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A general strategy for the highly stereoselective synthesis of HR22C16-like mitotic kinesin Eg5 inhibitors from both L- and D-tryptophans

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ABSTRACT

An efficient and general strategy for the highly stereoselective synthesis of HR22C16-like mitotic kinesin Eg5 inhibitors **1** from both L- and D-tryptophan methyl ester hydrohalides is described. (1*R*,3*S*)-*trans*-1,3-Disubstituted 1,2,3,4-tetrahydro-β-carbolines (1*R*,3*S*)-*trans*-**2** could be obtained in high yields and with high stereoselectivities from the Pictet–Spengler reaction of L-tryptophan methyl ester hydrohalide with some 3-acyloxyl benzaldehydes via a CIAT (crystal induced asymmetric transformation) process, whereas (1*R*,3*R*)-*cis*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines (1*R*,3*R*)-*cis*-**2** could also be obtained in high yields and with high stereoselectivities from a Pictet–Spengler reaction of D-tryptophan methyl ester hydrohalide with some other 3-acyloxyl benzaldehydes via a CIAT process. Both compounds (1*R*,3*S*)-*trans*-**2** and (1*R*,3*R*)-*cis*-**2** were efficiently converted into HR22C16-like mitotic kinesin Eg5 inhibitors **1** by the same one-pot procedure through tandem reactions. A total of eighteen target compounds **1** were obtained from six intermediate compounds **2** in 87–95% yields.

1. Introduction

Mitotic kinesin Eg5, also known as kinesin spindle protein (KSP), plays an important role in the formation and separation of bipolar spindles during human cell division. As a result, it is one of the most attractive target enzymes in antimitotic drug discovery.[1–9] Recently, antimitotic agents that target Eg5 rather than microtubules, have attracted great interest worldwide, because research on these agents might lead to the discovery of a new generation of anticancer drugs[10–31] without the mechanism-based side effects caused by the inhibition of tubulin.[32–35] HR22C16 and its analogues were selected using a phenotype-based screen for antimitotic agents and were subsequently identified as effective Eg5 inhibitors.[36] The structure of HR22C16 and its analogues **1** (Fig. 1) has a tetracyclic hydantoin-fused 1,2,3,4-tetrahydro-β-carboline scaffold, which bears a *meta*-hydroxy group on the aromatic ring at the C-5 position and possesses two stereogenic centers at C-5 and C-11a with the respective (*R*)- and (*S*)-configurations. Not only is the *meta*-hydroxyl phenyl group necessary, but also the absolute configurations of both the stereogenic centers are very important for the inhibitory activities on Eg5.[36,37] As a result, it is pivotal to construct the correct stereochemistry of both stereogenic centers with high stereoselectivities during the synthesis of HR22C16 and its analogues.

We have recently reported the first highly stereoselective approach to the mitotic kinesin Eg5 inhibitor HR22C16 and its analogues.[38] However, the substituent at the C-5 position is only limited to the 3-hydroxyphenyl group (R = H, Fig. 1), whereas the synthesis of HR22C16-like compounds that bear substituted 3-hydroxyphenyl groups (R ≠ H, Fig. 1) at the C-5 position remains a challenge. In order to solve this problem, we herein report a general strategy for a highly stereoselective synthesis of structurally diversified HR22C16-like mitotic kinesin Eg5 inhibitors with various 4-substituted 3-hydroxyphenyl groups at the C-5 position.

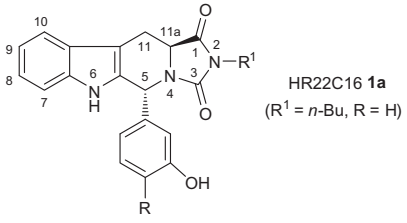

Figure 1. The structure of HR22C16 and its analogues **1**.

2. Results and discussion

We first attempted the Pictet–Spengler reaction of L-tryptophan methyl ester hydrohalides (X = Cl, Br) with various 3-acyloxyl benzaldehydes. As depicted in Scheme 1, a Pictet–Spengler reaction of L-tryptophan methyl ester hydrohalides with 3-acyloxyl benzaldehydes in isopropanol produced an epimeric mixture of *cis*- and *trans*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carboline hydrohalides

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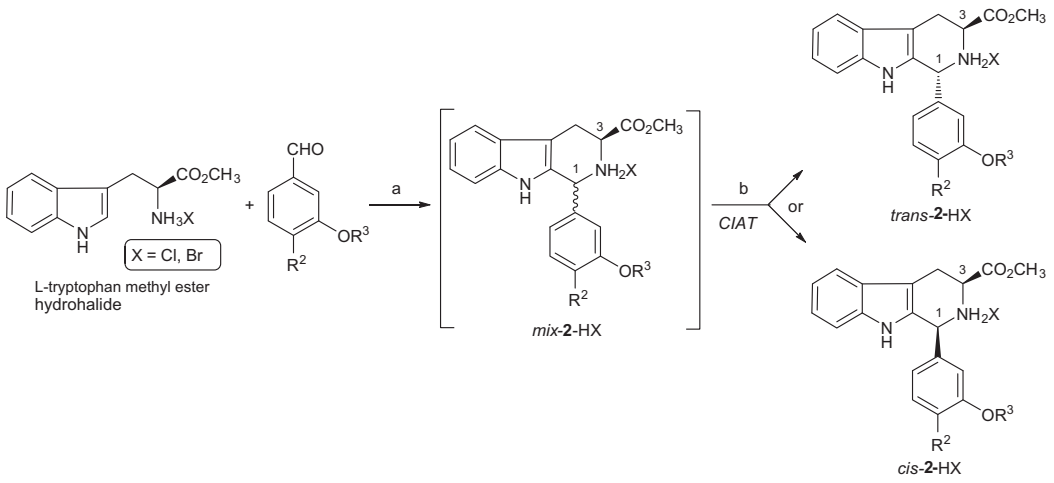


Scheme 1. Pictet–Spengler reaction of L-tryptophan methyl ester hydrohalides with 4-substituted ($R^2 \neq H$) or non-substituted ($R^2 = H$) 3-acyloxyl benzaldehydes to afford compounds *trans*- or *cis*-**2**-HX via a CIAT process. Reagents and conditions: (a) reflux for 5 h, in isopropanol; (b) reflux for 5–48 h in the mixed solvent of toluene and nitromethane with ratios as indicated in Table 1.

mix-**2**-HX (*cis*/*trans* ≈ 50:50). Isopropanol was then removed, and the subsequent CIAT (crystal induced asymmetric transformation)[39–50] process of a diastereomeric mixture *mix*-**2**-HX in a mixed solvent of toluene and nitromethane gave (1*R*,3*S*)-*trans*-**2**-HX or (1*S*,3*S*)-*cis*-**2**-HX in high yields and with excellent diastereoselectivities (Table 1). As can be seen from Table 1, both the *trans*- and *cis*-dominant diastereomer of 1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines **2** can be obtained from the above CIAT process. Although the yields of all products **2a**–**2f** are excellent, the stereoselectivities of the CIAT process depend significantly on the following factors: (a) protecting groups (R^3) of the *meta*-hydroxyl group; (b) substituents (R^2) on the *m*-acyloxyl benzaldehydes; (c) counter ions (X = Cl or Br) of the tryptophan methyl ester ammonium salts; and (d) the ratio of toluene and nitromethane in the mixed solvent. Herein, it is noteworthy that the conversion of the diastereomeric mixture *mix*-**2**-HX into the diastereomerically pure (1*R*,3*S*)-*trans*-**2**-HX or (1*S*,3*S*)-*cis*-**2**-HX might be the result of a CIAT process[39] rather than the thermodynamic control of a possibly reversible Pictet–Spengler reaction. The following interesting observations might also support this assumption. After refluxing in a mixed solvent of toluene and nitromethane (2:1), *mix*-**2d**-HCl was turned into *trans*-**2d**-HCl (Table 1, entry 7) whereas *mix*-**2d**-HBr was turned into *cis*-**2d**-HBr (Table 1, entry 8). Similarly, after refluxing in nitromethane, *mix*-**2e**-HCl was turned into *trans*-**2e**-HCl (Table 1, entry 9) whereas *mix*-**2e**-HBr was turned into *cis*-**2e**-HBr (Table 1, entry 10). The mechanism for the CIAT process of hydrochloride salts has been extensively studied in a previous article[39]; the CIAT process of hydrobromide salts is likely to follow the same mechanism pathway.

The *trans*- and *cis*-stereochemistry for each compound **2** listed in Table 1 was determined unequivocally by analyzing the correlation spots in its ^1H–^1H NOESY spectra. As depicted in Figure 2, for *trans*-**2**, there were two correlation spots (NOE) between H-3 and two neighboring protons (*ortho*-protons) on the aryl group at C-1, meaning that H-3 and the aryl group at C-1 were located on the same side of the piperidine ring; for *cis*-**2**, there was one correlation spot (NOE) between H-1 and H-3, meaning that H-1 and H-3 were located on the same side of the piperidine ring.

With the above obtained (1*R*,3*S*)-*trans*- and (1*S*,3*S*)-*cis*-1, 3-disubstituted 1,2,3,4-tetrahydro-β-carbolines **2** in hand, we next attempted the conversions of both *trans*-**2** and *cis*-**2** compounds into the target molecules HR22C16 and its analogues **1**. Our studies showed that *trans*-compounds (1*R*,3*S*)-*trans*-**2**, which have the desired configurations, can be readily converted into the title compounds **1** according to the synthetic route outlined in Scheme 2. However, the above *cis*-compounds (1*S*,3*S*)-*cis*-**2** have undesired

Table 1
CIAT (crystal induced asymmetric transformation) process of *mix*-**2**-HX at reflux in a mixed solvent of toluene and nitromethane to afford either *cis*- or *trans*-1,3-disubstituted 1,2,3,4-tetrahydro-β-carbolines **2** (see also Scheme 1)

Entry	R^2	R^3	X	Tol./CH_3NO_2 (ratio)	Time[a] (h)	Product **2**[b] (*cis*/*trans*)	Yield[c] (%)
1	H	Bz	Cl	2:1	18	**2a** (1:99)	95
2	H	Bz	Br	2:1	10	**2a** (1:99)	96
3	H	Ac	Cl	2:1	18	**2b** (99:1)	95
4	H	Ac	Br	2:1	12	**2b** (99:1)	96
5	OMe	Bz	Cl	2:1	8	**2c** (1:99)	94
6	OMe	Bz	Br	2:1	5	**2c** (1:99)	95
7	OMe	Ac	Cl	2:1	6	**2d** (1:99)	96
8	OMe	Ac	Br	2:1	20	**2d** (99:1)	93
9	OAc	Ac	Cl	0:1[d]	10	**2e** (1:99)	93
10	OAc	Ac	Br	0:1[d]	18	**2e** (99:1)	91
11	OBz	Bz	Cl	4:1	48	**2f** (5:95)	90
12	OBz	Bz	Br	4:1	36	**2f** (3:97)	91

[a] At reflux.
[b] The *cis*/*trans* ratios were determined by both high resolution ^1H NMR and HPLC analysis.
[c] Isolated yield based on two steps from L-tryptophan methyl ester hydrohalides (see Scheme 1).
[d] Nitromethane was used as the solvent.

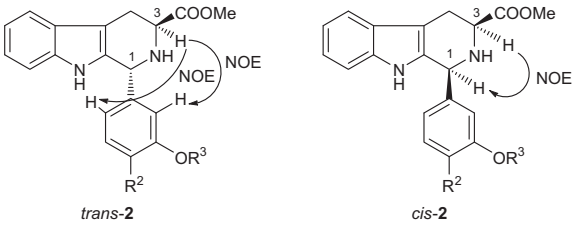
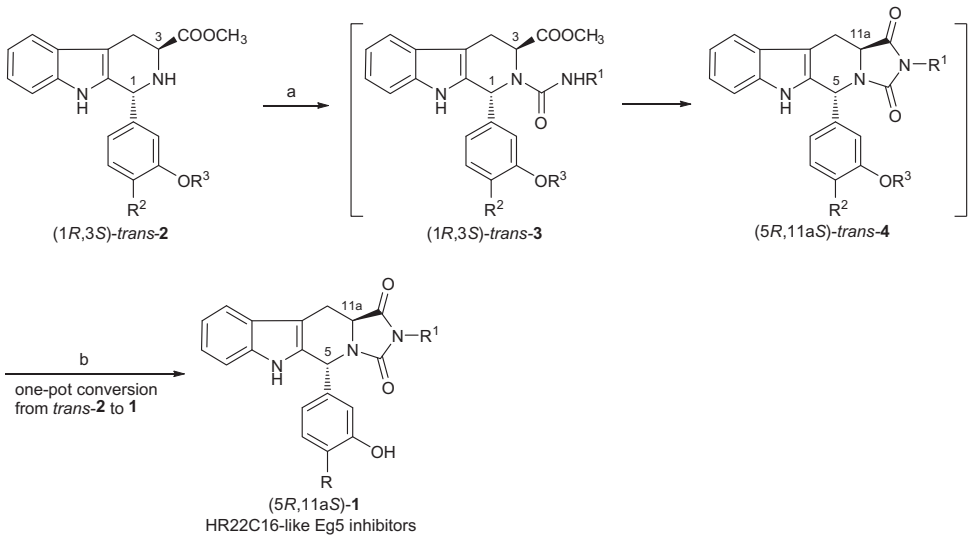


Figure 2. Determination of *trans*- and *cis*-stereochemistry of compounds **2** by NOEs.

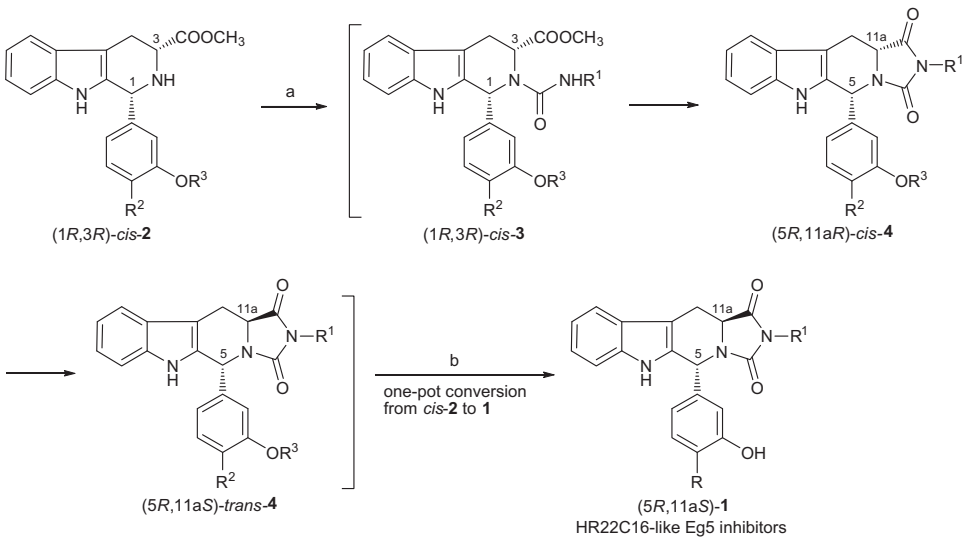
configurations, and thus cannot be transformed into the target compounds **1**. However, (1*R*,3*R*)-*cis*-**2**, which should be prepared from the Pictet–Spengler reaction of D-tryptophan methyl ester hydrohalides with aldehydes via the same CIAT process as described in Scheme 1, can be transformed into target compounds **1** according to another synthetic route as outlined in Scheme 3.

In the following text, compounds (1*R*,3*S*)-*trans*-**2a**, **2c**, **2e** and (1*R*,3*R*)-*cis*-**2b**, **2d**, **2e** were used as the key intermediates for the synthesis of HR22C16-like Eg5 inhibitors **1**; a total of eighteen compounds **1a**–**1r** were obtained in 87–95% yields; all of the results are summarized in Table 2.

As depicted in Scheme 2, *trans*-compounds (1*R*,3*S*)-*trans*-**2** can be efficiently converted into the title compounds **1** by a one-pot procedure. A stepwise method for the conversion of (1*R*,3*S*)-*trans*-**2** into **1** has been described in a previous article,[38] but the one-pot method shown in Scheme 2 is more efficient and practical. When (1*R*,3*S*)-*trans*-**2a**, **2c**, and **2e** were treated successively with 0.5 equiv of triphosgene, 5 equiv of Et_3N and 10 equiv of a primary amine (R^1NH_2) in dichloromethane, intermediate compounds (1*R*,3*S*)-*trans*-**3** were formed at first, which then underwent simultaneous cyclization to afford hydantoin-fused tetrahydro-β-carbolines (5*R*,11a*S*)-*trans*-**4**. After the dichloromethane was removed, crude compounds (5*R*,11a*S*)-*trans*-**4** were treated with 3 equiv of Et_3N at reflux in methanol to furnish title compounds



Scheme 2. One-pot synthesis of HR22C16-like Eg5 inhibitors (5*R*,11a*S*)-**1** from compounds (1*R*,3*S*)-*trans*-**2**. Reagents and conditions: (a) 0.5 equiv of triphosgene, 5 equiv of Et_3N, 0 °C for 15 min in CH_2Cl_2; then 10 equiv of R^1NH_2, 0 °C for 15 min and then refluxing for 3 h in CH_2Cl_2; (b) 3 equiv of Et_3N, refluxing for 3 h in CH_3OH.

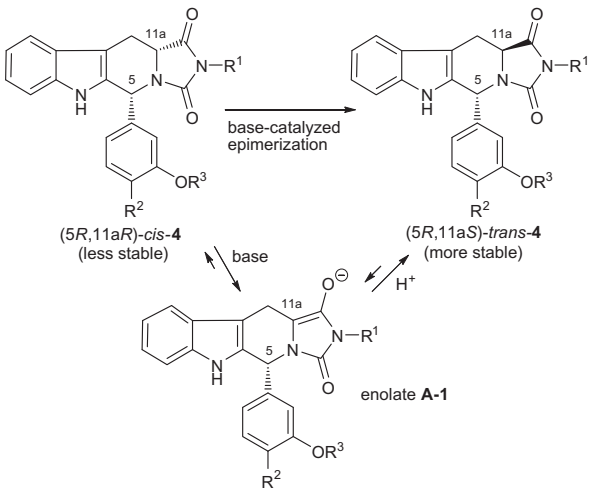


Scheme 3. One-pot synthesis of HR22C16-like Eg5 inhibitors (5*R*,11a*S*)-**1** from compounds (1*R*,3*R*)-*cis*-**2**. Reagents and conditions: (a) 0.5 equiv of triphosgene, 5 equiv of Et_3N, 0 °C for 15 min in CH_2Cl_2; then 10 equiv of R^1NH_2, 0 °C for 15 min and then refluxing for 3 h in CH_2Cl_2; (b) 3 equiv of Et_3N, refluxing for 3 h in CH_3OH.

Table 2
Synthesis of HR22C16-like Eg5 inhibitors **1** from *trans*- and *cis*-1,3-disubstituted tetrahydro-β-carbolines (THBCs) (1*R*,3*S*)-*trans*-**2** and (1*R*,3*R*)-*cis*-**2** via a one-pot procedure (see also Schemes 2 and 3)

Entry	THBCs **2**[a,b]	R^1	R^2	R^3	R	Product **1**	Yield[c] (%)
1	(1*R*,3*S*)-*trans*-**2a**	*n*-Bu	H	Bz	H	**1a**	95
2	(1*R*,3*S*)-*trans*-**2a**	*n*-Pr	H	Bz	H	**1b**	94
3	(1*R*,3*S*)-*trans*-**2a**	Hydroxyethyl	H	Bz	H	**1c**	92
4	(1*R*,3*S*)-*trans*-**2a**	Bn	H	Bz	H	**1d**	95
5	(1*R*,3*S*)-*trans*-**2c**	*i*-Pr	OMe	Bz	OMe	**1e**	92
6	(1*R*,3*S*)-*trans*-**2c**	5-Azido-pentyl	OMe	Bz	OMe	**1f**	92
7	(1*R*,3*S*)-*trans*-**2c**	Phenethyl	OMe	Bz	OMe	**1g**	87
8	(1*R*,3*S*)-*trans*-**2e**	*i*-Pr	OAc	Ac	OH	**1h**	93
9	(1*R*,3*R*)-*cis*-**2b**	5-Azido-pentyl	H	Ac	H	**1i**	93
10	(1*R*,3*R*)-*cis*-**2b**	*i*-Pr	H	Ac	H	**1j**	94
11	(1*R*,3*R*)-*cis*-**2b**	Phenethyl	H	Ac	H	**1k**	88
12	(1*R*,3*R*)-*cis*-**2d**	*n*-Pr	OMe	Ac	OMe	**1l**	90
13	(1*R*,3*R*)-*cis*-**2d**	*n*-Bu	OMe	Ac	OMe	**1m**	92
14	(1*R*,3*R*)-*cis*-**2d**	Hydroxyethyl	OMe	Ac	OMe	**1n**	87
15	(1*R*,3*R*)-*cis*-**2d**	Bn	OMe	Ac	OMe	**1o**	90
16	(1*R*,3*R*)-*cis*-**2e**	5-Azido-pentyl	OAc	Ac	OH	**1p**	91
17	(1*R*,3*R*)-*cis*-**2e**	Hydroxyethyl	OAc	Ac	OH	**1q**	90
18	(1*R*,3*R*)-*cis*-**2e**	Bn	OAc	Ac	OH	**1r**	94

[a] THBCs (1*R*,3*S*)-*trans*-**2a**, **2c**, and **2e** were prepared from L-tryptophane methyl ester hydrohalide via CIAT process (see also Scheme 1).
[b] THBCs (1*R*,3*R*)-*cis*-**2b**, **2d**, and **2e** were prepared from D-tryptophane methyl ester hydrohalide via CIAT process (see also Scheme 1).
[c] Isolated yield.



Scheme 4. Possible mechanism for the base-catalyzed epimerization of compounds (5*R*,11a*R*)-*cis*-**4** into compounds (5*R*,11a*S*)-*trans*-**4**.

(5*R*,11a*S*)-*trans*-**1a**–**1h** in high yields (Table 2, entries 1–8). The whole conversion from (1*R*,3*S*)-*trans*-**2** into (5*R*,11a*S*)-*trans*-**1** was performed in one pot without isolation of the intermediates (1*R*,3*S*)-*trans*-**3** and (5*R*,11a*S*)-*trans*-**4**.

As depicted in Scheme 3, *cis*-compounds (1*R*,3*R*)-*cis*-**2** can also be efficiently converted into title compounds **1** by the same one-pot procedure. When (1*R*,3*R*)-*cis*-**2b**, **2d**, and **2e** were treated successively with 0.5 equiv of triphosgene, 5 equiv of Et_3N and 10 equiv of a primary amine (R^1NH_2) in dichloromethane, intermediate compounds (1*R*,3*R*)-*cis*-**3** were formed at first, which then underwent simultaneous cyclization to afford hydantoin-fused tetrahydro-β-carbolines (5*R*,11a*R*)-*cis*-**4**, which were unstable and would rapidly change into more stable compounds (5*R*,11a*S*)-*trans*-**4** via a base-catalyzed epimerization at the C-11a position. After the dichloromethane was removed, crude compounds (5*R*,11a*S*)-*trans*-**4** were treated with 3 equiv of Et_3N at reflux in methanol to furnish title compounds (5*R*,11a*S*)-*trans*-**1i**–**1r** in high yields (Table 2, entries 9–18). Although four steps were involved, the whole conversion from compounds (1*R*,3*R*)-*cis*-**2** into compounds (5*R*,11a*S*)-*trans*-**1** was performed in one pot without isolation of the intermediate compounds (1*R*,3*R*)-*cis*-**3**, (5*R*,11a*R*)-*cis*-**4**, and (5*R*,11a*S*)-*trans*-**4**.

A plausible mechanism for the base-catalyzed epimerization of the less stable compounds (5*R*,11a*R*)-*cis*-**4** into more stable compounds (5*R*,11a*S*)-*trans*-**4** is proposed in Scheme 4. An enolate **A-1** might be involved in this base-catalyzed epimerization.[51] The reaction of the base (Et_3N or R^1NH_2) with the acidic proton at C-11a of compounds (5*R*,11a*R*)-*cis*-**4** produced the anion **A-1** which then underwent protonation to give the more stable compounds (5*R*,11a*S*)-*trans*-**4**. The epimerization seems to be reversible, since compounds (5*R*,11a*S*)-*trans*-**4** also underwent epimerization to form compounds (5*R*,11a*R*)-*cis*-**4**. However, the one-pot conversion of compounds (1*R*,3*R*)-*cis*-**2** into the title compounds (5*R*,11a*S*)-*trans*-**1** only gave the *trans*-diastereomer without contamination of the *cis*-diastereomer, implying that the epimerization of the *cis*-compounds (5*R*,11a*R*)-*cis*-**4** into the much more stable *trans* compounds (5*R*,11a*R*)-*trans*-**4** was fully complete during the one-pot conversion.

3. Conclusion

In conclusion, an efficient and general method for highly stereoselective synthesis of HR22C16-like mitotic kinesin Eg5 inhibitors has been developed. By using this method, HR22C16 and its analogues **1** can be synthesized from both L- and D-tryptophan methyl ester hydrohalides. If the CIAT process afforded *trans* intermediates **2**, then L-tryptophan was used as the starting material; conversely if the CIAT process afforded *cis* intermediates **2**, the D-tryptophan was used as the starting material. Since the CIAT process can be applicable for various substituted *m*-acyloxyl-benzaldehydes by tuning the ratio of toluene and nitromethane in a mixed solvent, the above method should be a general one. In addition, since the dominance of the *trans*- or *cis*-configurations of intermediates **2** cannot be predicted for the CIAT process for each aldehyde, the HR22C16-like Eg5 inhibitors **1** might be synthesized either from L-tryptophan methyl ester hydrohalides or from D-tryptophan methyl ester hydrohalides.

Herein, three *trans*-compounds (1*R*,3*S*)-*trans*-**2a**, **2c**, **2e** and three *cis*-compounds (1*R*,3*R*)-*cis*-**2b**, **2d**, **2e** were prepared; these six intermediate compounds were efficiently converted into HR22C16-like mitotic kinesin Eg5 inhibitors **1** by the same

one-pot procedure through tandem reactions. A total of eighteen title compounds **1a**–**1r** were obtained from the one-pot method in 87–95% yields.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AM-400, chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a Nicolet Magna IR-550. Mass spectra were recorded on HP5989A. Optical rotations were measured on a WZZ-1S automatic polarimeter at room temperature. Column chromatography was performed on silica gel (Qingdao Ocean Chemical Corp.). All chemicals were analytically pure. The L- or D-tryptophan methyl ester hydrochloride was prepared according to a known procedure.[52]

4.2. Procedure for the preparation of L- or D-tryptophan methyl ester hydrobromide

At first, L- or D-tryptophan methyl ester (10.00 g, 45.82 mmol) was dissolved in ethyl acetate (100 mL). The solution was then cooled to 0 °C with an ice-bath while being stirred. An aqueous solution of hydrobromic acid (9.28 g, 48% w/w, 55.05 mmol) was added dropwise over 15 min. and stirring was continued at 0 °C for one more hour. The product as an off-white solid was collected on a Büchner funnel by suction and washed with a small amount of ethyl acetate. The product was dried in warm air to produce L- or D-tryptophan methyl ester hydrobromide (12.88 g, 43.05 mmol) in a 94% yield, mp 204–205 °C. $[\alpha]_D^{20} = +15.2$ (*c* 3.1, CH_3OH) for the L-isomer; and $[\alpha]_D^{20} = -15.3$ (*c* 3.2, CH_3OH) for the D-isomer. ^{1}H NMR (D_2O) δ 3.25–3.40 (m, 2H), 3.71 (s, 3H), 4.32 (t, J = 6.5 Hz, 1H), 7.10 (dd, J_1 = 7.6 Hz, J_2 = 7.5 Hz, 1H), 7.19 (dd, J_1 = 8.1 Hz, J_2 = 7.5 Hz, 1H), 7.20 (s, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H). MS (EI) *m*/*z* (%) 218 (M^+, 100), 203 (10), 159 (12), 130 (21), 105 (1), 77 (1). IR (KBr) 3359, 3298, 1723, 1568, 1452, 1231, 749, 705 cm^{-1}.

4.3. General procedure for the preparation of intermediate compounds 2

To a solution of 4-substituted (or nonsubstituted) 3-acyloxyl benzaldehyde (12.00 mmol) in isopropanol (25 mL) was added powdered L- or D-tryptophan methyl ester hydrohalide (10.00 mmol). The mixture was heated at reflux while being stirred, and then stirring was continued for around 5 h at reflux. The reaction solution was then concentrated to dryness under vacuum to give a crude solid product. The crude solid product was then suspended in a mixed solvent (20 mL) of nitromethane and toluene with a ratio as indicated in Table 1. The suspension was heated at reflux, and then stirring was continued at reflux for 5–48 h (see also Table 1). The mixture was then cooled down to room temperature. A pale yellow solid was collected in a Büchner funnel by suction and rinsed with a small amount of a freshly mixed solvent of nitromethane and toluene. The solid was then partitioned between ethyl acetate (50 mL) and a saturated aqueous solution of K_2CO_3 (20 mL, 15% w/v). The organic layer was separated and dried over anhydrous $MgSO_4$. Evaporation of the solvent under vacuum gave a crude product which was purified by flash chromatography to afford compounds **2** in 90–96% yield (see also Table 1). Characterization data for all compounds **2** are as follows.

4.3.1. (1*R*,3*S*)-Methyl 1-(3-(benzoyloxy)phenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (1*R*,3*S*)-*trans*-2a

Mp 185–186 °C (lit.[38] mp 185–186 °C). $[\alpha]_D^{20} = -33.7$ (*c* 0.8, $CHCl_3$) {lit.[38] $[\alpha]_D^{20} = -33.5$ (*c* 0.9, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$) δ 2.37 (br s, 1H), 3.14 (ddd, J_1 = 15.4 Hz, J_2 = 6.8 Hz, J_3 = 1.2 Hz, 1H), 3.28 (dd, J_1 = 15.5 Hz, J_2 = 5.4 Hz, 1H), 3.72 (s, 3H), 3.99 (dd, J_1 = 6.3 Hz, J_2 = 5.9 Hz, 1H), 5.43 (s, 1H), 7.12–7.24 (m, 6H), 7.39 (dd, J_1 = 7.9 Hz, J_2 = 7.8 Hz, 1H), 7.48 (dd, J_1 = 7.9 Hz, J_2 = 7.7 Hz, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.62 (dd, J_1 = 7.5 Hz, J_2 = 7.6 Hz, 1H), 7.77 (br s, 1H, NH on the indole ring), 8.15 (d, J = 7.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 174.6, 165.9, 151.8, 144.6, 136.9, 134.3, 133.3, 130.8, 130.2, 129.9, 129.2, 127.4, 126.5, 122.5, 122.3, 122.04, 120.01, 118.8, 111.9, 109.0, 55.1, 52.73, 52.71, 25.5. MS (EI) *m*/*z* (%) 426 (M^+, 100), 411 (10), 365 (15), 321 (12), 261 (7), 234 (19), 229 (15), 217 (12), 206 (9), 169 (18), 144 (13), 105 (78), 77 (17). IR (KBr) 3395, 2980, 1735, 1605, 1454, 1271, 1225, 1065, 750, 705 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{22}N_2O_4$: 426.1580; found: 426.1585.

4.3.2. (1*R*,3*R*)-Methyl 1-(3-acetoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (1*R*,3*R*)-*cis*-2b

Mp 221–222 °C (lit.[38] mp 220–221 °C). $[\alpha]_D^{20} = +7.1$ (*c* 3.0, $CHCl_3$) {lit.[38] $[\alpha]_D^{20} = -7.2$ (*c* 3.3, $CHCl_3$) for the enantiomer}. ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 3.00 (ddd, J_1 = 15.0 Hz, J_2 = 11.1 Hz, J_3 = 2.4 Hz, 1H), 3.22 (ddd, J_1 = 15.1 Hz, J_2 = 4.2 Hz, J_3 = 1.8 Hz, 1H), 3.81 (s, 3H), 3.97 (dd, J_1 = 11.0 Hz, J_2 = 4.2 Hz, 1H), 5.26 (s, 1H), 7.08–7.16 (m, 4H), 7.22 (d, J = 7.4 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.39 (dd, J_1 = 7.8 Hz, J_2 = 7.7 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.55 (br s, 1H, NH on the indole ring). ^{13}C NMR ($CDCl_3$) δ 173.6, 170.1, 151.4, 143.1, 136.8, 134.6, 130.3, 127.4, 126.6, 122.40, 122.38, 122.2, 120.0, 118.6, 111.6, 109.2, 58.6, 57.3, 52.7, 26.1, 21.5. MS (EI) *m*/*z* (%) 364 (M^+, 100), 349 (7), 305 (55), 277 (32), 261 (25), 235 (64), 229 (27), 218 (28), 191 (5), 169 (29), 144 (28), 130 (4), 115 (6). IR (KBr) 3390, 2975, 1745, 1739, 1600, 1452, 1370, 1268, 1211, 744 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{20}N_2O_4$: 364.1423; found: 364.1426.

4.3.3. (1*R*,3*S*)-Methyl 1-(3-benzoyloxy-4-methoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (1*R*,3*S*)-*trans*-2c

Mp 197–198 °C. $[\alpha]_D^{20} = -36.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.30 (br s, 1H, NH), 3.09 (ddd, J_1 = 15.4 Hz, J_2 = 7.1 Hz, J_3 = 1.3 Hz, 1H), 3.24 (dd, J_1 = 15.4 Hz, J_2 = 5.4 Hz, 1H), 3.71 (s, 3H), 3.78 (s, 3H), 3.95 (dd, J_1 = 7.1 Hz, J_2 = 5.4 Hz, 1H), 5.30 (s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 2.1 Hz, 1H), 7.07–7.18 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 7.47 (dd, J_1 = 7.9 Hz, J_2 = 7.5 Hz, 2H), 7.53 (d, J = 7.3 Hz, 1H), 7.60 (dd, J_1 = 7.4 Hz, J_2 = 7.2 Hz, 1H), 7.87 (s, 1H, NH on the indole ring), 8.15 (dd, J_1 = 7.2 Hz, J_2 = 1.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 173.0, 163.7, 150.0, 138.8, 135.2, 133.8, 132.5, 132.1, 129.2, 128.1, 127.4, 125.75, 125.72, 121.9, 120.7, 118.2, 117.0, 111.3, 110.2, 107.1, 54.9, 52.9, 51.0, 50.9, 23.9. MS (EI) *m*/*z* (%) 456 (M^+, 100), 441 (12), 397 (23), 351 (12), 264 (8), 248 (9), 204 (8), 169 (14), 105 (52), 77 (11). IR (KBr) 3373, 2952, 2878, 1739, 1723, 1543, 1510, 1317, 1267, 1209, 1120, 1024, 745, 708 cm^{-1}. Anal. Calcd for $C_{27}H_{24}N_2O_5$: C, 71.04; H, 5.30; N, 6.14. Found: C, 71.31; H, 5.13; N, 6.10.

4.3.4. (1*R*,3*S*)-Methyl 1-(3-acetoxy-4-methoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (1*R*,3*S*)-*trans*-2d

Mp 85–86 °C. $[\alpha]_D^{20} = -29.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.30 (br s, 1H, NH), 3.08 (dd, J_1 = 15.5 Hz, J_2 = 6.8 Hz, 1H), 3.23 (dd, J_1 = 15.5 Hz, J_2 = 5.1 Hz, 1H), 3.70 (s, 3H), 3.79 (s, 3H), 3.91 (dd, J_1 = 6.8 Hz, J_2 = 5.6 Hz, 1H), 5.27 (s, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.90 (d, J = 2.3 Hz, 1H), 7.05–7.18 (m, 3H), 7.23 (d, J = 7.4 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.87 (s, 1H, NH on the indole ring). ^{13}C NMR ($CDCl_3$) δ 174.1, 169.2, 150.9, 139.7, 136.3, 134.8, 133.2, 126.9,

126.8, 122.9, 121.9, 119.4, 118.1, 112.3, 111.3, 108.3, 56.0, 54.0, 52.1, 52.0, 25.0, 20.6. MS (EI) *m*/*z* (%) 394 (M^+, 100), 379 (10), 335 (35), 278 (10), 248 (10), 204 (9), 169 (15), 144 (8), 115 (2), 103 (1), 77 (1). IR (KBr) 3382, 2950, 2842, 1764, 1736, 1511, 1450, 1369, 1268, 1202, 1119, 1023, 744 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.89; H, 5.48; N, 7.33.

4.3.5. (1*R*,3*R*)-Methyl 1-(3-acetoxy-4-methoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (1*R*,3*R*)-*cis*-2d

Mp 102–103 °C. $[\alpha]_D^{20} = +9.5$ (*c* 5.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H), 2.98 (ddd, J_1 = 15.0 Hz, J_2 = 11.2 Hz, J_3 = 2.5 Hz, 1H), 3.21 (ddd, J_1 = 15.0 Hz, J_2 = 4.2 Hz, J_3 = 1.8 Hz, 1H), 3.80 (s, 3H), 3.83 (s, 3H), 3.95 (dd, J_1 = 11.2 Hz, J_2 = 4.2 Hz, 1H), 5.17 (s, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 2.1 Hz, 1H), 7.07–7.17 (m, 2H), 7.19–7.28 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H, NH on the indole ring). ^{13}C NMR ($CDCl_3$) δ 173.2, 169.5, 151.2, 139.7, 136.4, 134.7, 133.6, 127.3, 127.0, 123.2, 121.8, 119.4, 118.1, 112.6, 111.2, 108.6, 57.8, 56.9, 56.0, 52.3, 25.7, 20.6. MS (EI) *m*/*z* (%) 394 (M^+, 100), 335 (34), 307 (20), 265 (15), 248 (16), 234 (10), 204 (7), 169 (11), 144 (7), 115 (1), 102 (1). IR (KBr) 3384, 2950, 2843, 1761, 1739, 1512, 1440, 1368, 1267, 1205, 1120, 787, 743, 699 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.14; H, 5.46; N, 7.02.

4.3.6. (1*R*,3*S*)-Methyl 1-(3,4-diacetoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (1*R*,3*S*)-*trans*-2e

Mp 75–76 °C. $[\alpha]_D^{20} = -38.5$ (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.22 (s, 3H), 2.26 (s, 3H), 2.33 (br s, 1H, NH), 3.07 (ddd, J_1 = 15.5 Hz, J_2 = 7.5 Hz, J_3 = 1.2 Hz, 1H), 3.24 (dd, J_1 = 15.5 Hz, J_2 = 5.1 Hz, 1H), 3.71 (s, 3H), 3.90 (dd, J_1 = 7.5 Hz, J_2 = 5.1 Hz, 1H), 5.26 (s, 1H), 7.03 (s, 1H), 7.09–7.21 (m, 4H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 8.04 (s, 1H, NH on the indole ring). ^{13}C NMR ($CDCl_3$) δ 174.0, 168.5, 168.4, 142.1, 141.7, 141.0, 136.4, 132.6, 126.8, 126.6, 123.5, 123.4, 122.0, 119.4, 118.2, 111.4, 108.4, 54.0, 52.2, 51.9, 25.0, 20.6, 20.5. MS (EI) *m*/*z* (%) 422 (M^+, 100), 363 (27), 321 (21), 277 (8), 234 (9), 169 (8), 144 (5), 115 (1). IR (KBr) 3386, 3057, 2951, 1773, 1736, 1502, 1452, 1436, 1371, 1258, 1210, 1178, 1107, 1011, 901, 744 cm^{-1}. Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.23; H, 5.23; N, 6.76.

4.3.7. (1*R*,3*R*)-Methyl 1-(3,4-diacetoxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (1*R*,3*R*)-*cis*-2e

Mp 78–79 °C. $[\alpha]_D^{20} = +5.6$ (*c* 7.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.29 (s, 3H), 2.99 (ddd, J_1 = 15.0 Hz, J_2 = 11.2 Hz, J_3 = 2.5 Hz, 1H), 3.22 (ddd, J_1 = 15.0 Hz, J_2 = 4.1 Hz, J_3 = 1.7 Hz, 1H), 3.80 (s, 3H), 3.95 (dd, J_1 = 11.2 Hz, J_2 = 4.1 Hz, 1H), 5.24 (s, 1H), 7.08–7.24 (m, 5H), 7.28 (dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, 1H), 7.53 (d, *J* = 7.1 Hz, 1H), 7.67 (s, 1H, NH on the indole ring). ^{13}C NMR ($CDCl_3$) δ 173.0, 168.39, 168.37, 142.3, 142.2, 139.8, 136.4, 134.0, 126.9, 123.8, 122.0, 119.6, 118.2, 111.2, 108.9, 57.9, 56.8, 52.3, 25.6, 20.6, 20.5. MS (EI) *m*/*z* (%) 422 (M^+, 100), 363 (34), 335 (21), 277 (12), 250 (18), 234 (19), 233 (14), 229 (11), 204 (9), 169 (15), 144 (10), 115 (2). IR (KBr) 3385, 2951, 2848, 1771, 1739, 1503, 1436, 1210, 1108, 900, 744 cm^{-1}. Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.31; H, 5.13; N, 6.88.

4.3.8. (1*R*,3*S*)-Methyl 1-(3,4-dibenzoyloxyphenyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (1*R*,3*S*)-*trans*-2f

Mp 231–232 °C. $[\alpha]_D^{20} = -47.5$ (*c* 0.4, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 3.19 (dd, J_1 = 15.4 Hz, J_2 = 7.0 Hz, 1H), 3.35 (dd, J_1 = 15.4 Hz, J_2 = 5.2 Hz, 1H), 3.73 (s, 3H), 4.07 (dd, J_1 = 7.0 Hz, J_2 = 6.0 Hz, 1H), 5.53 (s, 1H), 7.07–7.20 (m, 2H), 7.27–7.39 (m, 8H), 7.47–7.57 (m, 3H), 7.97 (dd, J_1 = 8.5 Hz, J_2 = 1.3 Hz, 2H), 8.02 (dd, J_1 = 8.5 Hz, J_2 = 1.3 Hz, 2H), 8.11 (s, 1H, NH on the indole ring). ^{13}C NMR (DMSO-d_6) δ 173.8, 163.60, 163.59, 142.4, 141.9, 141.2, 136.2, 134.1, 134.2, 133.7, 129.54, 129.53, 129.52, 129.51, 128.87, 128.86, 128.85, 128.84, 128.04, 128.02, 126.7, 126.5, 123.3, 123.1, 121.0, 118.4, 117.7, 111.2, 106.8, 53.3, 51.8, 51.7, 24.8. MS (EI) *m*/*z* (%) 546 (M^+, 19), 529 (5), 487 (4), 441 (5), 425 (2), 354 (2), 261 (3), 169 (3), 106 (6), 105 (100), 77 (16). IR (KBr) 3313, 3171, 1741, 1725, 1504, 1453, 1248, 1142, 1058, 1124, 1024, 750, 710 cm^{-1}. Anal. Calcd for $C_{33}H_{26}N_2O_6$: C, 72.52; H, 4.79; N, 5.13. Found: C, 72.33; H, 4.71; N, 5.10.

4.4. General procedure for the one-pot synthesis of HR22C16-like Eg5 inhibitors 1 from compounds 2

A solution of (1*R*,3*S*)-*trans*-**2** or (1*R*,3*R*)-*cis*-**2** (3.00 mmol) and triethylamine (15.00 mmol) in dichloromethane (20 mL) was cooled to 0 °C in an ice-bath. A freshly prepared solution of triphosgene (1.50 mmol) in dichloromethane (2 mL) was added dropwise over 1 min, and the reaction mixture was then stirred at 0 °C for around 15 min. A primary amine R^1NH_2 (30.00 mmol) was added, and the mixture was then stirred at 0 °C for around 15 min. The ice-bath was removed, and the mixture was heated and stirred at reflux for around 3 h. The reaction solution was then concentrated to dryness under vacuum, after which the residue was dissolved in methanol (20 mL). Triethylamine (9.00 mmol) was added, and the solution was heated and stirred at reflux for around 3 h. Removal of the solvent by vacuum distillation produced an oily residue which was then allowed to partition between ethyl acetate (40 mL) and dilute aqueous HCl solution (2 M, 20 mL). The organic phase was separated, washed with a saturated aqueous solution of sodium bicarbonate (15 mL), and dried over anhydrous sodium sulfate. Evaporation of the solvent under vacuum gave a crude product which was purified by flash chromatography to afford compounds **1** in 87–95% yield (see also Table 2). Characterization data for all compounds **1a**–**1r** are as follows.

4.4.1. (5*R*,11a*S*)-2-Butyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1a

Mp 107–108 °C (lit.[38] 107–108 °C). $[\alpha]_D^{20} = -231.5$ (*c* 0.3, $CHCl_3$). ^1H NMR (DMSO-d_6) δ 0.86 (t, *J* = 7.3 Hz, 3H), 1.20–1.28 (m, 2H), 1.45–1.52 (m, 2H), 2.78 (dd, J_1 = 13.9 Hz, J_2 = 11.2 Hz, 1H), 3.32–3.42 (m, 3H), 4.48 (dd, J_1 = 10.8 Hz, J_2 = 5.7 Hz, 1H), 6.12 (s, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 6.71 (s, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 7.01 (dd, J_1 = 7.3 Hz, J_2 = 7.2 Hz, 1H), 7.08 (dd, J_1 = 7.2 Hz, J_2 = 7.6 Hz, 1H), 7.15 (dd, J_1 = 7.9 Hz, J_2 = 8.6 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 9.46 (s, 1H), 10.93 (s, 1H, NH on the indole ring). ^{13}C NMR (DMSO-d_6) δ 172.6, 157.7, 154.3, 141.4, 136.7, 131.2, 129.8, 125.8, 121.7, 118.8, 118.5, 118.2, 115.1, 114.8, 111.4, 106.0, 52.8, 51.4, 37.7, 29.7, 22.8, 19.4, 13.5. MS (EI) *m*/*z* (%) 389 (M^+, 100), 296 (35), 261 (18), 234 (41), 218 (14), 206 (6), 196 (3), 169 (9), 115 (2). IR (KBr) 3340, 2954, 2929, 2870, 1757, 1701, 1591, 1458, 1426, 1328, 1240, 749 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{23}N_3O_3$: 389.1739; found: 389.1734.

4.4.2. (5*R*,11a*S*)-2-Propyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1b

Mp 122–123 °C (lit.[37] 120 °C). $[\alpha]_D^{20} = -202.4$ (*c* 0.5, $CHCl_3$). ^1H NMR (DMSO-d_6) δ 0.83 (t, *J* = 7.4 Hz, 3H), 1.45–1.62 (m, 2H), 2.81 (ddd, J_1 = 15.0 Hz, J_2 = 11.9 Hz, J_3 = 1.4 Hz, 1H), 3.31–3.43 (m, 3H), 4.50 (dd, J_1 = 10.8 Hz, J_2 = 5.7 Hz, 1H), 6.15 (s, 1H), 6.69–6.76 (m, 2H), 6.79 (d, *J* = 7.8 Hz, 1H), 7.02 (dd, J_1 = 7.6 Hz, J_2 = 7.8 Hz, 1H), 7.10 (dd, J_1 = 8.0 Hz, J_2 = 8.2 Hz, 1H), 7.17 (dd, J_1 = 8.2 Hz, J_2 = 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 9.46 (s, 1H), 10.94 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.6, 157.6, 154.3, 141.4, 136.6, 131.2, 129.7, 125.7, 121.6, 118.8, 118.4, 118.2, 115.0, 114.7, 111.4, 106.0, 52.7, 51.3, 39.6, 22.7, 20.9, 11.04. MS (EI) *m*/*z* (%) 375 (M^+, 100), 282 (30), 261 (18), 234

(31), 218 (13), 169 (11), 140 (2), 115 (3). IR (KBr) 3335, 2934, 1763, 1698, 1456, 1425, 1239, 745, 713 cm^{-1}. Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.41; H, 5.68; N, 11.13.

4.4.3. (5*R*,11a*S*)-2-Hydroxyethyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1c

Mp 256–257 °C. $[\alpha]_D^{20} = -238.1$ (*c* 0.6, CH_3OH). ^1H NMR (DMSO-d_6) δ 2.85 (dd, J_1 = 14.1 Hz, J_2 = 11.0 Hz, 1H), 3.30–3.42 (m, 1H), 3.44–3.61 (m, 4H), 4.46 (dd, J_1 = 11.0 Hz, J_2 = 5.8 Hz, 1H), 4.84 (dd, J_1 = 5.8 Hz, J_2 = 5.7 Hz, 1H), 6.15 (s, 1H), 6.70–6.85 (m, 3H), 7.04 (dd, J_1 = 7.4 Hz, J_2 = 7.2 Hz, 1H), 7.11 (dd, J_1 = 7.4 Hz, J_2 = 7.2 Hz, 1H), 7.17 (dd, J_1 = 7.8 Hz, J_2 = 7.7 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 9.48 (s, 1H), 10.93 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.7, 157.6, 154.4, 141.4, 136.6, 131.2, 129.8, 125.8, 121.6, 118.8, 118.5, 118.1, 115.1, 114.8, 111.4, 106.0, 57.6, 52.7, 51.3, 40.9, 22.6. MS (EI) *m*/*z* (%) 377 (M^+, 100), 360 (2), 332 (2), 284 (22), 261 (20), 234 (37), 218 (12), 204 (6), 169 (10), 115 (2). IR (KBr) 3291, 2940, 1763, 1699, 1455, 1426, 1237, 1045, 755, 714 cm^{-1}. Anal. Calcd for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.72; H, 5.14; N, 11.12.

4.4.4. (5*R*,11a*S*)-2-Benzyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1d

Mp 151–152 °C (lit.[38] 150–151 °C). $[\alpha]_D^{20} = -162.5$ (*c* 0.8, $CHCl_3$) {lit.[38] $[\alpha]_D^{20} = -162.6$ (*c* 0.9, $CHCl_3$)}. ^1H NMR (DMSO-d_6) δ 2.82 (dd, J_1 = 14.1 Hz, J_2 = 11.3 Hz, 1H), 3.40 (dd, J_1 = 15.1 Hz, J_2 = 5.7 Hz, 1H), 4.56–4.63 (m, 3H), 6.14 (s, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.71 (s, 1H), 6.77 (d, J = 7.7 Hz, 1H), 7.01 (dd, J_1 = 7.2 Hz, J_2 = 7.6 Hz, 1H), 7.09 (dd, J_1 = 7.5 Hz, J_2 = 7.6 Hz, 1H), 7.15 (dd, J_1 = 7.6 Hz, J_2 = 7.7 Hz, 1H), 7.22–7.34 (m, 6H), 7.54 (d, J = 7.8 Hz, 1H), 9.46 (s, 1H), 10.94 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.5, 157.7, 154.1, 141.4, 136.7, 136.6, 131.2, 129.8, 128.61, 128.60, 127.47, 127.42, 127.41, 125.8, 121.7, 118.9, 118.5, 118.2, 115.2, 114.9, 111.4, 106.0, 53.0, 51.6, 41.5, 22.8. MS (EI) *m*/*z* (%) 423 (M^+, 100), 422 (10), 345 (2), 332 (28), 261 (29), 234 (25), 218 (9), 206 (4), 169 (4), 115 (2). IR (KBr) 3411, 2980, 1765, 1703, 1602, 1453, 1240, 1142, 749, 702 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{21}N_3O_3$: 423.1583; found: 423.1579.

4.4.5. (5*R*,11a*S*)-2-Isopropyl-5-(3-hydroxy-4-methoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1e

Mp 221–222 °C. $[\alpha]_D^{20} = -231.9$ (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.39 (d, J = 6.9 Hz, 3H), 1.40 (d, J = 6.9 Hz, 3H), 2.79 (dd, J_1 = 15.3 Hz, J_2 = 11.0 Hz, 1H), 3.39 (dd, J_1 = 15.3 Hz, J_2 = 5.6 Hz, 1H), 3.79 (s, 3H), 4.17 (dd, J_1 = 11.0 Hz, J_2 = 5.6 Hz, 1H), 4.24–4.37 (m, 1H), 5.78 (s, 1H), 6.12 (s, 1H), 6.72–6.80 (m, 2H), 6.83 (dd, J_1 = 8.2 Hz, J_2 = 1.7 Hz, 1H), 7.11–7.23 (m, 2H), 7.26 (d, J = 7.3 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 8.20 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.4, 153.8, 147.6, 146.6, 136.6, 132.7, 131.5, 125.8, 121.6, 118.8, 118.1, 115.2, 112.4, 111.3, 105.9, 55.7, 52.1, 51.0, 42.7, 22.8, 19.5, 19.4. MS (EI) *m*/*z* (%) 405 (M^+, 100), 388 (8), 374 (9), 362 (6), 291 (12), 265 (14), 234 (15), 204 (7), 169 (7), 115 (2). IR (KBr) 3335, 2965, 2930, 1758, 1703, 1430, 1278, 1127, 805, 729 cm^{-1}. Anal. Calcd for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 67.94; H, 5.74; N, 10.51.

4.4.6. (5*R*,11a*S*)-2-(5-Azido-pentyl)-5-(3-hydroxy-4-methoxyphenyl)-6*H*-1,2,3,5, 11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1f

Mp 98–99 °C. $[\alpha]_D^{20} = -205.4$ (*c* 0.8, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.30–1.41 (m, 2H), 1.52–1.68 (m, 4H), 2.81 (dd, J_1 = 15.1 Hz, J_2 = 11.1 Hz, 1H), 3.22 (t, J = 6.9 Hz, 2H), 3.35–3.56 (m, 3H), 3.79 (s, 3H). 4.24 (dd, J_1 = 11.0 Hz, J_2 = 5.5 Hz, 1H), 5.80 (s, 1H), 6.14 (s, 1H), 6.71–6.79 (m, 2H), 6.82 (dd, J_1 = 8.2 Hz, J_2 = 1.9 Hz, 1H), 7.12–7.24 (m, 2H), 7.27 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 7.4 Hz, 1H), 8.24 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 173.1, 154.8, 147.1, 145.8, 136.7, 132.5, 130.8, 126.1, 122.6, 120.0, 119.9, 118.4, 114.4, 111.3, 110.9, 107.4, 55.9, 53.2, 51.7, 51.2, 38.4, 28.3, 27.7, 23.8, 23.3. MS (EI) *m*/*z* (%) 474 (M^+, 25), 446 (33), 416 (12), 388 (20), 362 (10), 317 (9), 291 (100), 276 (23), 248 (14), 234 (15), 204 (22), 169 (17), 115 (5). IR (KBr) 3336, 2934, 2096, 1764, 1702, 1454, 1273, 1128, 747 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_6O_4$: C, 63.28; H, 5.52; N, 17.71. Found: C, 63.02; H, 5.64; N, 17.89.

4.4.7. (5*R*,11a*S*)-2-Phenethyl-5-(3-hydroxy-4-methoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1g

Mp 117–118 °C. $[\alpha]_D^{20} = -192.4$ (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 2.69 (ddd, J_1 = 15.2 Hz, J_2 = 11.1 Hz, J_3 = 1.6 Hz, 1H), 2.92 (t, J = 7.8 Hz, 2H), 3.35 (dd, J_1 = 15.2 Hz, J_2 = 5.5 Hz, 1H), 3.65–3.78 (m, 2H), 3.81 (s, 3H), 4.17 (dd, J_1 = 11.1 Hz, J_2 = 5.5 Hz, 1H), 5.75 (s, 1H), 6.13 (s, 1H), 6.72–6.78 (m, 2H), 6.82 (dd, J_1 = 8.3 Hz, J_2 = 2 Hz, 1H), 7.12–7.29 (m, 8H), 7.53 (d, J = 7.3 Hz, 1H), 8.12 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 172.8, 154.6, 147.1, 145.9, 137.8, 136.7, 132.5, 130.8, 128.96, 128.95, 128.55, 128.54, 126.7, 126.2, 122.6, 120.1, 119.9, 118.4, 114.4, 111.4, 110.9, 107.5, 55.9, 53.2, 51.6, 39.8, 34.0, 23.2. HRMS (ESI) calcd for $C_{28}H_{25}N_3O_4Na$ $[M+Na]^+$: 490.1743; found: 490.1735. IR (KBr) 3339, 3059, 3026, 2935, 1765, 1704, 1511, 1454, 1272, 1129, 747, 701 cm^{-1}.

4.4.8. (5*R*,11a*S*)-2-Isopropyl-5-(3,4-dihydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1h

Mp 94–95 °C. $[\alpha]_D^{20} = -192.5$ (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.32 (d, J = 6.9 Hz, 3H), 1.33 (d, J = 6.9 Hz, 3H), 2.73 (dd, J_1 = 14.3 Hz, J_2 = 11.5 Hz, 1H), 3.32 (dd, J_1 = 15.2 Hz, J_2 = 5.5 Hz, 1H), 4.15 (dd, J_1 = 10.6 Hz, J_2 = 5.3 Hz, 1H), 4.20–4.32 (m, 1H), 6.00 (s, 1H), 6.54 (dd, J_1 = 8.1 Hz, J_2 = 1.4 Hz, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.76 (s, 2H), 6.92 (s, 1H), 7.06–7.17 (m, 2H), 7.20 (d, J = 7.4 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H), 8.34 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 173.3, 155.2, 144.4, 144.2, 136.6, 131.8, 130.7, 126.0, 122.7, 120.5, 119.9, 118.4, 115.8, 115.4, 111.3, 107.2, 53.0, 51.8, 44.1, 23.2, 19.7, 19.6. HRMS (ESI) calcd for $C_{22}H_{21}N_3O_4Na$ $[M+Na]^+$: 414.1430; found: 414.1431. IR (KBr) 3351, 2976, 2934, 1758, 1696, 1435, 1391, 1283, 1110, 745, 688 cm^{-1}.

4.4.9. (5*R*,11a*S*)-2-(5-Azido-pentyl)-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1i

Mp 127–128 °C (lit.[38] 127–128 °C). $[\alpha]_D^{20} = -204.6$ (*c* 0.3, $CHCl_3$) {lit.[38] $[\alpha]_D^{20} = -204.8$ (*c* 0.2, $CHCl_3$)}. ^1H NMR (DMSO-d_6) δ 1.23–1.31 (m, 2H), 1.49–1.57 (m, 4H), 2.80 (dd, J_1 = 14.0 Hz, J_2 = 11.2 Hz, 1H), 3.28 (t, J = 6.9 Hz, 2H), 3.34–3.43 (m, 3H), 4.48 (dd, J_1 = 10.8 Hz, J_2 = 5.7 Hz, 1H), 6.12 (s, 1H), 6.71 (d, J = 7.0 Hz, 1H), 6.72 (s, 1H), 6.77 (d, J = 7.7 Hz, 1H), 7.01 (dd, J_1 = 7.5 Hz, J_2 = 7.3 Hz, 1H), 7.09 (dd, J_1 = 7.2 Hz, J_2 = 7.4 Hz, 1H), 7.15 (dd, J_1 = 8.0 Hz, J_2 = 8.3 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 9.46 (br s, 1H), 10.93 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.6, 157.7, 154.3, 141.4, 136.7, 131.2, 129.8, 125.8, 121.7, 118.9, 118.5, 118.2, 115.1, 114.8, 111.4, 106.0, 52.8, 51.4, 50.5, 37.8, 27.8, 27.1, 23.3, 22.8. MS (EI) *m*/*z* (%) 444 (M^+, 31), 416 (41), 386 (13), 372 (11), 358 (22), 345 (5), 332 (12), 304 (4), 294 (22), 287 (11), 274 (3), 261 (100), 246 (5), 234 (41), 218 (15), 206 (12), 195 (3), 169 (13), 115 (4), 105 (4), 84 (5), 70 (7). IR (KBr) 3328, 2936, 2861, 2096, 1766, 1702, 1589, 1459, 1356, 1327, 1239, 1141, 749 cm^{-1}. HRMS (EI) calcd for $C_{24}H_{24}N_6O_3$: 444.1910; found: 444.1913.

4.4.10. (5*R*,11a*S*)-2-Isopropyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1j

Mp 177–178 °C. $[\alpha]_D^{20} = -223.8$ (*c* 0.8, $CHCl_3$). ^1H NMR (DMSO-d_6) δ 1.33 (d, J = 6.9 Hz, 3H), 1.34 (d, J = 6.9 Hz, 3H), 2.80 (ddd,

J_1 = 15.0 Hz, J_2 = 10.9 Hz, J_3 = 1.3 Hz, 1H), 3.30–3.43 (m, 1H), 4.15–4.28 (m, 1H), 4.43 (dd, J_1 = 10.9 Hz, J_2 = 5.7 Hz, 1H), 6.13 (s, 1H), 6.71–6.76 (m, 2H), 6.79 (d, J = 7.6 Hz, 1H), 7.03 (dd, J_1 = 7.6 Hz, J_2 = 7.5 Hz, 1H), 7.10 (dd, J_1 = 7.6 Hz, J_2 = 7.5 Hz, 1H), 7.17 (dd, J_1 = 8.1 Hz, J_2 = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 9.48 (s, 1H) 10.93 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.4, 157.6, 154.0, 141.4, 136.6, 131.2, 129.8, 125.8, 121.6, 118.8, 118.5, 118.1, 115.1, 114.8, 111.4, 105.9, 52.2, 51.3, 42.7, 22.7, 19.5, 19.4. MS (EI) m/z (%) 375 (M^+, 100), 332 (4), 282 (23), 261 (22), 234 (46), 218 (15), 169 (14), 115 (4). IR (KBr) 3344, 2979, 1758, 1689, 1435, 1235, 747, 712 cm^{-1}. Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.51; H, 5.60; N, 11.28.

4.4.11. (5*R*,11a*S*)-2-Phenethyl-5-(3-hydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1k

Mp 107–108 °C. $[\alpha]_D^{20} = -213.1$ (c 0.4, $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ 2.67 (ddd, J_1 = 15.0 Hz, J_2 = 10.9 Hz, J_3 = 1.3 Hz, 1H), 2.81–2.95 (m, 2H), 3.31 (dd, J_1 = 15.0 Hz, J_2 = 5.7 Hz, 1H), 3.65 (dd, J_1 = 7.4 Hz, J_2 = 7.3 Hz, 2H), 4.38 (dd, J_1 = 10.9 Hz, J_2 = 5.7 Hz, 1H), 6.13 (s, 1H), 6.70–6.80 (m, 3H), 7.02 (dd, J_1 = 7.6 Hz, J_2 = 7.7 Hz, 1H), 7.06–7.24 (m, 7H), 7.31 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 9.47 (s, 1H), 10.95 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.2, 157.6, 154.0, 141.2, 138.0, 136.6, 131.1, 129.7, 128.65, 128.64, 128.30, 128.31, 126.4, 125.7, 121.6, 118.8, 118.4, 118.2, 115.0, 114.7, 111.4, 106.0, 52.6, 51.3, 39.2, 33.1, 22.6. MS (EI) m/z (%) 437 (M^+, 100), 420 (2), 408 (1), 359 (2), 344 (15), 261 (13), 247 (7), 234 (25), 218 (8), 169 (7), 104 (2), 91 (4). IR (KBr) 3328, 2929, 1765, 1700, 1599, 1455, 1238, 1135, 747, 701 cm^{-1}. Anal. Calcd for $C_{27}H_{23}N_3O_3$: C, 74.12; H, 5.30; N, 9.60. Found: C, 74.23; H, 5.34; N, 9.85.

4.4.12. (5*R*,11a*S*)-2-Propyl-5-(3-hydroxy-4-methoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1l

Mp 127–128 °C. $[\alpha]_D^{20} = -223.7$ (c 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.4 Hz, 3H), 1.52–1.70 (m, 2H), 2.80 (dd, J_1 = 14.6 Hz, J_2 = 11.6 Hz, 1H), 3.32–3.51 (m, 3H), 3.77 (s, 3H), 4.21 (dd, J_1 = 11.0 Hz, J_2 = 5.5 Hz, 1H), 5.83 (s, 1H), 6.12 (s, 1H), 6.69–6.77 (m, 2H), 6.80 (d, J = 8.2 Hz, 1H), 7.11–7.23 (m, 2H), 7.26 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 8.34 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 173.2, 154.9, 147.0, 145.8, 136.7, 132.5, 130.9, 126.1, 122.6, 120.1, 119.9, 118.4, 114.4, 111.3, 110.9, 107.4, 55.8, 53.2, 51.6, 40.3, 23.4, 21.5, 11.2. MS (EI) m/z (%) 405 (M^+, 100), 388 (8), 374 (10), 282 (15), 264 (14), 234 (15), 204 (7), 169 (8), 115 (2). IR (KBr) 3341, 2934, 2963, 1765, 1702, 1511, 1454, 1273, 1126, 744 cm^{-1}. Anal. Calcd for $C_{23}H_{23}N_3O_4$: C, 68.13; H, 5.72; N, 10.36. Found: C, 68.23; H, 5.91; N, 10.18.

4.4.13. (5*R*,11a*S*)-2-Butyl-5-(3-hydroxy-4-methoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1m

Mp 119–120 °C. $[\alpha]_D^{20} = -226.9$ (c 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.26–1.37 (m, 2H), 1.54–1.65 (m, 2H), 2.83 (ddd, J_1 = 15.2 Hz, J_2 = 11.0 Hz, J_3 = 1.7 Hz, 1H), 3.41–3.57 (m, 3H), 3.82 (s, 3H), 4.25 (dd, J_1 = 11.0 Hz, J_2 = 5.5 Hz, 1H), 5.70 (s, 1H), 6.17 (s, 1H), 6.75–6.82 (m, 2H), 6.85 (dd, J_1 = 8.2 Hz, J_2 = 2.1 Hz, 1H), 7.13–7.24 (m, 2H), 7.28 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 8.08 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 173.1, 154.9, 147.0, 145.8, 136.7, 132.5, 130.9, 126.1, 122.6, 120.1, 119.9, 118.4, 114.4, 111.3, 110.9, 107.4, 55.9, 53.2, 51.6, 38.6, 30.2, 23.4, 20.0, 13.6. MS (EI) m/z (%) 419 (M^+, 100), 402 (10), 388 (11), 296 (14), 265 (13), 250 (10), 234 (12), 204 (5), 169 (6), 115 (1). IR (KBr) 3342, 2956, 2931, 1764, 1702, 1511, 1454, 1273, 1127, 744 cm^{-1}. Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02. Found: C, 68.81; H, 5.98; N, 10.22.

4.4.14. (5*R*,11a*S*)-2-Hydroxyethyl-5-(3-hydroxy-4-methoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1n

Mp 228–229 °C. $[\alpha]_D^{20} = -230.7$ (c 1.0, CH_3OH). ^{1}H NMR (DMSO-d_6) δ 2.83 (dd, J_1 = 14.1 Hz, J_2 = 11.2 Hz, 1H), 3.41 (dd, J_1 = 11.2 Hz, J_2 = 5.7 Hz, 1H), 3.42–3.60 (m, 4H), 3.75 (s, 3H), 4.41 (dd, J_1 = 10.8 Hz, J_2 = 5.7 Hz, 1H), 4.81 (dd, J_1 =5.6 Hz, J_2 = 5.5 Hz, 1H), 6.06 (s, 1H), 6.71–6.82 (m, 2H), 6.91 (d, J = 8.3 Hz, 1H), 7.03 (dd, J_1 = 7.7 Hz, J_2 = 7.1 Hz, 1H), 7.11 (dd, J_1 = 7.7 Hz, J_2 = 7.1 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 9.06 (s, 1H), 10.91 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.8, 154.3, 147.6, 146.6, 136.6, 132.7, 131.5, 125.8, 121.6, 118.8, 118.1, 115.2, 112.3, 111.3, 106.0, 57.6, 55.7, 52.6, 51.0, 40.9, 22.6. MS (EI) m/z (%) 407 (M^+, 100), 390 (6), 376 (8), 291 (11), 284 (12), 264 (12), 234 (11), 204 (7), 169 (7), 115 (2). IR (KBr) 3308, 2976, 2845, 1766, 1704, 1511, 1451, 1274, 1233, 1122, 1017, 750, 657, 610 cm^{-1}. Anal. Calcd for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 64.77; H, 5.34; N, 10.15.

4.4.15. (5*R*,11a*S*)-2-Benzyl-5-(3-hydroxy-4-methoxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1o

Mp 121–122 °C. $[\alpha]_D^{20} = -191.3$ (c 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.70 (ddd, J_1 = 15.2 Hz, J_2 = 11.1 Hz, J_3 = 1.6 Hz, 1H), 3.35 (dd, J_1 = 15.2 Hz, J_2 = 5.6 Hz, 1H), 3.75 (s, 3H), 4.23 (dd, J_1 = 11.1 Hz, J_2 = 5.6 Hz, 1H), 4.53 (d, J = 14.6 Hz, 1H), 4.66 (d, J = 14.6 Hz, 1H), 5.82 (s, 1H), 6.10 (s, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 6.80 (dd, J_1 = 8.2 Hz, J_2 = 2.1 Hz, 1H), 7.08–7.30 (m, 6H), 7.33–7.39 (m, 2H), 7.43–7.50 (m, 1H), 8.21 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 172.7, 154.6, 147.1, 145.9, 136.7, 136.1, 132.4, 130.7, 128.74, 128.73, 128.64, 128.63, 128.0, 126.1, 122.6, 120.2, 119.9, 118.4, 114.4, 111.3, 110.9, 107.4, 55.9, 53.3, 51.7, 42.3, 23.2. HRMS (ESI) calcd for $C_{27}H_{23}N_3O_4Na$ [M+Na]$^+$: 476.1586; found: 476.1581. IR (KBr) 3341, 3060, 3032, 2931, 2843, 1767, 1706, 1511, 1445, 1128, 749, 698 cm^{-1}.

4.4.16. (5*R*,11a*S*)-2-(5-Azido-pentyl)-5-(3,4-dihydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1p

Mp 152–153 °C. $[\alpha]_D^{20} = -180.9$ (c 0.6, CH_3OH). ^{1}H NMR (DMSO-d_6) δ 1.21–1.35 (m, 2H), 1.44–1.60 (m, 4H), 2.79 (dd, J_1 = 12.1 Hz, J_2 = 10.5 Hz, 1H), 3.22–3.50 (m, 5H), 4.43 (dd, J_1 = 10.5 Hz, J_2 = 5.6 Hz, 1H), 6.07 (s, 1H), 6.59 (d, J = 7.7 Hz, 1H), 6.70 (s, 1H), 6.71 (d, J = 7.9 Hz, 1H), 7.02 (dd, J_1 = 7.4 Hz, J_2 = 7.2 Hz, 1H), 7.09 (dd, J_1 = 7.6 Hz, J_2 = 7.2 Hz, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 8.95 (s, 1H), 8.96 (s, 1H), 10.92 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.6, 154.0, 145.4, 145.2, 136.6, 131.7, 131.0, 125.8, 121.5, 118.9, 118.7, 118.1, 115.6, 115.2, 111.3, 105.9, 52.5, 51.1, 50.4, 37.7, 27.7, 27.1, 23.3, 22.8. HRMS (ESI) calcd for $C_{24}H_{24}N_6O_4Na$ [M+Na]$^+$: 483.1757; found: 483.1757. IR (KBr) 3334, 2932, 2857, 2097, 1761, 1696, 1455, 1426, 1282, 1114, 746, 697 cm^{-1}.

4.4.17. (5*R*,11a*S*)-2-Hydroxyethyl-5-(3,4-dihydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1q

Mp 242–243 °C. $[\alpha]_D^{20} = -219.6$ (c 0.5, CH_3OH). ^{1}H NMR (DMSO-d_6) δ 2.83 (dd, J_1 = 14.1 Hz, J_2 = 11.2 Hz, 1H), 3.30–3.40 (m, 1H), 3.42–3.58 (m, 4H), 4.41 (dd, J_1 = 10.8 Hz, J_2 = 5.7 Hz, 1H), 4.81 (dd, J_1 = 5.3 Hz, J_2 = 5.5 Hz, 1H), 6.06 (s, 1H), 6.59 (dd, J_1 = 8.1 Hz, J_2 = 1.9 Hz, 1H), 6.65–6.75 (m, 2H), 7.02 (t, J = 7.3 Hz, 1H), 7.09 (t, J = 7.3 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 8.94 (s, 1H), 8.96 (s, 1H), 10.90 (s, 1H). ^{13}C NMR (DMSO-d_6) δ

172.8, 154.2, 145.3, 145.2, 136.6, 131.7, 131.0, 125.8, 121.6, 119.0, 118.7, 118.1, 115.6, 115.3, 111.3, 105.9, 57.6, 52.4, 51.0, 40.8, 22.7. HRMS (ESI) calcd for $C_{21}H_{19}N_3O_5Na$ [M+Na]$^+$: 416.1222; found: 416.1228. IR (KBr) 3642, 3274, 1758, 1697, 1519, 1457, 1391, 1286, 1031, 761, 654 cm^{-1}.

4.4.18. (5*R*,11a*S*)-2-Benzyl-5-(3,4-dihydroxyphenyl)-6*H*-1,2,3,5,11,11a-hexahydro-imidazo[1,5-*b*]-β-carboline-1,3-dione 1r

Mp 118–119 °C. $[\alpha]_D^{20} = -179.0$ (*c* 0.6, $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ 2.81 (dd, J_1 = 14.1 Hz, J_2 = 11.5 Hz, 1H), 3.35–3.50 (m, 1H), 4.55 (dd, J_1 = 10.8 Hz, J_2 = 5.7 Hz, 1H), 4.61 (s, 2H), 6.11 (s, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.73 (s, 1H), 7.02 (dd, J_1 = 7.5 Hz, J_2 = 7.4 Hz, 1H), 7.10 (dd, J_1 = 7.5 Hz, J_2 = 7.4 Hz, 1H), 7.20–7.38 (m, 6H), 7.54 (d, J = 7.7 Hz, 1H), 8.97 (s, 2H), 10.93 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 172.5, 153.9, 145.5, 145.3, 136.6, 136.6, 131.7, 130.9, 128.55, 128.54, 127.4, 127.35, 127.34, 125.8, 121.6, 119.0, 118.8, 118.1, 115.6, 115.3, 111.4, 105.8, 52.7, 51.2, 41.4, 22.8. HRMS (ESI) calcd for $C_{26}H_{21}N_3O_4Na$ [M+Na]$^+$: 462.1430; found: 462.1431. IR (KBr) 3353, 3061, 3033, 2930, 1763, 1700, 1451, 1329, 1284, 1237, 748, 698 cm^{-1}.

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