-(1′-Hydroxyeth-1′-yl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4e). (A) Yield 96%, (B) yield 92%. Mp 242–244 °C; ESIMS 300 $[M+H]^+$; IR (KBr): 3340, 2929, 1686, 1642, 1465, 1333, 744 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.00 (s, 1H), 7.98 (s, 1H), 7.29 (t, *J*=7.1 Hz, 1H), 7.25 (t, *J*=7.1 Hz, 1H), 7.09 (t, *J*=7.1 Hz, 1H), 6.97 (d, *J*=7.1 Hz, 1H), 4.81 (t, *J*=5.3 Hz, 1H), 4.63 (m, *J*=5.2 Hz, 1H), 4.45 (t, *J*=5.4 Hz, 2H), 4.22 (m, *J*=5.6 Hz, 1H), 2.90 (d, *J*=5.4 Hz, 2H), 2.15 (s, 1H), 1.22 (d, *J*=5.6 Hz, 3H). $[\alpha]_D^{20}$ −108.5 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 64.32; H, 5.80; N, 14.22.

3.7.6. (3*S*,12a*S*)-3-(*p*-Hydroxyphenylmethyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4f). (A) Yield 91%, (B) yield 90%. Mp 249–251 °C; ESIMS: 362 $[M+H]^+$; IR (KBr): 3342, 2936, 1682, 1643, 1464, 1333, 743 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.02 (s, 1H), 8.01 (s, 1H), 7.31 (t, *J*=7.0 Hz, 1H), 7.23 (t, *J*=7.2 Hz, 1H), 7.16 (d, *J*=7.0 Hz, 2H), 7.13 (d, *J*=7.0 Hz, 2H), 7.01 (t, *J*=7.2 Hz, 1H), 6.89 (d, *J*=7.0 Hz, 1H), 4.97 (s, 1H), 4.85 (d, *J*=5.2 Hz, 1H), 4.78 (t, *J*=5.4 Hz, 1H), 4.21 (m, *J*=5.2 Hz, 2H), 3.13 (d, *J*=5.2 Hz, 2H), 2.90 (d, *J*=5.4 Hz, 2H). $[\alpha]_D^{20}$ −122.3 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.61; H, 5.41; N, 11.47.

3.7.7. (5a*S*,14a*S*)-1,2,3,5,5a,6,11,12,14,14a-Decahydropyrrolo[1″,2″:4′5′]pyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4g). (A) Yield 90%, (B) yield 87%. Mp 233–235 °C; ESIMS 296 $[M+H]^+$; IR (KBr): 3344, 2934, 1684, 1643, 1460, 1332, 743 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.03 (s, 1H), 7.21 (t, *J*=7.2 Hz, 1H), 7.15 (t, *J*=7.2 Hz, 1H), 7.05 (t, *J*=7.2 Hz, 1H), 6.95 (d, *J*=7.2 Hz, 1H), 4.86 (t, *J*=5.5 Hz, 1H), 4.33 (t, *J*=5.4 Hz, 1H), 4.24 (d, *J*=5.5 Hz, 2H), 3.45 (t, *J*=5.4 Hz, 2H), 2.93 (d, *J*=5.3 Hz, 2H), 2.25 (d, *J*=5.4 Hz, 2H), 1.95 (t, *J*=5.4 Hz, 2H). $[\alpha]_D^{20}$ −89.1 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.01; H, 5.70; N, 14.14.

3.7.8. (3*S*,12a*S*)-3-Mercaptomethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4h). (A) Yield 91%, (B) yield 86%. Mp 237–239 °C; ESIMS: 302 $[M+H]^+$; IR (KBr): 3343, 2936, 1647, 1641, 1459, 1333, 741 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.03 (s, 1H), 8.00 (s, 1H), 7.28 (t, *J*=7.0 Hz, 1H), 7.15 (d, *J*=7.0 Hz, 1H), 7.08 (d, *J*=7.0 Hz, 1H), 6.89 (d, *J*=7.0 Hz, 1H), 4.93 (t, *J*=5.4 Hz, 1H), 4.79 (t, *J*=5.6 Hz, 1H), 4.29 (d, *J*=5.2 Hz, 2H), 2.92 (d, *J*=5.4 Hz, 2H), 3.07 (d, *J*=5.6 Hz, 2H), 1.65 (s, 1H). $[\alpha]_D^{20}$ −48.7 (*c* 1.00, CH_3OH). Anal. Calcd for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94. Found: C, 59.92; H, 5.13; N, 13.76.

3.7.9. (3*S*,12a*S*)-3-Methylmercaptoethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4i). (A) Yield 90%, (B) yield 85%. Mp 216–217 °C; ESIMS: 330 $[M+H]^+$; IR (KBr): 3341, 2934, 1648, 1643, 1458, 1332, 742 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.00 (s, 1H), 7.99 (s, 1H), 7.27 (t, *J*=7.0 Hz, 1H), 7.19 (t, *J*=7.0 Hz, 1H), 7.08 (t, *J*=7.0 Hz, 1H), 6.87 (d, *J*=7.0 Hz, 1H), 4.87 (t, *J*=5.4 Hz, 1H), 4.49 (t, *J*=5.2 Hz, 1H), 4.29 (d, *J*=5.3 Hz, 2H), 2.94 (d, *J*=5.4 Hz, 2H), 2.43 (t, *J*=5.3 Hz, 2H), 2.17 (d, *J*=5.3 Hz, 2H), 2.10 (s, 3H). $[\alpha]_D^{20}$ −65.3 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{17}H_{19}N_3O_2S$: C, 61.98; H, 5.81; N, 12.76. Found: C, 62.14; H, 5.89; N, 12.90.

3.7.10. (3*S*,12a*S*)-3-Carboxylethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4j). (A) Yield 85%, (B) yield 85%. Mp 236–238 °C; ESIMS: 417 $[M+H]^+$; IR (KBr): 3342, 3000, 2940, 1675, 1602, 1586, 1457, 1333, 750 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=9.99 (s, 1H), 8.00 (s, 1H), 7.30 (t, *J*=7.1 Hz, 1H), 7.22 (t, *J*=7.1 Hz, 1H), 7.18 (t, *J*=7.0 Hz, 2H), 7.13 (d, *J*=7.0 Hz, 2H), 7.08 (t, *J*=7.0 Hz, 1H), 7.06 (t, *J*=7.0 Hz, 1H), 7.01 (d, *J*=7.2 Hz, 1H), 6.85 (d, *J*=7.2 Hz, 1H), 5.33 (s, 2H), 4.92 (d, *J*=5.0 Hz, 1H), 4.43 (t, *J*=5.2 Hz, 1H), 4.21 (d, *J*=5.1 Hz, 2H), 2.94 (d,

J=5.2 Hz, 2H), 2.25 (t, J=5.5 Hz, 2H), 2.22 (t, J=5.5 Hz, 2H). $[\alpha]_D^{20}$ −109.4 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{24}H_{23}N_3O_4$: C, 69.05; H, 5.55; N, 10.07. Found: C, 68.90; H, 5.62; N, 10.21.

3.7.11. (3*S*,12a*S*)-3-Carboxylmethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4k). (A) Yield 93%, (B) yield 85%. Mp 255–257 °C; ESIMS: (*m*/*z*) 404 $[M+H]^+$; IR (KBr): 3346, 2923, 1678, 1600, 1589, 1507, 1460, 1335, 747 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ=9.98 (s, 1H), 8.20 (s, 1H), 7.30 (d, J=7.4 Hz, 1H), 7.23 (t, J=7.4 Hz, 1H), 7.20 (t, J=7.2 Hz, 2H), 7.13 (t, J=7.2 Hz, 2H), 7.10 (t, J=7.2 Hz, 1H), 7.03 (t, J=7.4 Hz, 1H), 6.92 (t, J=7.3 Hz, 1H), 5.35 (d, J=16.6 Hz, 1H), 5.33 (s, 2H), 4.22 (dd, J=11.0, 3.6 Hz, 1H), 4.17 (d, J=16.5 Hz, 1H), 4.12 (d, J=14.3 Hz, 1H), 3.16 (dd, J=14.0, 3.6 Hz, 1H), 2.96 (t, J=13.0 Hz, 1H), 2.81 (d, J=10.0 Hz, 2H). $[\alpha]_D^{20}$ −70 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42. Found: C, 68.35; H, 5.09; N, 10.27.

3.7.12. (3*S*,12a*S*)-3-(1′,3′-Imidazol-5′-methylene)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4l). (A) Yield 91%, (B) yield 86%. Mp 207–209 °C; ESIMS: 336 $[M+H]^+$; IR (KBr): 3344, 2925, 1677, 1601, 1587, 1505, 1458, 1333, 751 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=12.99 (s, 1H), 10.03 (s, 1H), 7.98 (s, 1H), 7.45 (s, 1H), 7.33 (t, J=7.0 Hz, 1H), 7.25 (t, J=7.0 Hz, 1H), 7.09 (t, J=7.0 Hz, 1H), 6.99 (t, J=7.0 Hz, 1H), 6.87 (s, 1H), 4.92 (t, J=5.2 Hz, 1H), 4.83 (t, J=5.5 Hz, 1H), 4.27 (d, J=5.5 Hz, 2H), 3.20 (d, J=5.5 Hz, 2H), 2.92 (d, J=5.1 Hz, 2H). $[\alpha]_D^{20}$ −88.3 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{18}H_{17}N_5O_2$: C, 64.47; H, 5.11; N, 20.88. Found: C, 64.62; H, 5.20; N, 21.03.

3.7.13. (3*S*,12a*S*)-3-Indolylmethyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4m). (A) Yield 90%, (B) yield 89%. Mp 176–180 °C; ESIMS: (*m*/*z*) 385 $[M+H]^+$; IR (KBr): 3329, 2938, 1683, 1465, 1338, 746 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ=10.76 (s, 1H), 10.74 (s, 1H), 8.43 (d, 1H, J=1.8 Hz, 1H), 7.50 (d, J=7.5 Hz, 1H), 7.28 (t, J=7.5 Hz, 1H), 7.26 (t, J=7.2 Hz, 1H), 7.24 (t, J=7.2 Hz, 1H), 7.22 (d, J=7.2 Hz, 1H), 7.20 (t, J=7.2 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 6.95 (t, 1H, J=7.5 Hz, 1H), 6.82 (s, 1H), 5.27 (d, J=16.2 Hz, 1H), 4.31 (d, J=2.4 Hz, 1H), 4.05 (d, J=16.5 Hz, 1H), 3.95 (dd, J=12.0, 4.5 Hz, 1H), 3.28 (dd, J=14.1, 3.6 Hz, 1H), 3.07 (dd, J=14.1, 4.2 Hz, 1H), 2.93 (d, J=3.5 Hz, 2H); ^{13}C NMR (DMSO-d_6, 300 MHz): δ=165.65, 164.64, 135.80, 135.71, 129.11, 127.62, 126.19, 124.00, 120.58, 118.45, 118.36, 118.10, 117.25, 110.81, 108.02, 105.42, 79.06, 55.77, 55.36, 30.17, 25.6. $[\alpha]_D^{20}$ −182 (*c* 0.34, $CHCl_3/CH_3OH$, 1:1, v/v). Anal. Calcd for $C_{23}H_{20}N_4O_2$: C, 71.86; H, 5.24; N, 14.57. Found: C, 72.04; H, 5.56; N, 14.33.

3.7.14. (3*S*,12a*S*)-3-(3′-Guanidinopropyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4n). (A) Yield 90%, (B) yield 87%. Mp 240–242 °C; ESIMS: 355 $[M+H]^+$; IR (KBr): 3339, 2941, 1680, 1456, 1342, 743 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.03 (s, 1H), 8.44 (s, 2H), 8.20 (s, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.23 (t, J=7.0 Hz, 1H), 7.15 (t, J=7.0 Hz, 1H), 7.02 (d, J=7.0 Hz, 1H), 6.95 (d, J=7.0 Hz, 1H), 4.92 (d, J=5.2 Hz, 1H), 4.35 (t, J=4.6 Hz, 1H), 4.23 (d, J=5.2 Hz, 2H), 2.91 (d, J=4.7 Hz, 2H), 2.66 (t, J=5.2 Hz, 2H), 1.95 (m, J=5.2 Hz, 2H), 1.56 (m, J=5.2 Hz, 2H). $[\alpha]_D^{20}$ −90.6 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{18}H_{22}N_6O_2$: C, 61.00; H, 6.26; N, 23.71. Found: C, 61.18; H, 6.33; N, 23.53.

3.7.15. (12a*S*)-2,3,6,7,12,12a-Hexahydropyrazino-[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4o). (A) Yield 95%, (B) yield 92%. Mp 247–249 °C; ESIMS: (*m*/*z*) 256 $[M+H]^+$; IR (KBr): 3307, 2986, 1646, 1455, 1328, 748 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ=10.94 (s, 1H), 8.26 (s, 1H), 7.43 (d, J=7.5 Hz, 1H), 7.33 (t, J=7.5 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 6.96 (t, J=7.5 Hz, 1H), 5.36 (d, J=16.5 Hz, 1H), 4.22 (m, J=13.0 Hz, 2H), 4.05 (d, J=17.7 Hz, 1H), 3.86 (d, J=17.7 Hz, 1H), 3.20 (m, J=13.5 Hz, 1H), 2.88 (t, J=13.5 Hz, 1H). ^{13}C NMR (DMSO-d_6, 300 MHz): δ=168.87, 167.66, 136.11, 134.02, 130.34, 124.63, 121.55, 120.21, 119.44, 111.22, 59.75, 52.76, 42.80, 24.77. $[\alpha]_D^{20}$ −135 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.65; H, 5.01; N, 16.67.

3.7.16. (3*S*,12a*S*)-3-Aminobutyl-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4p). (A) Yield 87%, (B) yield 83%. Mp 216–218 °C; EIMS: (*m*/*z*) 327 $[M+H]^+$; IR (KBr): 3324, 2936, 1683, 1463, 1336, 745 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ=9.92 (s, 1H), 8.21 (d, J=1.8 Hz, 1H), 7.41 (d, J=7.5 Hz, 1H), 7.28 (t, J=7.5 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 6.95 (t, 1H, J=7.5 Hz, 1H), 5.36 (d, J=16.5 Hz, 1H), 4.60 (t, J=6.8 Hz, 1H), 4.30 (dd, J=11.7, 4.5 Hz, 1H), 4.13 (dd, J=11.7, 4.5 Hz, 1H), 3.26 (dd, J=13.2, 3.3 Hz, 1H), 2.79 (dd, J=13.5, 5.1 Hz, 1H), 2.70 (t, J=4.8 Hz, 2H), 2.01 (s, 2H), 1.80 (m, J=4.8 Hz, 2H), 1.60 (m, J=4.8 Hz, 2H), 1.32 (m, J=4.8 Hz, 2H). $[\alpha]_D^{20}$ −48 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17. Found: C, 66.01; H, 6.58; N, 17.41. In the preparation of **4p**, both procedure A and B included a procedure of removing Z: After the cyclization, a colorless powder of 922 mg (2.0 mmol) of the cyclization product was mixed with 50 mg of Pd/C (5%) and 25 ml of formic acid in methanol (4.4%), and agitated with hydrogen at room temperature for 24 h. The reaction mixture was filtrated and evaporated to give the title compound as colorless powder. The yield given here was the total yield.

3.7.17. (3*S*,12a*S*)-3-(Propionamide-2′-yl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4q). (A) Yield 93%, (B) yield 93%. Mp 251–253 °C; ESIMS: 327 $[M+H]^+$; IR (KBr): 3344, 2939, 1684, 1465, 1332, 746 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.01 (s, 1H), 7.98 (s, 1H), 7.27 (t, J=7.2 Hz, 1H), 7.19 (t, J=7.2 Hz, 1H), 7.03 (d, J=7.2 Hz, 1H), 6.85 (d, J=7.2 Hz, 1H), 6.11 (s, 2H), 4.93 (d, J=5.5 Hz, 1H), 4.44 (t, J=5.4 Hz, 1H), 4.27 (d, J=5.5 Hz, 2H), 2.92 (d, J=5.2 Hz, 2H), 2.17 (t, J=5.4 Hz, 2H), 2.11 (t, J=5.4 Hz, 2H). $[\alpha]_D^{20}$ −62 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.71; H, 5.64; N, 17.35.

3.7.18. (3*S*,12a*S*)-3-(Acetylamine-1′-yl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4r). (A) Yield 91%, (B) yield 87%. Mp 247–249 °C; ESIMS: 313 $[M+H]^+$; IR (KBr): 3341, 2942, 1681, 1463,

1336, 741 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.03 (s, 1H), 8.00 (s, 1H), 7.27 (t, J=7.2 Hz, 1H), 7.19 (t, J=7.2 Hz, 1H), 7.05 (d, J=7.2 Hz, 1H), 6.87 (d, J=7.2 Hz, 1H), 6.06 (s, 2H), 4.93 (d, J=5.3 Hz, 1H), 4.45 (t, J=5.2 Hz, 1H), 4.23 (d, J=5.3 Hz, 2H), 2.92 (d, J=5.4 Hz, 2H), 2.65 (t, J=5.3 Hz, 2H). $[\alpha]_D^{20}$ −45.2 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.38; H, 5.08; N, 17.76.

3.7.19. (3*S*,12a*S*)-3-(2′-Methylpropyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4s). (A) Yield 87%, (B) yield 88%. Mp 231–233 °C; ESIMS: 312 $[M+H]^+$; IR (KBr): 3343, 2943, 1682, 1465, 1335, 743 cm^{-1}; ^1H NMR (BHSC-500, DMSO-d_6): δ=10.02 (s, 1H), 7.98 (s, 1H), 7.27 (t, J=7.2 Hz, 1H), 7.19 (t, J=7.2 Hz, 1H), 7.03 (d, J=7.2 Hz, 1H), 6.85 (d, J=7.2 Hz, 1H), 4.93 (t, J=5.3 Hz, 1H), 4.45 (t, J=5.2 Hz, 1H), 4.26 (dd, J=10.0, 4.4 Hz, 1H), 4.15 (dd, J=10.0, 3.9 Hz, 1H), 2.92 (d, J=6.2 Hz, 2H), 2.65 (t, J=5.3 Hz, 2H), 1.83 (m, J=5.3 Hz, 1H), 1.07 (d, J=5.3 Hz, 6H). $[\alpha]_D^{20}$ −52 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.60; H, 6.71; N, 13.66.

3.7.20. (3*S*,12a*S*)-3-(1′-Methylpropyl)-2,3,6,7,12,12a-hexahydropyrazino[1′,2′:1,6]pyrido[3,4-*b*]indole-1,4-dione (4t). (A) Yield 98%, (B) yield 87%. Mp 219–220 °C, ESIMS: (*m*/*z*) 312 $[M+H]^+$; IR (KBr): 3328, 2936, 1669, 1455, 1388, 1369, 744 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ=11.12 (s, 1H), 8.64 (d, J=2.1 Hz, 1H), 7.40 (d, J=7.3 Hz, 1H), 7.30 (t, J=7.3 Hz, 1H), 7.00 (t, J=7.3 Hz, 1H), 6.95 (t, J=7.3 Hz, 1H), 5.30 (d, J=16.0 Hz, 1H), 4.25 (dd, J=11.0, 4.0 Hz, 1H), 4.17 (d, J=17.3 Hz, 1H), 3.22 (dd, J=15.0, 3.3 Hz, 1H), 2.96 (m, J=13.0 Hz, 1H), 2.83 (t, J=13.0 Hz, 1H), 2.61 (m, J=6.0 Hz, 1H), 1.35 (m, J=6.0 Hz, 2H), 1.07 (d, J=6.0 Hz, 3H), 0.97 (t, J=6.0 Hz, 6H). ^{13}C NMR (DMSO-d_6, 300 MHz): δ=167.00, 166.48, 136.13, 130.37, 126.51, 121.44, 118.96, 117.40, 111.20, 105.81, 56.30, 53.11, 46.12, 26.75, 34.34, 23.30, 14.82, 11.77. $[\alpha]_D^{20}$ −73.7 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.22; H, 6.61; N, 13.68.

3.8. The racemization detection condition during the synthesis of 4a–t

Upon removal of the reaction solvent and the volatile side products (i.e., CH_3OH, $(CH_3)_3COH$, CO_2, and H_2O), the crude compounds **4a–t** were directly analyzed by HPLC. The compounds **4a–t** were analyzed using reverse-phase HPLC on a C18-Si column (NovaPak 3.9×150 mm, Waters). Mobile phase: A, 0.1% TFA in water; B, 0.8% TFA in acetonitrile; Elution was performed with 5% B for 40 min and followed by a linear gradient of 5–80% B for 40 min, after maintaining 80% B for 10 min, and followed by a linear gradient of 80–5% B within 10 min. In all cases, the purity of compounds **4a–t** was found to be higher than 98%.

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