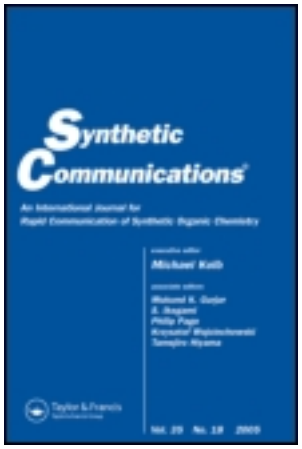


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of a Novel Series of 1,6-Disubstituted-3-(cyclohexylmethoxy)-β-carboline Derivatives via Minisci Reaction

Guowu Lin [a b], Yue Wang [a], Qingfa Zhou [a], Jian Wang [a], Taotao Yang [a], Zhanwei Wang [a] & Tao Lu [c]

[a] College of Basic Science, China Pharmaceutical University, Nanjing, China

[b] Department of Structural Biology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

[c] Key Laboratory of Drug Quality Control and Pharmacovigilance, China Pharmaceutical University, Ministry of Education, Nanjing, China

Accepted author version posted online: 07 Dec 2011.Version of record first published: 26 Mar 2012.

To cite this article: Guowu Lin , Yue Wang , Qingfa Zhou , Jian Wang , Taotao Yang , Zhanwei Wang & Tao Lu (2012): Synthesis of a Novel Series of 1,6-Disubstituted-3-(cyclohexylmethoxy)-β-carboline Derivatives via Minisci Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:13, 1895-1910

To link to this article: http://dx.doi.org/10.1080/00397911.2010.546552

Synthetic Communications®, 42: 1895–1910, 2012

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.546552

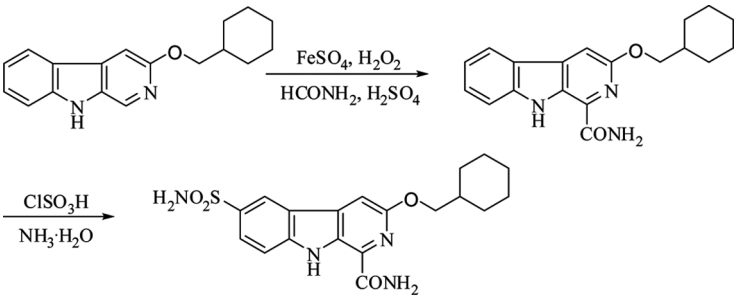
Taylor & Francis
Taylor & Francis Group

SYNTHESIS OF A NOVEL SERIES OF 1,6-DISUBSTITUTED-3-(CYCLOHEXYLMETHOXY)-β-CARBOLINE DERIVATIVES VIA MINISCI REACTION

Guowu Lin,[1,2] Yue Wang,[1] Qingfa Zhou,[1] Jian Wang,[1] Taotao Yang,[1] Zhanwei Wang,[1] and Tao Lu[3]

[1]*College of Basic Science, China Pharmaceutical University, Nanjing, China*
[2]*Department of Structural Biology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA*
[3]*Key Laboratory of Drug Quality Control and Pharmacovigilance, China Pharmaceutical University, Ministry of Education, Nanjing, China*

GRAPHICAL ABSTRACT



Abstract *A facile and efficient route for the synthesis of 1,6-disubstituted-3-cyclohexylmethoxy-β-carboline derivatives via the Minisci reaction has been described with good yields and selectivity. A novel series of β-carboline derivatives with various substituents at 1-, 3-, and 6-positions were designed and synthesized from the starting material (±)-tryptophan on the basis of harmine chemical structure. The mechanism of the 1-substituted β-carboline derivatives by means of a nucleophilic radical was also described, and the x-ray analysis confirmed the structures of 11-7.*

Keywords β-Carboline; electron-withdrawing; harmine; synthesis; x-ray

INTRODUCTION

Malignant tumors have long threatened human health. Thus, the discovery and development of novel therapeutic agents are of great importance for the treatment of

Received October 29, 2010.
Address correspondence to Tao Lu and Yue Wang, State Key Laboratory of Natural Medicines, College of Basic Science, China Pharmaceutical University, Nanjing 210009, China. E-mail: lut163@163.com; zwy_1115@126.com

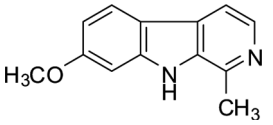


Figure 1. Structure of harmine.

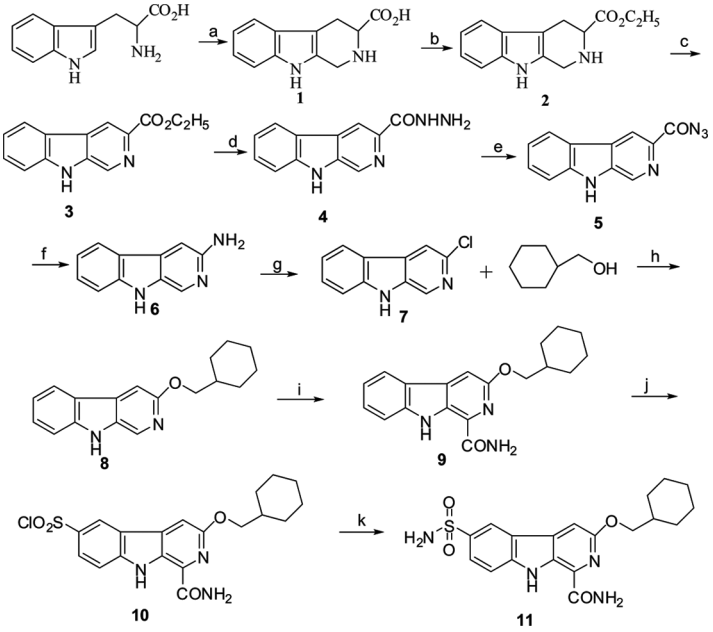
maligancy. One of the successful and effective approaches in the search for new antitumor agents from natural products is to synthesize novel compounds by simple chemical modification of natural leading compounds.

The β-carboline alkaloids, containing a planar tricyclic system, are a large group of naturally occurring and synthetic alkaloids,[1] which have a broad spectrum of biochemical effects and pharmaceutical properties. These compounds have been shown to intercalate into DNA; to inhibit CDK, topisomerase, and monoamine oxidase; and to interact with benzodiazepine receptors (BZ), 5-hydroxy serotonin receptors (5-HT), and dopamine (DA) and imidazoline receptors.[2] The harmine (Fig. 1) is one of the most representative β-carboline alkaloids, originally isolated from seeds of *Pegannum harmala* L. Research[3] over the past few decades demonstrated that harmine and its derivatives were highly cytotoxic against human tumor cell lines, while they had remarkable neurotoxic effects including tremors, twitching, and jumping in experimental animal models.[4] To enhance antitumor activities and decrease acute toxicity, we tried to introduce appropriate substituents into the 1-, 3-, and 6-positions in β-carboline nucleus on the basis of the structure–activity relationship research and the combination principle of drug molecular design.

In this study, we designed and synthesized numerous β-carboline derivatives with various substituents at 1-, 3-, and 6-positions in the β-carboline scaffold on the basis of harmine chemical structure. It is possible to discover and obtain new compounds with comparable activity and less toxicity than harmine. Moreover, this study will further elucidate the structure–activity relationships (SARs) of these compounds with regard to antitumor activity and neurotoxicity/acute toxicity in future research. Herein, we report a facile synthesis of a novel series of derivatives derived from harmine for the purpose of investigating their possible antineoplastic and kinase inhibition activity.

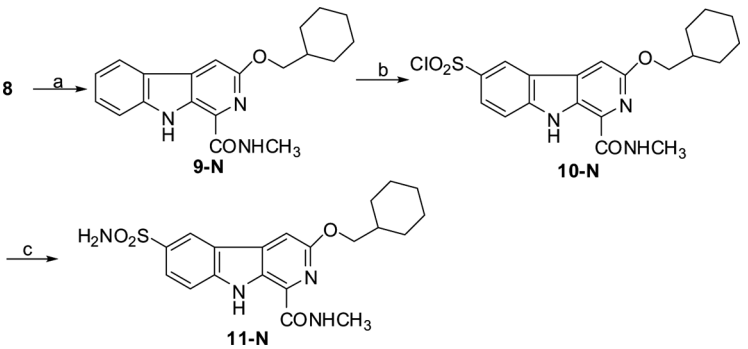
RESULTS AND DISCUSSION

The new 1,6-disubstituted-3-cyclohexylmethoxy-β-carboline derivatives were prepared following the reaction sequences depicted in Schemes 1–3. Herein, (±)-tryptophan was chosen as the starting material for the study, which was converted into 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (**1**) according to the Pictet–Spengler[5] reaction in good yield. The treatment of **1** with excess thionyl chloride in anhydrous EtOH at reflux for 6 h gave ethyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylate (**2**) as a white solid. Then, ethyl β-carboline-3-carboxylate (**3**) was dehydrogenated with $KMnO_4$ in dimethylformamide (DMF) at room temperature for 24 h. 3-Amino-β-carboline (**6**) was prepared by a Curtius rearrangement reaction starting with ethyl β-carboline-3-carboxylate (**3**). Refluxing of **3** with 85% hydrazine hydrate in MeOH gave the hydrazide (**4**), which after treatment with sodium nitrite yielded the azide (**5**). When **5** was refluxed for several minutes in HCl solution,

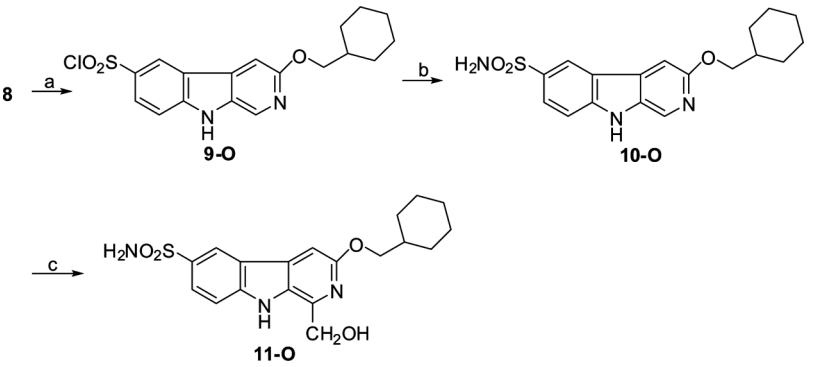


Scheme 1. (a) HCHO, NaOH; (b) C_2H_5OH, $SOCl_2$; (c) $KMnO_4$, DMF, rt; (d) $NH_2NH_2 \cdot H_2O$, MeOH, reflux; (e) $NaNO_2$, HCl; (f) reflux, then NaOH; (g) $NaNO_2$, concentrated HCl; (h) NaH, DABCO; (i) $FeSO_4$, H_2O_2, $HCONH_2$, concentrated H_2SO_4, 10–15 °C; (j) $ClSO_3H$; and (k) $NH_3 \cdot H_2O$.

rearrangement to the amine (**6**) occurred in good yield. 3-Chloro-β-carboline (**7**) was obtained by carrying out the reaction in concentrated hydrochloric acid saturated with dry hydrogen chloride gas under standard Sandmeyer conditions. Compound **7** was heated with DABCO (1,4-diazabicyclo [2.2.2]octane) and NaH in the presence of an excess of dry cyclohexylmethanol for 24 h at reflux to give 3-cyclohexylmethoxy-β-carboline (**8**). Subsequently, we treated **8** with $FeSO_4$ and H_2O_2 in different reagents (including formamide or *N*-methylformamide), under mild conditions (10–15 °C) via the Minisci reaction,[6] giving the expected



Scheme 2. (a) $FeSO_4$, H_2O_2, $HCONHCH_3$, concentrated H_2SO_4, 10–15 °C; (b) $ClSO_3H$; and (c) $NH_3 \cdot H_2O$.



Scheme 3. (a) $ClSO_3H$; (b) $NH_3 \cdot H_2O$; and (c) $FeSO_4$, H_2O_2, CH_3OH, concentrated H_2SO_4, 10–15 °C.

products 1-carbamoyl-3-cyclohexylmethoxy-β-carboline (**9**) in 60% yield and 1-*N*-methylcarbamoyl-3-cyclohexylmethoxy-β-carboline (**9-N**) (Scheme 2) in 57% yield according to procedure A. The key intermedates **9** and **9-N** were converted into the target molecules (**11-X**) in 45–80% yields (Table 1) through both the chlorosulfonation in dry chlorosulfonic acid and subsequent aminolysis with different amines using the method B. Another kind of title compound, 1-hydroxymethyl-3-cyclohexylmethoxy-6-aminosulfonyl-β-carboline (**11-O**), was achieved by chlorosulfonation and subsequent aminolysis to give 3-cyclohexylmethoxy-6-aminosulfonyl-β-carboline (**10-O**) and then the hydroxymethyl substituent to **10-O** was introduced at 1-positon using the procedure C[7] (Scheme 3).

Based on the classic Minisci reaction mechanism, according to the literature[6] and our experimental results, the reaction mechanism of β-carboline derivatives with a variety of nucleophilic radicals was presumed as shown in Scheme 4. The overall process is summarized as follows: (i) Generation of the nucleophilic radical. Here. R^1 was generated from different reagents (R^1-H) by $FeSO_4$ and H_2O_2 redox system (Eq. 1). (ii) Addition to the protonated β-carboline ring. In our experiment, β-carboline ring was protonated by concentrated sulfuric acid (Eq. 2). (iii) Rearomatization of the radical adducts. The mechanism illustrated by Eq. 3 has been envisaged in the rearomatization step of the heteroaromatic substitution.

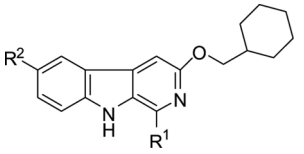
$$\begin{aligned} &H_2O_2 + Fe^{2+} \longrightarrow Fe^{3+} + OH^- + HO^\bullet \\ &HO^\bullet + R^1 - H \longrightarrow H_2O +^\bullet R^1 \end{aligned} \tag{1}$$

At the same time, we have obtained the colorless block crystals of **11-7** from methanol/ethyl acetate at room temperature (Fig. 2). CCDC 757533 contains the supplementary crystallographic data of compound **11–7.** These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

CONCLUSION

We described a convenient and efficient route for the synthesis of the 1,6-disubstituted-3-cyclohexylmethoxy-β-carboline derivatives in moderate to good

Table 1. Synthesis of various 1,6-disubstituted-3-cyclohexylmethoxy-β-carboline derivatives



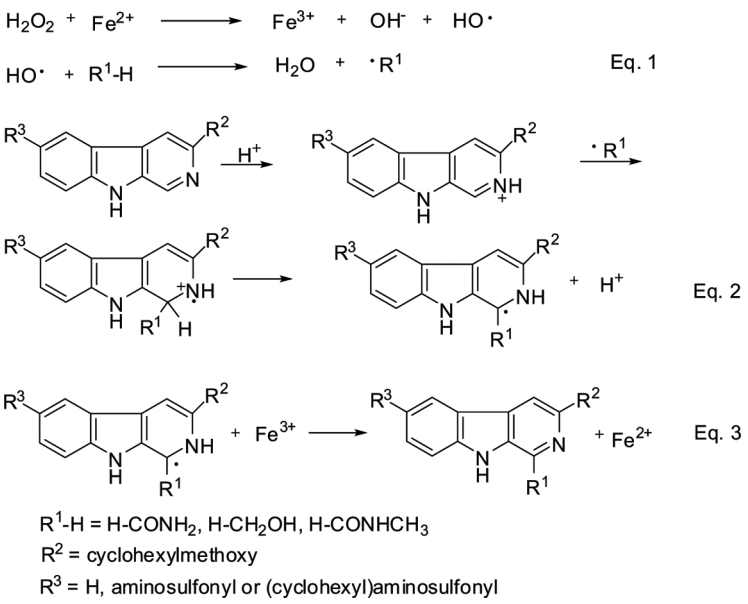
Compound	R^1	R^2	Melting point (°C)[a]	Yield (%)[b]
8	-H	-H	145–147	60
9	$-CONH_2$	-H	233–235	60
9-N	$-CONHCH_3$	-H	253–255	57
11	$-CONH_2$	$-SO_2NH_2$	304–306	65
11-1	$-CONH_2$	$-SO_2NHCH_3$	294–296	75
11-2	$-CONH_2$	$-SO_2NHCH_2CH_2OH$	288–289	55
11-3	$-CONH_2$	$-SO_2NH(CH_2)_3$-morpholinyl	199–201	60
11-4	$-CONH_2$	$-SO_2$-N-hydroxyethylpiperazine-1-yl	203–204	72
11-5	$-CONH_2$	$-SO_2NH$-pyridine-2-yl	321–323	45
11-6	$-CONH_2$	$-SO_2$-N-methylpiperazine-1-yl	207–209	78
11-7	$-CONH_2$	$-SO_2NH$-cyclohexyl	191–193	73
11-8	$-CONH_2$	$-SO_2NHCH_2CH_2SO_2CH_3$	253–255	76
11-9	$-CONH_2$	$-SO_2NH$-cyclopropyl	299–301	80
11-N	$-CONHCH_3$	$-SO_2NH_2$	309–310	60
11-N-1	$-CONHCH_3$	$-SO_2NH$-cyclohexyl	315–316	65
11-N-2	$-CONHCH_3$	$-SO_2NHCH_3$	297–298	75
11-N-3	$-CONHCH_3$	$-SO_2NHCH_2CH_2OH$	281–283	58
11-N-4	$-CONHCH_3$	$-SO_2NH\ CH_2CH(OH)CH_2OH$	265–267	52
10-O	-H	$-SO_2NH_2$	314–315	62
10-O-1	-H	$-SO_2NH$-cyclohexyl	311–312	70
11-O	$-CH_2OH$	$-SO_2NH_2$	251–253	60
11-O-1	$-CH_2OH$	$-SO_2NH$-cyclohexyl	236–238	65

[a]Determined with a digital melting-point apparatus and reported uncorrected.
[b]Isolated yield by column chromatography.

yields. This method offered a facile way to introduce various electron-withdrawing substituents to the β-carboline scaffold at the 1-positon, which will broaden the application scope of the skeleton of β-carbolines. This type of reaction for preparation of 1-substituted β-carboline derivatives has been widely applied in our laboratory.[7] In addition, the mechanism of the 1-substituted β-carboline derivatives by means of nucleophilic radical is described. We have synthesized 22 new title compounds, which were confirmed by infrared (IR), ^{1}H NMR, mass spectrometry, and elemental analysis. The data of all the compounds were given in the experimental section. The compound **11-7** was confirmed by x-ray analysis.

EXPERIMENTAL

Unless otherwise specified, reagents were purchased from commercial suppliers and used without further purification. Reaction progress was monitored using analytical thin-layer chromatography (TLC) on precoated Merck silica-gel Kiesegel 60 F254 plates, and the spots were detected under ultraviolet light (254 nm). Melting



Scheme 4. Mechanism for the synthesis of 1-substituted β-carboline derivatives.

points were determined with a digital melting-point apparatus and are reported uncorrected. ^{1}H NMR spectra were recorded at 300 MHz on Bruker ARX 300 spectrometers. IR spectra were measured on a Jasco FT/IR-430 spectrophotometer. Mass spectra were recorded on an a Quattro MicroMS Micromass UK mass spectrometer and were recorded on an electrospray ionization (ESI) mass spectrometer as the value m/z. Elemental analyses were carried out with a GG315-Vario EL III instrument. The x-ray measurements were made on a Rigaku Raxis Rapid diffractometer with graphite monochromatized Mo Kα radiation ($\lambda = 0.71069$ Å) using ω scan mode.

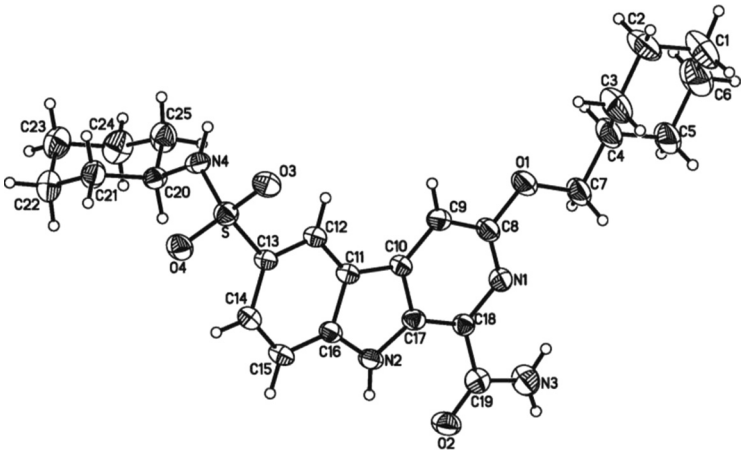


Figure 2. ORTEP drawing of x-ray crystal structure of compound **11-7**.

1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid (1)

The preparation of 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid was achieved by the method of Synder et al.[8] A mixture of (±)-tryptophan (10.2 g, 0.05 mol), NaOH (2.0 g, 0.05 mol), and H_2O (40 mL) was stirred until clear, and then formalin (30%, 5 g, 0.05 mol) was added. The mixture was stirred at room temperature for 3 h and subsequently refluxed for another 3 h until there were no starting materials left (TLC control). It was then neutralized (pH 5) with glacial acetic acid and cooled. The precipitate formed was collected by filtration, washed with water (2×15 mL), and dried in vacuo to give the product as a pale white solid **1** (9.7 g, 90%); mp 306–308 °C.[9]

Ethyl 1,2,3,4-Tetrahydro-β-carboline-3-carboxylate (2)

The acid **1** (10.8 g, 0.05 mol) and dry EtOH (180 mL) were placed in a 250-ml, three-necked, round-bottomed flask equipped with a magnetic stirrer and a drying tube. The stirring mixture was cooled to 0 °C, and then thionyl chloride (12 mL) was added gradually for 30 min. The resulting mixture was held at reflux under nitrogen for 6 h until there were no starting materials left (TLC control). Exess EtOH was removed by evaporation under reduced pressure, and the residue was triturated with water (120 mL), followed by neutralization with saturated solution of NaOH and extraction with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (1×100 mL) and dried with $MgSO_4$, and the solvent was removed under vacuum to provide an oil, which was crystallized from ethyl acetate to provide white solid **2** (10.7 g, 88%); mp 184–186 °C.[10]

Ethyl β-Carboline-3-carboxylate (3)

$KMnO_4$ (44.5 g, 100 mmol) was added gradually for 30 min to a cooled, rapidly stirring solution of **2** (12.2 g, 0.05 mol) in DMF (200 mL), and then the resulting mixture was stirred for 24 h at room temperature. The suspension was filtered, and the precipitate was washed with DMF (2×100 mL). The combined organic solvent was removed under reduced pressure to provide a brown residue, which was crystallized from ethyl acetate to give white powder **3** (9.0 g, 75%); mp 244–246 °C.[11]

β-Carboline-3-carbohydrazide (4)

A solution of ethyl β-carboline-3-carboxylate (**3**) (12.0 g, 0.05 mol) in MeOH (120 mL) containing hydrazine hydrate (85%, 20 mL) was refluxed for 6 h until there were no starting materials left (TLC control). The resulting mixture was cooled, and the precipitate that formed was collected by fitration, washed with MeOH (1×30 mL), and dried under vacuum, yielding compound **4** (10.3 g, 85%). An analytical sample was recrystallized from 95% MeOH, giving silver solid; mp 288–290 °C.[12]

3-(Azidocarbonyl)-β-carboline (5)

A suspension of the hydrazide **4** (12.1 g, 0.05 mol) in water (200 mL) was dissolved by the dropwise addition of concentrated HCl (10 mL). The pale yellow solution was cooled to 0–5 °C before the addition of a solution of sodium nitrite (3.6 g, 0.053 mol) in water (10 mL). After stirring for 30 min at 0 °C, the mixture was made basic with saturated aqueous $NaHCO_3$, and the precipitate that formed was collected by filtration, washed with water, and dried in a dessicator under vacuum, yielding crude **5** (8.8 g, 75%) as a yellow solid with a tendency to decompose. The material was used without further purification for the following steps.

3-Amino-β-carboline (6)

A suspension of the azide **5** (11.85 g, 0.05 mol) in a mixture of water (200 mL) and concentrated HCl (10 mL) was brought to reflux, during which carbon dioxide was evolved and the starting material disappeared. After refluxing for 30 min, the reaction mixture was cooled, the precipitate that formed was collected by filtration and washed with water, and an analytical sample was recrystallized from EtOH, yielding **6** (6.4 g, 70%) as yellow powder; mp 288–290 °C.[12]

3-Chloro-β-carboline (7)

A mechanically stirred solution of 3-amino-β-carboline (**6**) (9.2 g, 0.05 mol) in concentrated HCl (150 ml) was cooled to 0–5 °C and saturated carefully with dry hydrogen chloride gas for 30 min. Sodium nitrite solid (3.6 g, 0.053 mol) was added in batches to the homogeneous solution that resulted, and the solution was allowed to stir for 2 h at 0–5 °C. The mixture was then made basic (pH 8) with concentrated NH_4OH. The aqueous layer was extracted with ethyl acetate (3×100 mL), and the organic extracts were combined and dried with Mg_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography to yield 3-chloro-β-carboline **(7)** as a pale yellow solid (5.05 g, 50%); mp 276–277 °C.[13]

3-Cyclohexylmethoxy-β-carboline (8)

3-Chloro-β-carboline (**7**) (10.1 g, 0.05 mol), DABCO (0.1 equiv.[14]), NaH solid (1.44 g, 0.06 mol), and dry cyclohexylmethanol (200 mL) were placed in a 250-ml, single-necked, round-bottomed flask equipped with a magnetic stirrer and a drying tube. The stirring mixture was refluxed for 24 h under nitrogen until there were no starting materials left (TLC control). The resulted mixture was cooled to room temperature, poured into ice water (100 mL), neutralized (pH 7–8) by addition of glacial acetic acid, and extracted with ethyl acetate (3×30 mL). The organic solvent was removed in vacuo. The residue was purified by flash column chromatography to afford the adduct 3-cyclohexylmethoxy-β-carboline (**8**) as a pale yellow solid (8.4 g, yield 60%); mp 145–147 °C IR (KBr) 3132, 2923, 2848, 1631, 1502, 1452, 1375, 1251, 1224, 1186, 1041, 740, 632 cm^{-1}; MS m/z 282.22 $(M+1)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.18 (s, 1H, indole), 8.49 (s, 1H, ArH), 8.17 (d,

1H, $J = 7.9$ Hz, ArH), 7.46–7.50 (m, 3H, ArH), 7.14 (m, 1H, ArH), 4.20 (d, 2H, $J = 5.6$ Hz, -CH_2O), 0.8–1.9 (m, 11H, cyclohexyl). Anal. calcd. (%) for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found (%): C, 77.14; H, 7.22; N, 9.96.

Procedure A

Procedure A offers a facile way to introduce various electron-withdrawing substituents (such as carbamoyl and *N*-methylcarbamoyl) to β-carboline derivatives at the 1-positon.

1-Carbamoyl-3-cyclohexylmethoxy-β-carboline (9). 3-Cyclohexylmethoxy-β-carboline (**8**) (1.4 g, 5 mmol), formamide (100 mL), and concentrated H_2SO_4 (2 mL) were placed in a 150-ml, single-necked, round-bottomed flask equipped with a magnetic stirrer. The stirred mixture was cooled to 10–15 °C. A saturated solution of $FeSO_4$ and H_2O_2 (30% solution in water) were added simultaneously over a period of 10 min and stirring was continued. The addition of $FeSO_4$ and H_2O_2 was repeated until there was no starting material left (TLC control[15]). The reacted mixture was poured into water (300 mL) followed by neutralization (pH 8) with saturated solution of sodium carbonate and extraction with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (1×100 mL) and dried with $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by flash column chromatography to afford the corresponding compound 1-carbamoyl-3-cyclohexylmethoxy-β-carboline (**9**) as a pale yellow solid (0.98 g, yield 60%); mp 233–235 °C IR (KBr) 3320, 3125, 2933, 2850, 1675, 1621, 1600, 1590, 1559, 1448, 1316, 1251, 1120, 990, 760, 595, 563 cm^{-1}; MS m/z 224.23 $(M+1)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.20 (1H, s, indole), 8.20 (1H, d, $J = 8.0$ Hz, ArH), 8.00 (1H, s, ArH), 7.75 (1H, s, ArH), 7.67-7.69 (2H, m, -$CONH_2$), 7.51 (1H, m, ArH), 7.16 (2H, m, ArH), 4.23 (2H, d, $J = 5.0$ Hz, -CH_2O), 0.9–1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found (%): C, 70.60; H, 6.57; N, 12.98.

1-*N*-Methylcarbamoyl-3-cyclohexylmethoxy-β-carboline (9-n). Prepared from **8** according to procedure A, yield 57%; mp 253–255 °C IR (KBr) 3332, 3150, 2926, 2830, 1648, 1560, 1555, 1440, 1326, 1130, 993, 732, 603, 551, 521 cm^{-1}; MS m/z 336.11 $(M-1)^-$; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.41 (1H, s, indole), 8.67 (1H, m, ArH), 7.58 (1H, d, $J = 8.8$ Hz, ArH), 7.78 (1H, d, $J = 9.1$ Hz, ArH), 7.71 (1H, m, -CONH), 7.53 (1H, m, ArH), 7.15 (1H, m, ArH), 4.27 (2H, d, $J = 5.3$ Hz, -CH_2O), 2.9 (3H, d, $J = 4.7$ Hz, -CH_3N), 0.9–1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{20}H_{23}N_3O_2$: C, 71.19; H, 6.87; N, 12.45. Found (%): C, 71.17; H, 6.90; N, 12.44.

Procedure B

Procedure B is typical procedure for the synthesis of 1-substituted-3-cyclohexylmethoxy-6-aminosulfonyl-β-carboline derivatives, exemplified by the preparation of 1-carbamoyl-3-cyclohexylmethoxy-6-aminosulfonyl-β-carboline **11**.

To a single-necked, round-bottomed flask equipped with a drying tube and a magnetic stir bar, 10 mL of dry chlorosulfonic acid were added. The stirring mixture was allowed to cool at 0 °C, and 1-carbamoyl-3-cyclohexylmethoxy-β-carboline (**9**) (0.32 g, 1 mmol) was added to this solution in batches. The resulting mixture was kept at 0–5 °C until there were no starting materials left (TLC control). The reacted mixture was quenched by pouring it onto ice water (50 mL); the precipitate that formed was collected by suction filtration, washed with cold water, and dried under vacuum, giving 0.33 g (78%) of 1-carbamoyl-3-cyclohexylmethoxy-6-chlorosulfonyl-β-carboline (**10**), which was used without further purification.

Excess concentrated aqueous ammonia (5 mL) was added to a suspension of 1-carbamoyl-6-chlorosulfonyl-β-carboline (0.33 g, 0.77 mmol) in cold water (30 mL). After the resulting mixture was stirred at room temperature until there were no starting materials left (TLC control), the solvent was removed under reduced pressure, and the residues were purified by flash chromatography using an eluent MeOH-$CHCl_3$ to give the title compound (**11**) as a pale yellow solid (0.20 g, yield 65%). Other compounds were synthesized similarly.

1-Carbamoyl-3-cyclohexylmethoxy-6-aminosulfonyl-β-carboline (11). Prepared from **9** according to procedure B, yield 65%; mp 304–306 °C, IR (KBr) 3465, 3346, 3319, 2923, 2850, 1672, 1631, 1606, 1560, 1479, 1442, 1321, 1251, 1153, 1132, 1085, 1051, 1022, 941, 746, 622, 590, 511 cm^{-1}; MS m/z 401.84 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.64 (1H, s, indole), 8.70 (1H, s, ArH), 8.07 (1H, s, ArH), 7.97 (1H, d, $J = 7.9$ Hz, ArH), 7.89 (1H, m, ArH), 7.69–7.81 (2H, m, -$CONH_2$), 7.22 (2H, m, -SO_2NH_2), 4.23 (2H, d, $J = 5.2$ Hz, -CH_2O), 1.0–2.0 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{19}H_{22}N_4O_4S$: C, 56.70; H, 5.51; N, 13.92; S, 7.97. Found (%): C, 56.67; H, 5.55; N, 13.90; S, 7.96.

1-Carbamoyl-3-cyclohexylmethoxy-6-methylaminosulfonyl-β-carboline (11-1). Prepared from **9** according to procedure B, yield 75%; mp 294–296 °C, IR (KBr) 3483, 3379, 3286, 2923, 2850, 1664, 1631, 1575, 1471, 1438, 1361, 1315, 1244, 1188, 1149, 1080, 1022, 825, 748, 703, 661, 619, 590, 536, 478 cm^{-1}; MS m/z 416.05 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.70 (1H, s, indole), 8.70 (1H, s, ArH), 8.09 (1H, s, ArH), 7.92 (1H, d, $J = 11.0$ Hz, ArH), 7.88 (1H, m, ArH), 7.78–7.84 (2H, m, -$CONH_2$), 7.27 (1H, m, -SO_2NH), 4.23 (2H, d, $J = 5.9$ Hz, -CH_2O), 2.4 (3H, d, $J = 5.0$ Hz, -CH_3N), 1.0-2.0 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{19}H_{14}N_6O_3S$: C, 56.15; H, 3.47; N, 20.68; S, 7.89. Found (%): C, 56.18; H, 3.45; N, 20.70; S, 7.86.

1-Carbamoyl-3-cyclohexylmethoxy-6-(2-hydroxyethyl)aminosulfonyl-β-carboline (11-2). Prepared from **9** according to procedure B, yield 55%; mp 288–289 °C, IR (KBr) 3504, 3446, 3263, 2921, 2848, 1674, 1633, 1604, 1579, 1564, 1479, 1440, 1359, 1319, 1253, 1149, 1074, 1053, 950, 889, 752, 632, 586, 547, 460 cm^{-1}; MS m/z 446.14 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.69 (1H, s, indole), 8.71 (1H, s, ArH), 8.08 (1H, s, ArH), 7.93 (1H, s, ArH), 7.90 (1H, m, ArH), 7.78–7.83 (2H, m, -$CONH_2$), 7.34 (1H, t, $J = 8.2$ Hz, -SO_2NH), 4.62 (1H, t, $J = 4.5$ Hz, -OH), 4.24 (2H, d, $J = 5.4$ Hz, -CH_2O), 3.3 (2H, m, -CH_2O), 2.8 (2H, m, -CH_2N), 1.0–1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for

$C_{21}H_{26}N_4O_5S$: C, 56.49; H, 5.87; N, 12.55; S, 7.18. Found (%): C, 56.51; H, 5.93; N, 12.54; S, 7.17.

1-Carbamoyl-3-cyclohexylmethoxy-6-(*N*-(3-morpholinopropyl)aminosulfonyl-β-carboline (11-3). Prepared from **9** according to procedure B, yield 60%; mp 199–201 °C, IR (KBr) 3407, 3344, 3355 (N-H), 3263, 3205, 3064, 2923, 2854, 1674, 1633, 1593, 1573, 1440, 1319, 1242, 1197, 1143, 1033, 1022, 865, 756, 624, 582, 549 cm^{-1}; MS m/z 531.31 $(M+1)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.69 (1H, s, indole), 8.7 (1H, s, ArH), 8.08 (1H, s, ArH), 7.94 (1H, m, ArH), 7.70–7.83 (2H, m, -$CONH_2$), 7.42 (1H, m, -SO_2NH), 4.23 (2H, d, $J = 4.9$ Hz, -CH_2O), 3.34 (4H, q, -$CH_2O \times 2$), 2.79 (2H, m, -CH_2NSO_2), 2.15–2.17 (6H, m, -$CH_2N \times 3$), 1.89 (2H, m, -CH_2), 1.0–1.8 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{26}H_{35}N_5O_5S$: C, 58.96; H, 6.66; N, 13.22; S, 6.05. Found (%): C, 58.94; H, 6.71; N, 13.25; S, 6.00.

1-Carbamoyl-3-cyclohexylmethoxy-6-(4-(2-hydroxyethyl)piperazin-1-yl) sulfonyl-β-carboline (11-4). Prepared from **9** according to procedure B, yield 72%; mp 203–204 °C, IR (KBr) 3460, 3348, 3419, 3278, 2923, 2850, 1674, 1633, 1568, 1475, 1438, 1352, 1323, 1247, 1155, 1134, 1081, 1056, 948, 756, 630, 584, 543 cm^{-1}; MS m/z 517.26 $(M+1)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 1.77 (1H, s, indole), 8.70 (1H, s, ArH), 8.09 (1H, s, ArH), 7.86 (1H, m, ArH), 7.78 (1H, m, ArH), 7.97–8.05 (2H, m, -$CONH_2$), 4.31 (1H, t, $J = 5.6$ Hz, -OH), 4.23 (2H, d, $J = 5.0$ Hz, -CH_2O), 3.36 (2H, q, -CH_2O), 2.7-2.8 (8H, m, -$CH_2N \times 4$), 2.33 (2H, t, $J = 6.0$ Hz, -CH_2N), 1.0–2.0 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{25}H_{33}N_5O_5S$: C, 58.23; H, 6.45; N, 13.58; S, 6.22. Found (%): C, 58.25; H, 6.52; N, 13.56; S, 6.21.

1-Carbamoyl-3-cyclohexylmethoxy-6-(pyridin-2-yl)aminosulfonyl-β-carboline (11-5). Prepared from **9** according to procedure B, yield 45%; mp 321–323 °C, IR (KBr) 3490, 3412, 3112, 3055, 2929, 2854, 1672, 1630, 1606, 1560, 1477, 1360, 1310, 1249, 1190, 1130, 1050, 1037, 930, 745, 593, 550, 524 cm^{-1}; MS m/z 479.19 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.65 (1H, s, indole), 8.82 (1H, s, ArH), 8.06 (1H, s, ArH), 7.9–8.0 (4H, m, ArH), 7.74–7.77 (2H, m, -$CONH_2$), 7.64 (1H, m, ArH), 7.20 (1H, s, -SO_2NH), 6.83 (1H, m, ArH), 4.23 (2H, d, $J = 4.3$ Hz, -CH_2O), 1.0–1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{24}H_{25}N_5O_4S$: C, 60.11; H, 5.25; N, 14.60; S, 6.69. Found (%): C, 60.09; H, 5.20; N, 14.63; S, 6.68.

1-Carbamoyl-3-cyclohexylmethoxy-6-(4-methylpiperazin-1-yl)sulfonyl-β-carboline (11-6). Prepared from **9** according to procedure B, yield 78%; mp 207–209 °C, IR (KBr) 3452, 3407, 2925, 2852, 2798, 1674, 1633, 1600, 1595, 1575, 1469, 1440, 1352, 1326, 1290, 1242, 1153, 1089, 1026, 948, 754, 634, 582, 543, 513 cm^{-1}; MS m/z 487.20 $(M+1)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.78 (1H, s, indole), 8.70 (1H, s, ArH), 8.11 (1H, s, ArH), 8.01 (1H, d, $J = 7.2$ Hz, ArH), 7.88 (1H, m, ArH), 7.80 (2H, m, -$CONH_2$), 4.24 (2H, d, $J = 3.1$ Hz, -CH_2O), 2.90 (4H, t, -$CH_2N \times 2$), 2.35 (4H, t, -$CH_2N \times 2$), 2.11 (3H, s, -CH_3), 1.0-1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{24}H_{31}N_5O_4S$: C, 59.36; H, 6.43; N, 14.42; S, 6.60. Found (%): C, 59.35; H, 6.47; N, 14.40; S, 6.63.

1-Carbamoyl-3-cyclohexylmethoxy-6-(cyclohexyl)aminosulfonyl-β-carboline (11-7). Prepared from **9** according to procedure B, yield 73%; mp 191–193 °C, IR (KBr) 3490, 3352, 3190, 2921, 2852, 1670, 1635, 1558, 1475, 1442, 1353, 1323, 1294, 1245, 1201, 1147, 1083, 1029, 991, 871, 752, 711, 601, 514, 474 cm^{-1}; MS m/z: 484.09 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.70 (s, 1H, indole), 8.70 (s, 1H, ArH), 8.10 (s, 1H, ArH), 7.96 (m, 1H, ArH), 7.92 (s, 1H, ArH), 7.82 (m, 2H, -$CONH_2$), 7.51 (m, 1H, -SO_2NH), 4.24 (d, 2H, $J = 5.2$ Hz, -CH_2O), 2.9 (m, 1H, -CHN), 1.0–2.0 (m, 21H, cyclohexyl). Anal. calcd. (%) for $C_{25}H_{32}N_4O_4S$: C, 61.96; H, 6.66; N, 11.56; S, 6.62. Found (%): C, 61.99; H, 6.69; N, 11.54; S, 6.60.

1-Carbamoyl-3-cyclohexylmethoxy-6-(*n*-(2-(methylsulfonyl)ethyl))aminosulfonyl-β-carboline (11-8). Prepared from **9** according to procedure B, yield 76%; mp 253–254 °C, IR (KBr) 3428, 3400, 3180, 2922, 2830, 1673, 1630, 1610, 1550, 1423, 1345, 1245, 1128, 1030, 1011, 955, 905, 740, 600, 570, 534 cm^{-1}; MS m/z: 507.47 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.66 (1H, s, indole), 8.67 (1H, s, ArH), 8.08 (1H, s, ArH), 7.90 (1H, m, ArH), 7.87(1H, s, ArH), 7.82 (2H, m, -$CONH_2$), 7.51 (1H, m, -SO_2NH), 4.24 (2H, d, $J = 3.8$ Hz, -CH_2O), 3.7 (2H, t, -CH_2SO_2), 3.5 (2H, t, -CH_2N), 2.9 (3H, s, -CH_3), 1.0–2.0 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{22}H_{28}N_4O_6S_2$: C, 51.95; H, 5.55; N, 11.02; S, 12.61. Found (%): C, 51.93; H, 5.57; N, 11.00; S, 12.64.

1-Carbamoyl-3-cyclohexylmethoxy-6-(cyclopropyl)aminosulfonyl-β-carboline (11-9). Prepared from **9** according to procedure B, yield 80%; mp 299–301 °C, IR (KBr) 3494, 3409, 3251, 2925, 2848, 1674, 1637, 1569, 1475, 1444, 1363, 1319, 1240, 1190, 1147, 1026, 964, 879, 819, 754, 619, 582, 541, 503, 451 cm^{-1}; MS m/z: 442.10 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.72 (1H, s, indole), 8.72 (1H, s, ArH), 8.10 (1H, s, ArH), 7.95 (1H, s, ArH), 7.91 (1H, d, ArH), 7.82-7.85 (2H, m, -$CONH_2$), 7.76 (1H, m, -SO_2NH), 4.23 (2H, d, $J = 3.9$ Hz, -CH_2O), 1.0-2.0 (16H, m, cyclohexyl and cyclopropyl). Anal. calcd. (%) for $C_{22}H_{26}N_4O_4S$: C, 59.71; H, 5.92; N, 12.66; S, 7.25. Found (%): C, 59.73; H, 5.96; N, 12.64; S, 7.24.

1-*N*-Methylcarbamoyl-3-cyclohexylmethoxy-6-aminosulfonyl-β-carboline (11-N). Prepared from **9-N** according to procedure B, yield 60%; mp 309–310 °C, IR (KBr) 3400, 3352, 3303, 3103, 2923, 2848, 1647, 1577, 1541, 1469, 1423, 1342, 1218, 1153, 1122, 1070, 1008, 921, 862, 813, 752, 665, 597, 553, 507 cm^{-1}; MS m/z: 416.07 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.85 (1H, s, indole), 8.68 (1H, d, $J = 8.0$ Hz, ArH), 8.57 (1H, d, $J = 6.9$ Hz, ArH), 8.40 (1H, d, $J = 7.4$ Hz, ArH), 7.91 (1H, m, -CONH), 7.81 (1H, m, ArH), 7.31 (2H, m, -SO_2NH_2), 4.28 (2H, d, $J = 4.1$ Hz, -CH_2O), 3.0 (3H, s, -CH_3N), 0.9-1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{20}H_{24}N_4O_4S$: C, 57.68; H, 5.81; N, 13.45; S, 7.70. Found (%): C, 57.69; H, 5.85; N, 13.43; S, 7.71.

1-*N*-Methylcarbamoyl-3-cyclohexylmethoxy-6-(cyclohexyl)aminosulfonyl-β-carboline (11-N-1). Prepared from **9-N** according to procedure B, yield 65%; mp 315–316 °C, IR (KBr) 3379, 3357, 3240, 2929, 2854, 1656, 1539, 1440, 1413, 1348, 1315, 1222, 1155, 1122, 1070, 1002, 929, 881, 815, 657, 601, 547, 439 cm^{-1}; MS m/z: 499.20 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.89 (1H, s, indole), 8.70

(1H, m, ArH), 8.60 (1H, d, $J = 8.8$ Hz, ArH), 8.37 (1H, s, ArH), 7.93 (1H, m, -CONH), 7.85 (1H, m, ArH), 7.60 (1H, m, $-SO_2NH$), 4.28 (2H, d, $J = 4.5$ Hz, $-CH_2O$), 2.9 (3H, m, $-CH_3N$), 2.85 (1H, m, $-CHNSO_2$), 0.8-1.9 (21H, m, cyclohexyl × 2). Anal. calcd. (%) for $C_{26}H_{34}N_4O_4S$: C, 62.63; H, 6.87; N, 11.24; S, 6.43. Found (%): C, 62.64; H, 6.91; N, 11.23; S, 6.45.

1-*N*-Methylcarbamoyl-3-cyclohexylmethoxy-6-methylaminosulfonyl-β-carboline (11-N-2). Prepared from **9-N** according to procedure B, yield 75%; mp 297–298 °C, IR (KBr) 3381, 3360, 3230, 2920, 2833, 1655, 1557, 1428, 1410, 1350, 1319, 1261, 1133, 1030, 999, 923, 730, 570, 533 cm^{-1}; MS m/z: 430.26 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.65 (1H, s, indole), 8.71 (1H, m, ArH), 8.58 (1H, d, $J = 10.1$ Hz, ArH), 8.40 (1H, s, ArH), 7.87 (1H, m, -CONH), 7.81 (1H, m, ArH), 7.50 (1H, m, $-SO_2NH$), 4.28 (2H, d, $J = 3.9$ Hz, $-CH_2O$), 2.9 (3H, d, $J = 4.1$ Hz, $-CH_3N$), 2.4 (3H, d, $J = 4.7$ Hz, $-CH_3NSO_2$), 0.9–1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{21}H_{26}N_4O_4S$: C, 58.59; H, 6.09; N, 13.01; S, 7.45. Found (%): C, 58.60; H, 6.14; N, 13.00; S, 7.43.

1-*N*-Methylcarbamoyl-3-cyclohexylmethoxy-6-(2-hydroxyethyl)aminosulfonyl-β-carboline (11-N-3). Prepared from **9-N** according to procedure B, yield 58%; mp 281–283 °C, IR (KBr) 3542, 4430, 3340, 3139, 2921, 2852, 1649, 1577, 1531, 1429, 1353, 1321, 1218, 1155, 1120, 1066, 929, 810, 744, 659, 613, 551,466, 435 cm^{-1}; MS m/z: 459.99 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.90 (1H, s, indole), 8.69 (1H, m, ArH), 8.58 (1H, m, ArH), 8.35 (1H, s, ArH), 7.92 (1H, m, -CONH), 7.83 (1H, m, ArH), 7.55 (1H, m, $-SO_2NH$), 4.55 (1H, t, -OH), 4.28 (2H, d, $J = 5.0$ Hz, $-CH_2O$), 3.35 (2H, m, $-CH_2O$), 2.94 (2H, m, $-CH_2N$), 2.8 (3H, d, $J = 2.9$ Hz, $-CH_3N$), 1.0–1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{22}H_{28}N_4O_5S$: C, 57.37; H, 6.13; N, 12.17; S, 6.96. Found (%): C, 57.36; H, 6.16; N, 12.16; S, 6.99.

1-*N*-Methylcarbamoyl-3-cyclohexylmethoxy-6-(*N*-(2,3-dihydroxypropyl))aminosulfonyl-β-carboline (11-N-4). Prepared from **9-N** according to procedure B, yield 52%; mp 265–267 °C, IR (KBr) 3578, 3556, 3421, 3320, 3119, 2925, 2844, 1646, 1550, 1430, 1350, 1178, 1156, 1119, 1040, 1000, 990, 750, 571, 546, 500 cm^{-1}; MS m/z: 490.37 $(M-1)^-$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.90 (1H, s, indole), 8.7 (1H, m, ArH), 8.6 (1H, m, ArH), 8.35 (1H, s, ArH), 7.93 (1H, m, -CONH), 7.86 (1H, m, ArH), 7.44 (1H, m, $-SO_2NH$), 4.7–4.8 (2H, m, -OH × 2), 4.28 (2H, d, $J = 3.3$ Hz, $-CH_2O$), 2.8–2.9 (5H, d, $J = 1.7$ Hz, $-CH_2CHCH_2$), 0.9-1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{23}H_{30}N_4O_6S$: C, 56.31; H, 6.16; N, 11.42; S, 6.54. Found (%): C, 56.28; H, 6.19; N, 11.40; S, 6.52.

3-Cyclohexylmethoxy-6-aminosulfonyl-β-carboline (10-O). Prepared from **8** according to procedure B, yield 62%; mp 314–315 °C, IR (KBr) 3440, 3400, 3215, 2923, 2843, 1553, 1430, 1327, 126, 1150, 1032, 997, 813, 676, 558, 478 cm^{-1}; MS m/z 360.83 $(M+1)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.66 (1H, s, indole), 8.67 (1H, s, ArH), 8.50 (1H, s, ArH), 7.96 (1H, m, ArH), 7.62 (2H, m, $-CONH_2$), 7.23 (2H, s, $-SO_2NH_2$), 4.10 (2H, d, $J = 4.6$ Hz, $-CH_2O$), 1.1-2.0 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{18}H_{21}N_3O_3S$: C, 60.15; H, 5.89; N, 11.69; S, 8.92. Found (%): C, 60.14; H, 5.92; N, 11.67; S, 8.94.

3-Cyclohexylmethoxy-6-(cyclohexyl)aminosulfonyl-β-carboline (10-O-1). Prepared from **8** according to procedure B, yield 70%; mp 311–312 °C, IR (KBr) 3441, 3240, 3152, 2920, 2845, 1553, 1467, 1310, 1243, 1130, 1051, 1026, 918, 736, 587, 545, 511 cm^{-1}; MS m/z 442.98 $(M+1)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.69 (1H, s, indole), 8.67 (1H, s, ArH), 8.50 (1H, s, ArH), 7.90 (1H, d, $J = 8.9$ Hz, ArH), 7.62 (2H, m, -$CONH_2$), 7.46 (1H, d, $J = 11.2$ Hz, -SO_2NH), 4.10 (2H, d, $J = 4.0$ Hz, -CH_2O), 2.92 (1H, m, -$CHNSO_2$), 0.8-2.0 (21H, m, cyclohexyl × 2). Anal. calcd. (%) for $C_{24}H_{31}N_3O_3S$: C, 65.28; H, 7.08; N, 9.52; S, 7.26. Found (%): C, 65.29; H, 7.13; N, 9.50; S, 7.24.

Procedure C

Procedure C is isgeneral procedure for the synthesis of 1-hydroxymethyl-3-cyclohexylmethoxy-6-aminosulfonyl-β-carboline derivatives.

1-Hydroxymethyl-3-cyclohexylmethoxy-6-aminosulfonyl-β-carboline (11-O). 3-Cyclohexylmethoxy-6-aminosulfonyl-β-carboline (1.8 g, 5 mmol), 100 mL MeOH, and 2 mL concentrated sulfuric acid were placed in a 150-ml single-necked, round-bottomed flask equipped with a magnetic stirrer. The stirred mixture was cooled to 10–15 °C. Then a saturated solution of $FeSO_4$ and H_2O_2 (30% solution in water) was added over a period of 10 min, and stirring was continued. The addition of $FeSO_4$ and H_2O_2 was be repeated until there is no starting material left (TLC control). The reaction mixture was poured into water (300 mL), followed by neutralization with a saturated solution of sodium carbonate and extraction with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (1 × 100 mL) and dried with $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by flash column chromatography to afford the corresponding adduct 1-hydroxymethyl-3-(1*H*-benzo[*d*]imidazol-2-yl)-6-aminosulfonyl-β-carboline (**11-O**) as a white solid (1.2 g, yield 60%); mp 251–253 °C, IR (KBr) 3456, 3410, 3215, 3156, 2920, 2843, 1601, 1533, 1434, 1330, 1290, 1191, 1155, 1032, 1000, 803, 663, 552, 503 cm^{-1}; MS m/z 390.81 $(M+1)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.39 (1H, s, indole), 8.64 (1H, s, ArH), 7.92 (1H, d, $J = 12.3$ Hz, ArH), 7.69 (1H, d, $J = 7.9$ Hz, ArH), 7.50 (1H, s, ArH), 7.19 (2H, s, -SO_2NH_2), 5.53 (1H, t, -OH), 4.87 (2H, d, $J = 2.1$ Hz, -CH_2), 4.09 (2H, d, $J = 3.9$ Hz, -CH_2O), 2.9 (1H, m, -CHN), 1.0-1.9 (11H, m, cyclohexyl). Anal. calcd. (%) for $C_{19}H_{23}N_3O_4S$: C, 58.59; H, 5.95; N, 10.79; S, 8.23. Found (%): C, 58.61; H, 5.63; N, 10.76; S, 8.22.

1-Hydroxymethyl-3-cyclohexylmethoxy-6-(cyclohexyl)aminosulfonyl-β-carboline (11-O-1). Prepared from **10-O-1** according to procedure C, yield 65%; mp 236–238 °C, IR (KBr) 3431, 3323, 3245, 3153, 2923, 2852, 1631, 1583, 1479, 1442, 1325, 1294, 1191, 1139, 1051, 1026, 935, 748, 607, 543, 497 cm^{-1}; MS m/z 473.15 $(M+1)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.42 (1H, s, indole), 8.64 (1H, s, ArH), 7.90 (1H, d, $J = 11.8$ Hz, ArH), 7.70 (1H, d, $J = 9.7$ Hz, ArH), 7.54 (1H, m, ArH), 7.41 (1H, d, $J = 8.9$ Hz, -SO_2NH), 5.53 (1H, t, -OH), 4.87 (2H, d, $J = 4.5$ Hz, -CH_2OH), 4.08 (2H, d, $J = 5.0$ Hz, -CH_2O), 2.94 (1H, m, -$CHNSO_2$), 0.8-1.9 (21H, m, cyclohexyl × 2). Anal. calcd. (%) for $C_{24}H_{31}N_3O_3S$: C, 65.28; H, 7.08; N, 9.52; S, 7.26. Found (%): C, 65.29; H, 7.13; N, 9.50; S, 7.24.

ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (No. 30973609), the Natural Science Foundation of Jiangsu Province (Program No. BK2009303), the Fundamental Research Funds for the Central Universities (Program No. 2J10004), and Specialized Research Fund for the Doctoral Program of Higher Education (Program No. 20100096110007) for financial support. This study was also supported by the Project Program of State Key Laboratory of Natural Medicines, China Pharmaceutical University (No. JKGP201105).

REFERENCES

1. (a) Lippke, K. P.; Schunack, W. G.; Wenning, W.; Muller, W. E. β-Carbolines as benzodiazepine receptor ligands: 1: Synthesis and benzodiazepine receptor interaction of esters of β-carboline-3-carboxylic acid. *J. Med. Chem.* **1983**, *26*, 499–503; (b) Airaksinen, M. M.; Kari, I. The β-Carboline, psychoactive compounds in the mammalian body, part I: Occurrence, origin, and metabolism. *Med. Biol.* **1981**, *59*, 21–34; (c) Hagen, T. J.; Skolnick, P.; Cook, J. M. Synthesis of 6-substituted β-carbolines that behave as benzodiazepine receptor antagonists or inverse agonists. *J. Med. Chem.* **1987**, *30*, 750–753; (d) Zhou, T. S.; Ye, W. C.; Wang, Z. T. The β-Carboline alkaloids from *Hypodematium squamuloso-plilosum*. *Phytochemistry* **1998**, *49*, 1807–1809; (e) Kusurkar, R. S.; Goswami, S. K.; Vyas, S. M. Efficient one-pot synthesis of anti-HIV and antitumor compounds: Harman and substituted harmans. *Tetrahedron Lett.* **2003**, *44*, 4761–4763.
2. (a) Xiao, S.; Lin, W.; Wang, C.; Yang, M. Synthesis and biological evaluation of DNA targeting flexible side-chain substituted β-carboline derivatives. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 437–441; (b) Grella, B.; Teitler, M.; Smith, C.; Herrick-Davis, K.; Glennon, R. A. Binding of β-carbolines at 5-HT2 serotonin receptors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4421–4425; (c) Abdel-Fattah, A. F. M.; Matsumoto, K.; Gammaz, H. A. F.; Watanabe, H. Hypothermic effect of harmala alkaloid in rats: Involvement of serotonergic mechanism. *Pharmacol. Biochem. Behav.* **1995**, *52*, 421–426; (d) Song, Y.; Kesuma, D.; Wang, J.; Deng, Y.; Duan, J.; Wang, J. H.; Qi, R. Z. Specific inhibition of cyclin-dependent kinases and cell proliferation by harmine. *Biochem. Biophys. Res. Commun.* **2004**, *317*, 128–132; (e) Cain, M.; Weber, R. W.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C.; Crawley, J. N.; Paul, S. M.; Skolnick, P. β-Carbolines: Synthesis and neurochemical and pharmacological actions on brain benzodiazepine receptors. *J. Med. Chem.* **1982**, *25*, 1081–1091; (f) Dodd, R. H.; Ouannes, C.; de Carvalho, L. P.; Valin, A.; Venault, P. 3-Amino-β-carboline derivatives and the benzodiazepine receptor: Synthesis of a selective antagonist of the sedative action of diazepam. *J. Med. Chem.* **1985**, *28*, 824–828; (g) Hollinshead, S. P.; Trudell, M. L.; Skolnick, P.; Cook, J. M. Structural requirements for agonist actions at the benzodiazepine receptor: Studies with analogs of 6-(benzyloxy)-4-(methoxymethyl)-β-carboline-3-carboxylic acid ethyl ester. *J. Med. Chem.* **1990**, *33*, 1062–1069; (h) Glennon, R.; Grella, B.; Tyacke, R. J.; Lau, A.; Westaway, J.; Hudson, A. Binding of β-carbolines at imidazoline I_2 receptors: A structure–affinity investigation. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 999–1002.
3. (a) Abdel-Moty, S. G.; Sakai, S.; Aimi, N.; Takayama, H.; Kitajima, M.; E1-Shorbagi, A.; Ahmed, A. N.; Omar, N. M. Synthesis of cytotoxic 1-polyhydroxyalkyl-β-carboline derivatives. *Eur. J. Med. Chem.* **1997**, *32*, 1009–1017; (b) Al-Allaf, T. A. K.; Rashan, L. J. Synthesis and cytotoxic evaluation of the first *trans*-palladium (II) complex with naturally occurring alkaloid harmine. *Eur. J. Med. Chem.* **1998**, *33*, 817–820; (c) Ishida, J.; Wang, H.-K.; Bastow, K. F.; Hu, C.-Q.; Lee, K.-H. Cytotoxicity of harmine and

β-carboline analogs. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3319–3324; (d) Molina, P.; Fresneda, P. M.; Garcia-Zafra, S.; Almendros, P. An iminophosphorane-mediated efficient synthesis of the alkaloid eudistomin U of marine origin. *Tetrahedron Lett.* **1995**, *36*, 3581–3582.

4. Cao, R.; Chen, Q.; Hou, X.; Chen, H.; Guan, H.; Ma, Y.; Peng, W.; Xu, A. Synthesis, acute toxicities, and antitumor effects of novel 9-substituted β-carboline derivatives. *Bioorg. Med. Chem.* **2004**, *12*, 4613–4623.
5. (a) Whaley, W. M.; Govindachari, T. R. Synthesis of isoquinolines. *Org. React.* **1951**, *6*, 74–150; (b) Whaley, W. M.; Govindachari, T. R. The Pictet–Spengler synthesis of tetrahydroisoquiolines and related compounds. *Org. React.* **1951**, *6*, 151–190.
6. (a) Minisci, F.; Galli, R.; Cecere, M.; Malatesta, V.; Caronna, T. Nucleophilic character of alkyl radicals: New syntheses by alkyl radicals generated in redox processes. *Tetrahedron Lett.* **1968**, *54*, 5609–5612; (b) Minisci, F.; Gardini, G. P. A new selectibe type of aromatic substitution: Homolytic amidation. *Tetrahedron Lett.* **1970**, *1*, 15–16; (c) Minisci, F. Novel applications of free-radical reactions in preparative organic chemistry. *Synthesis* **1973**, 1–24.
7. Lu, T.; Lin, G.-W.; Chen, Y.-D.; Wang, Y.; Zhang, L.-Y.; Sun, N.-Y.; Hao, L.-H.; Zhu, Y. Preparation of β-carbolines as cyclin-dependent kinase 2 inhibitors. CN Patent 101475571 A, **2009**.
8. Snyder, H. R.; Walker, H. G.; Werber, F. X. The synthesis of β-carbolines, V: 1-Amino-β-carboline. *J. Am. Chem. Soc.* **1959**, *71*, 527–529.
9. Lippke, K.; Schunack, W.; Wenning, W.; Muller, W. β-Carbolines as benzodiazepine receptor ligands, 1: Synthesis and benzodiazapine receptor interaction of esters of β-carboline-3-carboxylic acid. *J. Med. Chem.* **1983**, *26*, 499–503.
10. Saxena, A. K.; Jain, P. C.; Anand, N.; Dua, P. R. Agents acting on the central nervous system-XV, 2-substituted 1,2,3,4,6,7,12,12a-octahydroprazino-(2′,1′:6,1)pyrido(3,4-*b*)indoles: A new class of central nervous system depressants. *J. Med. Chem.* **1973**, *16*, 560–564.
11. Agarwal, S. K.; Saxena, A. K.; Jain, P. C. Studies on β-carbolines: Synthesis of 3-amino-9*H*-pyrido [3,4-*b*]-indole and its reaction with carbethoxy-isothiocyanate and benzoyl isothiocyanate. *Indian J. Chem.* **1980**, *19B*, 45–47.
12. Dodd, R. H.; Ouannes, C.; Carvalho, L. P.; Valin, A.; Venault, P.; Chapouthier, G.; Rossier, J.; Potier, P. 3-Amino-β-carboline derivatives and the benzodiazepine receptor: Synthesis of a selective antagonist of the sedative action of diazepam. *J. Med. Chem.* **1985**, *28*, 824–828.
13. Allen, M. S.; Hagen, T. J.; Trudell, M. L.; Codding, P. W.; Skolnik, P.; Cook, J. M. Synthesis of novel 3-substituted β-carbolines as benzodiazepine receptor ligands: Probing the benzodiazepine receptor pharmacophore. *J. Med. Chem.* **1988**, *31*, 1854–1861.
14. Linn, J. A.; McLean, E. W.; Kelley, J. L. 1,4-Diazabicyclo[2.2.2]octane (DABCO)-catalysed hydrolysis and alcoholysis reactions of 2-amino-9-benzyl-6-chloro-9*H*-purine. *J. Chem. Soc., Chem. Commun.* **1994**, *8*, 913–914.
15. Kast, O.; Bracher, F. Unexpected *ipso*-substitutions at the β-carboline nucleus. *Synth. Commun.* **2003**, *33*, 3843–3850.