# Synthesis and Biological Activities of Novel Chiral Fluorinated β-Carboline Derivatives



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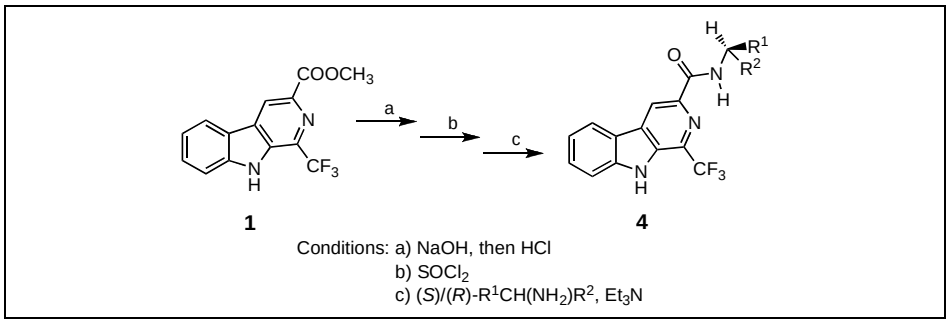


A series of unreported chiral β-carbolines **4** with trifluoromethyl group at position-1 and chiral carboxamide chains or amino acid ester chains at position-3 has been designed and synthesized. The results of bioassay *in vitro* show that compounds **4e**, **4i** and **4k** show 78.8%, 84.0% and 78.9% inhibition on monoamine oxidase, in 1 mmol/L, respectively, and compound **4e** also exhibit 60.9% inhibitory activity on tumor lung cell A-549 in $10^{-5}$ mmol/L. In view of different configuration, the inhibitory activity on monoamine oxidase of *S*-enantiomer of the target compound is better than that of *R*-enantiomer.

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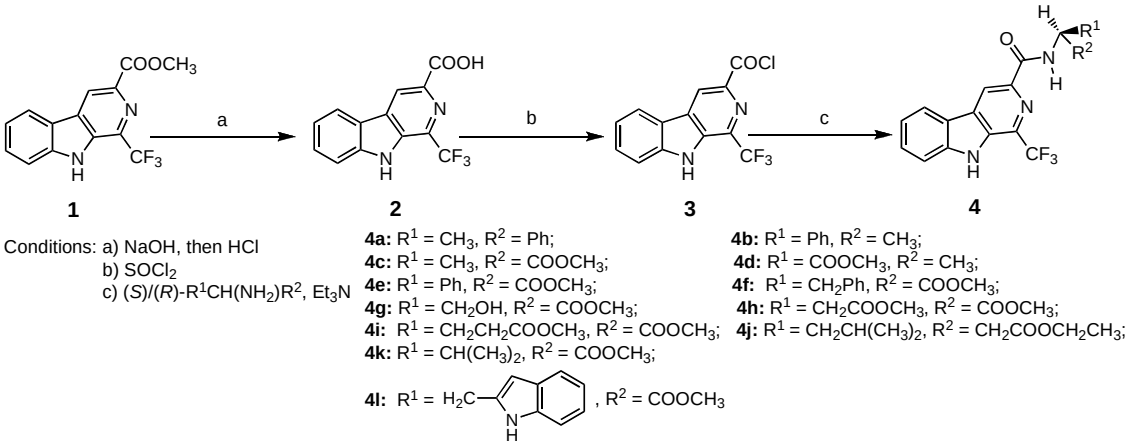
## INTRODUCTION

Numerous β-carboline derivatives have been reported to have various biological properties. Some of them have been shown to possess CNS (central nervous system) activities, binding with high affinity to the central benzodiazepine receptors (BZR) [1] and recent reports reveal that some β-carboline compounds, such as, β-carboline (norharman) and 1-methyl-β-carboline (harman) are potent inhibitors of monoamine oxidase which plays a significant physiological role in the CNS and peripheral organs [2]. Some β-carboline derivatives also exhibit antitumor [3], anti-HIV [4], antiviral [5], antimicrobial [6], antiplasmodial [7] and insecticidal activities [8]. In view of these facts, study of synthesis and biological activities of β-carbolines has received increasing attention. As far as structure-activity relationship is concerned, series of structure modification on β-carboline mother nucleus have been carried out and found that appropriate substituents introduced to the position-1 and 3 could contribute to enhancing antitumor activities of the compounds. Side chains at position-3, such as different carboxylate or carboxamide chains could reinforce the DNA intercalating ability of the compound and boost the cytotoxicity to tumor cell lines [4b,9]. Amino acid ester side chain, having base-specific contacts with DNA bases and high bioavailability, has also been introduced to the position-3 and the derivatives have been thought of as promising lead antitumor compounds [10].

Organic fluorine compounds play an important role in various fields such as agrochemicals and pharmaceuticals presumably due to their intrinsic properties and the biological activity of a compound may be dramatically changed by replacement of an appropriate hydrogen atom by a fluorine atom [11]. As a result, trifluoromethylated compounds have received special attention. Much current effort has been devoted to the development of methods for generating trifluoromethylated analogues [12]. In our previous research, we have developed a novel synthesis of introducing trifluoromethyl group to the position-1 of β-carbolines [13]. Because chirality is a central factor in biological phenomena and it is common that the enantiomers of a chiral drug show striking differences in terms of biological activity, potency, toxicity and transport mechanisms, enantiomeric pure products are therefore desirable ones in drug synthesis in recent years [14]. Based on the above idea, we now report the synthesis and biological activities of a series of unreported chiral β-carbolines with trifluoromethyl group at position-1 and chiral carboxamide chains or amino acid ester chains at position-3. The preliminary results of bioassay show that some of them possess good inhibition activities on tumor lung cell A-549 and monoamine oxidase.

**Scheme I**




## RESULTS AND DISCUSSION

The synthetic pathway for the title compounds **4** is shown in Scheme 1. The preparation of β-carboline-3-carboxylic acid **2** has previously been reported by Bergman and coworkers [15]. Herein, compound **2** could be synthesized by the hydrolysis of β-carboline **1** in the alkaline conditions in 88% yield. β-Carboline **1** was prepared according to the literature method [13] by one-pot reaction of tryptophan methyl ester hydrochloride, trifluoroacetic acid and triphenylphosphine and this is a facile route to introduce trifluoromethyl group to the basic β-carboline ring. The compound **2** was subjected to chlorination with thionyl chloride to provide the compound **3**. And then novel single chiral β-carboline-3-carboxamide derivatives **4** could be synthesized by the reaction of compound **3** with various easily accessible (*S*)/(*R*)-amino acid methyl esters and (*S*)/(*R*)-1-phenylethylamine in 55-96% yields. It was found that the whole reactive process of synthesis of compounds **4** could be quickly finished at mild condition and yielded satisfactory results. The structures of compounds **4** were confirmed by ir, $^{1}$H nmr, $^{13}$C nmr, LC-MS spectroscopy and elemental analysis.

Monoamine oxidase bioassay *in vitro* of some target compounds was investigated according to the previous literature [16]. The results are summarized in Table 1. The results of Table 1 show that some compounds exhibit good inhibitory activity, for example, in 1 mmol/L, compounds **4e**, **4i** and **4k** showed 78.8%, 84.0% and 78.9% inhibition, respectively. Compared **4a** with **4b**, **4c** with **4d**, it can be found that the inhibitory activity of *S*-enantiomer is better than *R*-enantiomer and the compounds with amino acid ester side chain lead a better effect. It may be because amino acids are the fundamental building blocks of biological system and many natural products and they are sometimes *S*-configuration in nature. Because monoamine oxidase plays a significant physiological role in the CNS and peripheral organs, monoamine oxidase inhibitors are useful as antidepressants or Parkinson's disease [2b]. The results of monoamine oxidase assay may indicate that these novel compounds may be promising head lead compounds to cure neurodegenerative diseases.

**Table 1**

Inhibitory Activity on Monoamine Oxidase of Compounds **4** (%)

| Compound | 0.01 mmol/L | 0.1 mmol/L | 1 mmol/L |
|---|---|---|---|
| **4a** | 7.4 | 25.6 | 37.5 |
| **4b** | 8.3 | 22.9 | 31.5 |
| **4c** | 9.4 | 35.5 | 73.6 |
| **4d** | 2.6 | 28.4 | 68.5 |
| **4e** | 6.9 | 29.0 | 78.8 |
| **4i** | 8.2 | 30.7 | 84.0 |
| **4j** | 8.9 | 22.9 | 75.3 |
| **4k** | 9.4 | 31.4 | 78.9 |

The inhibitory activities of lung cancer cell A-549 of some target compounds *in vitro*, such as, compounds **4h**, **4i**, **4l** and **4e** were done following the sulforhodamine B (SRB) protein coloration method [17] and found that compound **4e** exhibit good inhibitory rate, 76.4% in $10^{-4}$ mmol/L and 60.9% in $10^{-5}$ mmol/L, others only show weak inhibition in $10^{-4}$ mmol/L.

Further study on the biological activities of these compounds is underway.

In summary, unreported chiral β-carbolines **4** with trifluoromethyl group at position-1 and chiral carboxamide chains or amino acid ester chains at position-3 have been designed and synthesized. The preliminary results of bioassay show that some of them not only possess good inhibitory activities on monoamine oxidase but also exhibit good antitumor activities on tumor lung cell A-549. The results of the bioassay indicate that the inhibitory activity on monoamine oxidase of *S*-enantiomer of the target compound is better than

*R*-enantiomer. The results also indicate that some of the fluorinated β-carbolines may be promising lead compounds of antitumor drugs, antidepressants and curing Parkinson's disease. It is worthwhile to optimize the structures.

## EXPERIMENTAL

Nmr spectra were obtained using an AVANCE-300 spectrometer 300 MHz for $^1$H nmr and 75 MHz for $^{13}$C nmr and reported as parts per million (ppm) from the internal standard tetramethylsilane. Ir spectra were taken on EQUINOX-55 Infrared spectrometer. Mass spectra were recorded on an Agilent 1100LC/MSD Trap SL spectrometer. Elementary analyses were taken on an Elementar Vario MICRO analyzer. Optical rotations were measured with a Rudolph AUTOPOL IV automatic polarimeter. Melting points were determined on X4 microscopic melting apparatus (uncorrected).

Methyl 1-(trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (**1**) was prepared from tryptophan methyl ester hydrochloride according to literature procedure [13] in 69% yield.

**Preparation of 1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid (2)**. To a solution of **1** (1.20 g, 3.40 mmoles) in methanol (40 mL) was added 18% aqueous sodium hydroxide solution (25 mL), and the mixture was stirred at 60°C for 2 hours. The brown solution was neutralized with concentrated hydrogen chloride to pH 1, and filtered, and the white solid was recrystallized from acetone:petroleum (1:4, v/v). 1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid was obtained in 88% yield, mp 202-203°C. $^1$H nmr (deuteriochloroform): δ 7.43 (t, *J* = 7.4 Hz, 1H, 6-H), 7.67-7.87 (m, 2H, 7-H and 8-H), 8.48 (d, *J* = 7.9 Hz, 1H, 5-H), 9.15 (s, 1H, 4-H), 11.44 (s, 1H, 9-H); ms: m/z 279 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3285, 1743, 1598, 1507.

**Preparation of 1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl Chloride (3)**. To a solution of **2** (0.25 g, 0.90 mmol) in dry chloroform (30 mL) was added thionyl chloride (3 mL). The mixture was refluxed for 4 hours, and then the solvent was removed under pressure, the residue was purified on a silica gel column. Elution of the column with acetone:petroleum (1:1, v/v) gave pale yellow solids in 97% yield, mp 88-90°C. $^1$H nmr (deuteriochloroform): δ 7.49 (t, *J* = 7.2 Hz, 1H, 6-H), 7.61-7.75 (m, 2H, 7-H and 8-H), 8.23 (d, *J* = 8.0 Hz, 1H, 5-H), 9.02 (s, 1H, 4-H), 9.34 (s, 1H, 9-H); ms: m/z 297 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3139, 1756, 1592, 1498. *Anal.* Calcd. for $C_{13}H_6ClF_3N_2O$: C, 52.28; H, 2.03; N, 9.38. Found: C, 55.20; H, 2.03; N, 0.35.

**General Procedure for the Preparation of Fluorinated β-carbolines 4a-l**. To a solution of (*S*)-1-phenylethylamine (0.09 g, 0.90 mmol), chloroform (20 mL) and triethylamine (0.09 g, 0.90 mmol) was added dropwise intermediate **3** in acetone (15 mL) in 0.5 hours at 0°C and then the solution was stirred for 10 minutes at room temperature. After evaporation, the residue was separated on a silica gel column.

**(*S*)-1-(Trifluoromethyl)-*N*-(1-phenylethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (4a)**. This compound was obtained as white solids in 81%, mp 183-185°C. $[\alpha]^{20}_D$ = -71.36 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 1.69 (d, *J* = 6.9 Hz, 3H, $CH_3$), 5.42-5.47 (m, 1H, CH), 7.23-7.46 (m, 6H), 7.56-7.61 (m, 2H, 7-H and 8-H), 8.15 (d, *J* = 7.9 Hz, 1H, 5-H), 8.34 (d, *J* = 8.3 Hz, 1H, CONH), 9.06 (s, 1H, 4-H), 9.39 (s, 1H, 9-H); $^{13}$C nmr (deuteriochloroform): δ 22.24, 48.93, 112.06, 117.14, 121.01, 121.55, 122.02, 126.06, 127.20, 128.60, 130.03, 132.89, 133.06, 139.49, 141.08, 143.28, 163.47; ms: m/z 382 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3375, 1667, 1599, 1500. *Anal.* Calcd. for $C_{21}H_{16}F_3N_3O$: C, 65.79; H, 4.21; N, 10.96. Found: C, 65.67; H, 4.22; N, 10.92.

**(*R*)-1-(Trifluoromethyl)-*N*-(1-phenylethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide (4b)**. This compound was obtained as white solids in 90% yield, mp 183-185°C. $[\alpha]^{20}_D$ = 72.75 (c = 1; ethyl acetate). $^1$H nmr (deuteriochloroform): δ 1.69 (d, *J* = 6.9 Hz, 3H, $CH_3$), 5.42-5.47 (m, 1H, CH), 7.23-7.46 (m, 6H), 7.56-7.61 (m, 2H, 7-H and 8-H), 8.16 (d, *J* = 7.9 Hz, 1H, 5-H ), 8.34 (d, *J* = 8.2 Hz, 1H, CONH), 9.07 (s, 1H, 4-H), 9.35 (s, 1H, 9-H); $^{13}$C nmr (deuteriochloroform): δ 22.23, 48.91, 112.04, 117.16, 121.02, 121.57, 122.04, 126.07, 127.21, 128.60, 130.04, 132.91, 133.05, 139.54, 141.06, 143.28, 163.45; ms: m/z 382 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3375, 1667, 1599, 1500. *Anal.* Calcd. for $C_{21}H_{16}F_3N_3O$: C, 65.79; H, 4.21; N, 10.96. Found: C, 65.69; H, 4.20; N, 10.93.

**(*S*)-*N*-[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]alanine Methyl Ester (4c)**. This compound was obtained as white solids in 92% yield, mp 228-229°C. $[\alpha]^{20}_D$ = -4.09 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 1.63 (d, *J* = 7.1 Hz, 3H, $CH_3$), 3.85 (s, 3H, $OCH_3$), 4.82-4.86 (m, 1H, CH), 7.40 (t, *J* = 7.3 Hz, 1H, 6-H), 7.58-7.69 (m, 2H, 7-H and 8-H), 8.11 (d, *J* = 8.1 Hz, 1H, 5-H), 8.32 (d, *J* = 6.8 Hz, 1H, CONH), 8.67 (s, 1H, 4-H), 9.27 (s, 1H, 9-H); $^{13}$C nmr (deuteriochloroform): δ 18.16, 48.35, 52.59, 112.28, 116.82, 121.01, 121.62, 122.06, 130.16, 132.75, 132.92, 138.91, 141.08, 163.85, 173.69; ms: m/z 364 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3342, 1743, 1663, 1501, 1167, 1122. *Anal.* Calcd. for $C_{17}H_{14}F_3N_3O_3$: C, 55.89; H, 3.86; N, 11.50. Found: C, 55.84; H, 3.85; N, 11.47.

**(*R*)-*N*-[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]alanine Methyl Ester (4d)**. This compound was obtained as white solids in 87% yield, mp 228-229°C; $[\alpha]^{20}_D$ = 3.80 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 1.64 (d, *J* = 7.2 Hz, 3H, $CH_3$), 3.86 (s, 3H, OCH3), 4.78-4.88 (m, 1H, CH),7.40 (t, *J* = 7.3 Hz, 1H, 6-H), 7.58-7.69 (m, 2H, 7-H and 8-H), 8.09 (d, *J* = 8.1 Hz, 1H, 5-H ), 8.30 (d, *J* = 7.4 Hz, 1H, CONH), 8.61 (s, 1H, 4-H), 9.34 (s, 1H, 9-H); $^{13}$C nmr (deuteriochloroform): δ 18.16, 48.35, 52.65, 112.32, 116.80, 120.98, 121.60, 122.05, 130.16, 132.71, 132.89, 138.77, 141.08, 163.88, 173.76; ms: m/z 364 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3339, 1744, 1664, 1600, 1501, 1167, 1122. *Anal.* Calcd. for $C_{17}H_{14}F_3N_3O_3$: C, 55.89; H, 3.86; N, 11.50. Found: C, 55.80; H, 3.85; N, 11.53.

**(*S*)-α-{[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]amino}benzeneacetic Acid Methyl Ester (4e)**. This compound was obtained as white solids in 58% yield, mp 82-84°C. $[\alpha]^{20}_D$ = 97.60 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 3.83 (s, 3H, $OCH_3$), 5.83 (d, *J* = 7.2 Hz, 1H, CH), 7.37-7.71 (m, 9H, Ph-H, 5-, 6-, 7-, and 8-H), 8.18 (d, *J* = 7.9 Hz, 1H, CONH), 8.84 (s, 1H, 4-H), 9.08 (s, 1H, 9-H); $^{13}$C nmr (deuteriochloroform): δ 54.04, 57.70, 114.18, 119.06, 121.74, 122.50, 123.94, 125.07, 128.94, 129.73, 130.23, 131.48, 134.19, 138.19, 139.23, 143.45, 163.45, 172.21; ms: m/z 426 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3392, 3251, 1748, 1670, 1629, 1530, 1499, 1251, 1183, 1125. *Anal.* Calcd. for $C_{22}H_{16}F_3N_3O_3$: C, 61.83; H, 3.77; N, 9.83. Found: C, 61.75; H, 3.76; N, 9.85.

**(*S*)-*N*-[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]phenylalanine Methyl Ester (4f)**. This compound was obtained as white solids in 55% yield, mp 179-180°C. $[\alpha]^{20}_D$ =

35.56 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 3.29 (d, *J* = 6.1 Hz, 2H, $CH_3$), 3.78 (s, 3H, $OCH_3$), 5.05-5.12 (m, 1H, CH), 7.29-7.35 (m, 5H, Ph-H), 7.47 (t, *J* = 6.9 Hz, 1H, 6-H), 7.59-7.68 (m, 2H, 7-H and 8-H), 8.19 (d, *J* = 7.5 Hz, 1H, 5-H ), 8.40 (d, *J* = 7.9 Hz, 1H, CONH), 8.87 (s, 1H, 4-H), 8.91 (s, 1H, 9-H); $^{13}$C nmr (deuteriochloroform): δ 37.68, 52.16, 53.16, 112.02, 116.19, 120.62, 121.22, 121.61, 126.98, 128.50, 128.94, 129.77, 132.28, 132.44, 135.44, 138.29, 140.71, 163.51, 172.06; ms: m/z 440 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3345, 1745, 1676, 1628, 1535, 1498, 1191, 1123. *Anal.* Calcd. for $C_{23}H_{18}F_3N_3O_3$: C, 62.58; H, 4.11; N, 9.52. Found: C, 62.52; H, 4.10; N, 9.50.

**(*S*)-*N*-[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]serine Methyl Ester (4g)**. This compound was obtained as white solids in 64% yield, mp 215-217°C; $[\alpha]^{20}_D$ = 17.20 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 2.68-2.76 (m, 2H, $CH_2$), 3.87 (s, 3H, $OCH_3$), 4.93-4.96 (m, 1H, CH), 7.43 (t, *J* = 7.2 Hz, 1H, 6-H), 7.61-7.72 (m, 2H, 7-H and 8-H), 8.23 (d, *J* = 8.2 Hz, 1H, 5-H), 8.78 (d, *J* = 7.9 Hz, 1H, CONH), 8.46 (s, 1H, 4-H), 9.05 (s, 1H, 9-H); $^{13}$C nmr (dimethyl sulfoxide-$d_6$): δ 52.29, 54.76, 61.39, 112.93, 117.75, 120.52, 121.24, 122.72, 130.21, 132.64, 132.92, 138.25, 142.21, 163.49, 171.04; ms: m/z 380 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3371, 3282, 1744, 1650, 1538, 1502, 1189, 1124. *Anal.* Calcd. for $C_{17}H_{14}F_3N_3O_4$: C, 53.55; H, 3.70; N, 11.02. Found: C, 53.60; H, 3.69; N, 11.05.

**(*S*)-*N*-[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]aspartic Acid Dimethyl Ester (4h)**. This compound was obtained as white solids in 96% yield, mp 184-186°C. $[\alpha]^{20}_D$ = 12.79 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 3.05 (dd, *J* = 16.8 Hz, 5.0 Hz, 1H, $CH_2$), 3.20 (dd, *J* = 16.9 Hz, 4.9 Hz, 1H, $CH_2$), 3.77 (s, 3H, $OCH_3$), 3.85 (s, 3H, $OCH_3$), 5.15-5.20 (m, 1H, CH), 7.41 (t, *J* = 7.3 Hz, 1H, 6-H), 7.62-7.70 (m, 2H, 7-H and 8-H), 8.14 (d, *J* = 8.0 Hz, 1H, 5-H ), 8.77-8.80 (m, 2H, 4-H and CONH), 9.21 (s, 1H, 9-H ); $^{13}$C nmr (dimethyl sulfoxide-$d_6$): δ 35.79, 48.83, 51.82, 52.53, 112.92, 117.93, 120.53, 121.22, 122.70, 130.18, 132.57, 132.95, 138.18, 142.18, 163.59, 171.17, 171.22; ms: m/z 422 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3383, 1736, 1671, 1601, 1520, 1497, 1173, 1134. *Anal.* Calcd. for $C_{19}H_{16}F_3N_3O_5$: C, 53.91; H, 3.81; N, 9.93. Found: C, 54.03; H, 3.80; N, 9.89.

**(*S*)-*N*-[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]glutamic Acid Dimethyl Ester (4i)**. This compound was obtained as white solids in 55% yield, mp 111-113°C. $[\alpha]^{20}_D$ = 4.39 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 2.26-2.30 (m, 2H, $CH_2$), 2.43-2.57 (m, 2H, $CH_2$), 3.86 (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 7.39 (t, *J* = 6.9 Hz, 1H, 6-H), 7.59-7.70 (m, 2H, 7-H and 8-H), 8.16 (d, *J* = 7.8 Hz, 1H, 5-H ), 8.45 (d, *J* = 8.2 Hz, 1H, CONH), 8.85 (s, 1H, 4-H ), 9.11 (s, 1H, 9-H); $^{13}$C nmr (dimethyl sulfoxide-$d_6$): δ 27.50, 31.28, 52.67, 53.01, 53.51, 114.16, 119.11, 121.77, 122.44, 123.90, 131.40, 133.77, 134.16, 139.62, 143.43, 165.23, 173.25, 174.14; ms: m/z 436 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3341, 1740, 1659, 1534, 1501, 1200, 1134. *Anal.* Calcd. for $C_{20}H_{18}F_3N_3O_5$: C, 54.92; H, 4.15; N, 9.61. Found: C, 54.75; H, 4.16; N, 9.59.

**(*S*)-β-{[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]amino}-5-methylhexanoic Acid Ethyl Ester (4j)**. This compound was obtained as white solids in 89% yield, mp 130-132°C; $[\alpha]^{20}_D$ = 2.80 (c = 1; ethanol: ethyl acetate = 3:2, v/v); $^1$H nmr (deuteriochloroform): δ 1.04 (d, *J* = 5.4 Hz, 6H, $2CH_3$), 1.36 (t, *J* = 7.1 Hz, 3H, $CH_3$), 1.79-1.88 (m, 3H, $CH_2CH$), 4.29 (q, *J* = 7.1 Hz, 2H, $CH_2$), 4.81-4.88 (m, 1H, CH), 7.40 (t, *J* = 6.9 Hz, 1H, 6-H), 7.57-7.69 (m, 2H, 7-H and 8-H ), 8.06 (d, *J* = 7.9 Hz, 1H, 5-H), 8.23 (d, *J* = 8.0 Hz, 1H, CONH), 8.54 (s, 1H, 4-H), 9.40 (s, 1H, 9-H); $^{13}$C nmr (deuteriochloroform): δ 14.18, 21.97, 22.90, 25.09, 41.36, 51.24, 61.51, 112.36, 116.66, 120.96, 121.52, 121.95, 130.08, 132.65, 132.82, 138.76, 141.10, 164.02, 173.32; ms: m/z 420 ($M^+$-1); ir ($cm^{-1}$, potassium bromide): 3340, 1745, 1662, 1537, 1500, 1174, 1124. *Anal.* Calcd. for $C_{21}H_{22}F_3N_3O_3$: C, 59.85; H, 5.62; N, 9.97. Found: C, 59.92; H, 5.63; N, 9.92.

**(*S*)-*N*-[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]valine Methyl Ester (4k)**. This compound was obtained as white solids in 60% yield, mp 158-160°C; $[\alpha]^{20}_D$ = 2.40 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 1.10 (d, *J* = 6.9 Hz, 6H, $2CH_3$), 2.39-2.46 (m, 1H, CH), 3.87 (s, 3H, $OCH_3$), 4.72-4.76 (m, 1H, CH), 7.40 (t, *J* = 7.8 Hz, 1H, 6-H), 7.57-7.68 (m, 2H, 7-H and 8-H ), 8.05 (d, *J* = 7.9 Hz, 1H, 5-H), 8.38 (d, *J* = 8.5 Hz, 1H, CONH), 8.47 (s, 1H, 4-H), 9.55 (s, 1H, 9-H); ms: m/z 392 ($M^+$-1); $^{13}$C nmr (deuteriochloroform): δ 17.84, 19.27, 30.98, 52.28, 57.72, 112.40, 116.61, 120.96, 121.49, 121.90, 130.04, 132.66, 132.85, 138.70, 141.16, 164.25, 172.80; ir ($cm^{-1}$, potassium bromide): 3345, 1747, 1663, 1534, 1498, 1170, 1124. *Anal.* Calcd. for $C_{19}H_{18}F_3N_3O_3$: C, 58.01; H, 4.61; N, 10.68. Found: C, 57.94; H, 4.60; N, 10.71.

**(*S*)-α-{[1-(Trifluoromethyl)-9*H*-pyrido[3,4-*b*]indole-3-carbonyl]amino}-3-(1*H*-indol-2-yl)propanoic Acid Methyl Ester (4l)**. This compound was obtained as white solids in 84% yield, mp 166-167°C; $[\alpha]^{20}_D$ = 59.58 (c = 1; ethyl acetate); $^1$H nmr (deuteriochloroform): δ 3.46-3.57 (d, *J* = 6.5 Hz, 2H, $CH_2$), 3.79 (s, 3H, $OCH_3$), 5.06-5.12 (m, 1H, CH), 7.10-7.60 (m, 2H, 7-H and 8-H ), 8.06 (d, *J* = 8.2 Hz, 1H, 5-H), 8.20 (s, 1H, N-H), 8.47 (d, 1H, *J* = 7.9 Hz, CONH), 8.52 (s, 1H, 4-H), 9.23 (s, 1H, 9-H); $^{13}$C nmr (dimethyl sulfoxide-$d_6$): δ 27.09, 52.23, 53.18, 109.08, 111.61, 112.91, 117.68, 118.23, 118.66, 120.50, 121.20, 122.68, 123.96, 127.30, 130.17, 132.53, 132.85, 136.32, 138.15, 142.16, 163.48, 172.13; ir ($cm^{-1}$, potassium bromide): 3326, 1737, 1663, 1534, 1500, 1188, 1133. ms: m/z 479 ($M^+$-1); *Anal.* Calcd. for $C_{25}H_{19}F_3N_4O_3$: C, 62.50; H, 3.99; N, 11.66. Found: C, 62.62; H, 3.98; N, 11.69.

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