Synthesis of Analogues of Flazin, in Particular, Flazinamide, as Promising Anti-HIV Agents

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Flazin isolated from the fruiting bodies of *Suillus granulatus* was found to possess weak anti-HIV activity (EC_{50} = 2.36 μM, *TI* = 12.1). To establish a SAR study, 46 flazin analogues were synthesized, and their anti-HIV activities were evaluated *in vitro*. Among them, flazinamide (**9a**) showed the most potent activity with an EC_{50} value of 0.38 μM and a *TI* value of 312.0. The results suggested that appropriate substituents at positions 3, 1′, and 5′ of flazin might play a crucial role in determining their anti-HIV activities, and that flazinamide can be considered as a promising, readily available anti-HIV agent.

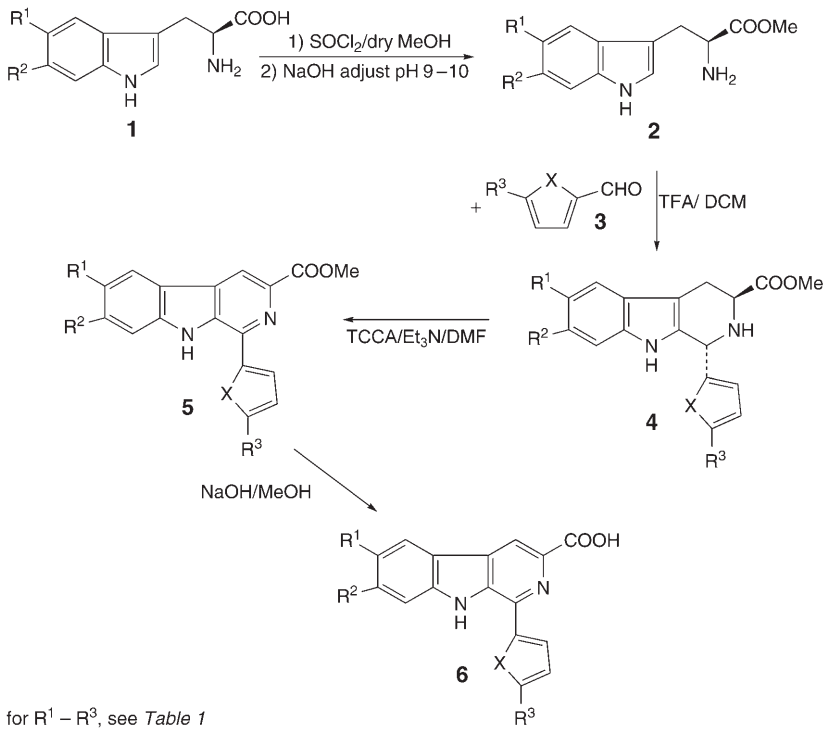
Introduction. – The global estimates of WHO/UNAIDS pointed to 42 million people infected with HIV/AIDS at the end of 2006, with 5 million newly infected people and 3 million deaths [1]. Although the use of the highly active antiretroviral therapy (HAART) has significantly reduced death rates from AIDS in developed countries, this existing drug therapy encounters problems such as the surge of drug-resistant viruses and poisoning caused by long-term drug usage [2]. In view of these realities, there is a compelling need to continue searching for new drugs with novel mechanisms of action.

In continuation of our research on bioactive metabolites of higher fungi from China [3–7], we recently identified a β-carboline alkaloid, flazin (**6a**), from the fruiting bodies of *Suillus granulatus*, with weak anti-HIV-1 activity (EC_{50} value of 2.36 μM, *TI* 12.1) [8]. Flazin (**6a**) was first isolated from sake (Japanese rice wine) in 1936, its structure was determined in 1986 [9], and its ^{1}H- and ^{13}C-NMR data were assigned in 2002 [10]. Some previous reports focused on the effects of β-carboline alkaloids on the central nervous system [11–14]. In 2000, *Lee* and co-workers were just first to report anti-HIV activity of a β-carboline alkaloid [15]. They prepared 28 derivatives of harmine and found that *N*-butylharmine was the most potent compound (EC_{50} = 0.037 μM) and possessed a good therapeutic index of 210 [16]. *Yang* and co-workers also found that some β-carboline derivatives inhibit HIV replication by interfering with the Tat-TAR interaction [17]. Inspired by these results, we designed and synthesized a series of flazin analogues in the present investigation, and possibly discovered new

compounds with comparable activity and lower toxicity than flazin. Moreover, this study will establish structure–activity relationships (SAR) of flazin analogues. We report here the synthesis and anti-HIV activities of novel flazin analogues with various substituents in positions 3, 6, 7, 9, 1′, and 5′.

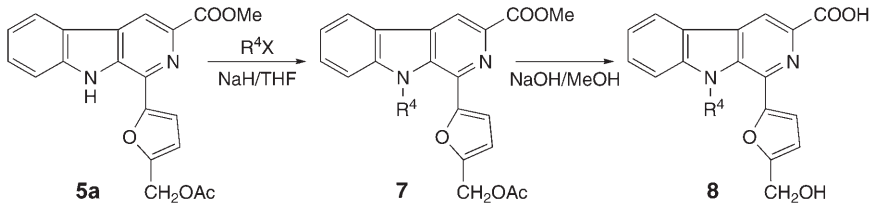
Results and Discussion. – 1. *Synthesis.* A series of novel flazin analogues with various substituents in positions 6, 7, 1′ and 5′ were designed and synthesized from the commercially available appropriate L-tryptophan and an appropriate aldehyde. The synthetic route is outlined in *Scheme 1*, and included four steps. First, substituted (−)-L-tryptophan methyl esters **2** were synthesized according to known procedures from the substituted (−)-L-tryptophan (**1**) [18]. Second, a *Pictet–Spengler* reaction of the substituted (−)-L-tryptophan methyl esters **2** and substituted aldehydes **3**, according to modified literature procedures [19][20], afforded diastereoisomeric mixtures of methyl 1,2,3,4-tetrahydro-β-carboline-3-carboxylates **4**. Third, the conversion of these diastereoisomeric mixtures to substituted methyl β-carboline-3-carboxylates **5** was carried out by oxidation with trichlorocyanuric acid (TCCA) in DMF according to the method of *Tilstam et al.* [21][22]. Finally, substituted methyl β-carboline-3-carboxylates **5** were saponified by NaOH in MeOH to give the corresponding flazin analogues **6**.

Scheme 1. *Synthetic Route of Flazin Analogues* **5**–**6**



Previous studies with harmine derivatives have shown that substitution of alkyl groups at N(9) of β-carboline ring system promotes the anti-HIV activity [16]. For this reason, two flazin analogues were designed and synthesized with a Me group or an Et group at N(9). The N(9)-position of compounds **5a** were alkylated by the action of NaH in anhydrous DMF, followed by addition of the relevant appropriate alkylating agent to afford compounds **7**, and then saponification in alkaline solution to provide the corresponding flazin analogues **8** as outlined in *Scheme 2*.

Scheme 2. *Synthetic Route of Flazin Analogues* **8**



for R^4, see *Table 2*

Many previous reports were focused on the effects of carboxamide derivatives on the HIV-1 reverse transcriptase [23–26]. Carboxy modification at C(3) of flazin would be expected to enhance anti-HIV activities, consequently a number of flazin analogues were designed and synthesized with substituents ranging from CH_2OH group to 2-hydroxylethylamide group. Synthetic route was outlined in *Scheme 3*. The compounds of type **5** were transformed into the corresponding amides through treatment with aqueous NH_3, NH_2OH, $MeNH_2$, and $HOCH_2CH_2NH_2$ to furnish the corresponding flazin analogues **9**, **10**, **11** and **12**, respectively. The hydrazinolysis of compound **5** in 85% $NH_2NH_2 \cdot H_2O$ provided the corresponding flazin analogues **13**, and reduction of compound **5** by $NaBH_4$ in anhydrous THF afforded the corresponding flazin analogues **14**.

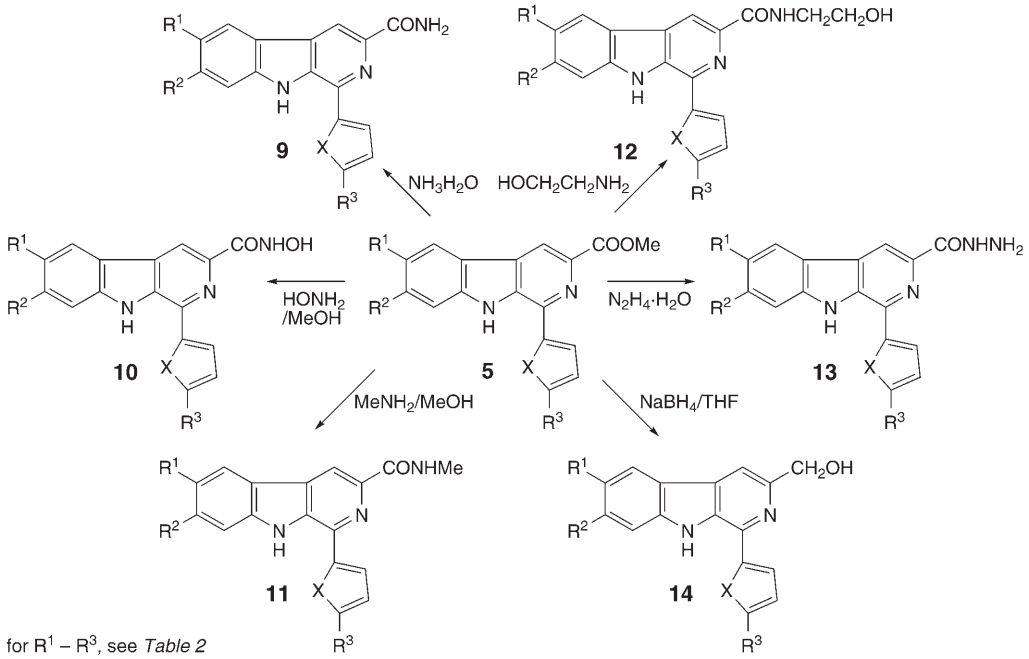
The chemical structures of all flazin analogues synthesized were confirmed by MS, and ^1H- and ^{13}C-NMR data (see *Exper. Part*).

2. *Anti-HIV Activity Evaluation*. All flazin analogues were evaluated for their inhibitory activity against HIV-1 replication in acutely infected C8166 cells, following the previously described methods [27][28] and the results are shown in *Tables 1* and *2*.

As it can be seen in *Table 2*, **9a** (1-[5-(hydromethyl)furan-2-yl]-β-carboline-3-carboxamide), named flazinamide, was among the more potent compounds (EC_{50} = 0.38 μM) in this series, and it possessed the best therapeutic index (*TI*) of 312.0. Compound **9c** (1-(5-methylfuran-2-yl)-β-carboline-3-carboxamide) was the most potent compound (EC_{50} = 0.19 μM) in this series, but it exhibited only a moderate *TI* value of 47.8. Compounds **9e** (1-(thiophen-2-yl)-β-carboline-3-carboxamide), **11c** (1-[5-(hydroxymethyl)furan-2-yl]-*N*-methyl-β-carboline-3-carboxamide), and **13d** (1-(thiophen-2-yl)-β-carboline-3-carbohydrazide) were also potent (EC_{50} 0.44, 0.46, and 0.50 μM, resp.) and showed good therapeutic indices (152.0, 134.0, and 130.0, resp.).

By comparing the anti-HIV inhibitory activities of the compounds in *Tables 1* and *2*, the following trends became evident. *a*) Amide modification of carboxy group at C(3) of flazin **9**–**13** except **13b** and **13c** led to enhanced anti-HIV activity compared with

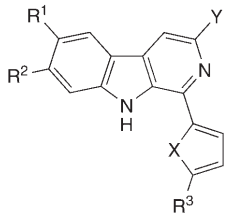
Scheme 3. *Synthetic Route of Flazin Analogues* **9**–**14**



flazin (**6a**); however, introduction of a carboxylate group or a CH_2OH group at C(3) of flazin (such as **5**, **14**) yielded inactive compounds. Thus, the substituent at C(3) can affect the activity of flazin analogues dramatically. *b*) Compared with **6b** and **5c**, compounds **6h** and **6i**, which have a S-atom in the 1′-position, enhance the anti-HIV activities, but compound **6j** and **6k**, which have CH=CH moiety in the 1′-position, showed diminished potency. This implied that the substituent in the 1′-position also played an important role for the anti-HIV activity of flazin. *c*) An H-atom and a Me group instead of a CH_2OH group at C(5′) of **6b** and **6c** showed lower activities than flazin (**6a**). Thus, the CH_2OH group of flazin (**6a**) seems to be important for activity in this series of compounds. *d*) Compared with **6a**, compound **6d** and **6g** retained some activity, but compound **6e** and **6f** exhibited decreased anti-HIV activity. Introduction of an appropriate group at C(6) and C(7) of flazin (**6a**) led to increase of the anti-HIV activities. *e*) Alkylation of the indole N-atom (*i.e.*, **8a** and **8b**) of flazin (**6a**) failed to increase the anti-HIV activity, it rather indicated that *N*-alkylation was unfavorable for the anti-HIV activity of **6a**.

A thorough analysis of the anti-HIV activities of flazin analogues indicated that: *1*) the anti-HIV potencies of flazin analogues were enhanced by the introduction of appropriate substituents at C(3), and in positions 1′ and 5′ in flazin; *2*) the flazinamide (**9a**; $EC_{50}=0.38$ μM, $TI=312.0$) with the $CONH_2$ group at C(3), O-atom in position 1′, and CH_2OH group at C(5′) represented the optimal combination for enhancing anti-HIV activity; *3*) the flazinamide structure **9a** might be an important basis for the design and synthesis of new anti-HIV drugs. Recently, the molecular-mechanism study of

Table 1. *Anti-HIV-1 Activities of Flazin Analogues* **5** *and* **6**



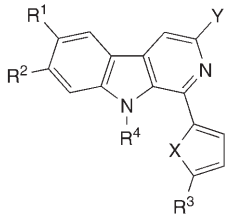
Compound	R^1	R^2	R^3	X	Y	CC_{50} [μM][a])	EC_{50} [μM][b])	TI[c])
5a	H	H	CH_2OAc	O	COOMe	69.70 ± 1.05	18.60 ± 0.13	3.74
5b	H	H	H	O	COOMe	30.70 ± 0.35	10.10 ± 0.38	3.04
5c	H	H	Me	O	COOMe	23.00 ± 0.31	16.80 ± 0.25	1.37
5d	F	H	CH_2OAc	O	COOMe	32.70 ± 0.61	16.10 ± 0.34	2.03
5e	Me	H	CH_2OAc	O	COOMe	95.10 ± 0.23	30.50 ± 0.03	3.12
5f	MeO	H	CH_2OAc	O	COOMe	20.40 ± 0.31	14.50 ± 0.47	1.40
5g	H	F	CH_2OAc	O	COOMe	95.70 ± 2.11	14.20 ± 0.71	6.76
5h	H	H	H	S	COOMe	11.60 ± 0.21	2.31 ± 0.12	5.00
5i	H	H	Me	S	COOMe	22.20 ± 0.36	3.58 ± 0.17	6.20
5j	H	H	H	CH=CH	COOMe	30.70 ± 1.50	10.10 ± 0.23	3.04
5k	H	H	Me	CH=CH	COOMe	18.40 ± 1.52	11.80 ± 0.27	1.56
5l	H	H	F	CH=CH	COOMe	70.50 ± 0.69	24.40 ± 1.18	2.89
6a	H	H	CH_2OH	O	COOH	28.50 ± 2.44	2.36 ± 0.38	12.10
6b	H	H	H	O	COOH	28.50 ± 1.33	4.69 ± 0.21	6.08
6c	H	H	Me	O	COOH	21.60 ± 2.12	3.30 ± 0.42	6.53
6d	F	H	CH_2OH	O	COOH	15.00 ± 0.94	4.40 ± 0.96	3.42
6e	Me	H	CH_2OH	O	COOH	41.10 ± 2.99	2.09 ± 0.38	19.70
6f	MeO	H	CH_2OH	O	COOH	14.30 ± 0.25	5.01 ± 0.29	2.85
6g	H	F	CH_2OH	O	COOH	153.00 ± 9.78	3.12 ± 0.60	48.90
6h	H	H	H	S	COOH	30.80 ± 1.66	1.01 ± 0.09	30.60
6i	H	H	Me	S	COOH	36.90 ± 0.64	2.00 ± 0.15	18.50
6j	H	H	H	CH=CH	COOH	77.00 ± 1.18	24.10 ± 0.21	4.61
6k	H	H	Me	CH=CH	COOH	53.40 ± 0.72	18.10 ± 0.75	2.95
6l	H	H	F	CH=CH	COOH	77.10 ± 0.99	22.00 ± 0.91	3.51
AZT[d])	–	–	–	–	–	500 ± 1.67	0.009 ± 0.001	55600

[a]) CC_{50} is concentration of drug that causes 50% reduction in total cell number. [b]) EC_{50} is concentration of drug that reduces syncytia formation by 50%. [c]) Therapeutic index (TI) is a ratio of the CC_{50} value/EC_{50} value. [d]) AZT was used as positive control.

flazinamide showed that it might interfere in the early stage of HIV life-cycle [29]. Therefore, flazinamide (**9a**) can be considered as a promising and readily available anti-HIV agent.

Conclusions. – In conclusion, we have synthesized a series of flazin analogues with various substituents in positions 3, 6, 7, 9, 1′, and 5′. To evaluate the anti-HIV activities of the compounds synthesized, cytopathic-effect inhibition assay were tested on human C8166 cells infected with HIV-1_{IIIB}, and cell cytotoxicity experiments were also conducted on C8166 cells based on MTT cytotoxicity assay method. Most of the

Table 2. *Anti-HIV-1 Activities of Flazin Analogues* **8**–**14**



Compound	R^1	R^2	R^3	R^4	X	Y	CC_{50} [μM][a])	EC_{50} [μM][b])	TI[c])
8a	H	H	H	Me	O	COOH	46.80 ± 1.38	7.06 ± 1.07	6.62
8b	H	H	H	Et	O	COOH	40.70 ± 0.38	6.64 ± 0.53	6.12
9a	H	H	CH_2OH	H	O	$CONH_2$	118.00 ± 1.32	0.38 ± 0.07	312.00
9b	H	H	H	H	O	$CONH_2$	20.10 ± 1.76	0.26 ± 0.01	78.50
9c	H	H	Me	H	O	$CONH_2$	8.83 ± 0.19	0.19 ± 0.02	47.60
9d	H	F	CH_2OH	H	O	$CONH_2$	15.90 ± 0.53	0.32 ± 0.06	49.10
9e	H	H	H	H	S	$CONH_2$	67.60 ± 4.94	0.44 ± 0.07	152.00
10a	H	H	H	H	O	CONHOH	3.60 ± 0.24	0.83 ± 0.03	4.35
10b	H	H	H	H	S	CONHOH	3.31 ± 0.06	0.57 ± 0.07	5.84
10c	H	H	CH_2OH	H	O	CONHOH	47.40 ± 2.10	1.76 ± 0.37	26.90
11a	H	H	H	H	O	CONHMe	> 68.70 ± 0.78	1.35 ± 0.05	> 50.90
11b	H	H	H	H	S	CONHMe	18.20 ± 0.03	0.21 ± 0.02	87.40
11c	H	H	CH_2OH	H	O	CONHMe	> 62.30 ± 1.98	0.46 ± 0.06	> 134.00
12a	H	H	CH_2OH	H	O	$CONH(CH_2)_2OH$	2.17 ± 0.11	0.62 ± 0.08	3.53
12b	H	H	H	H	O	$CONH(CH_2)_2OH$	3.19 ± 0.36	0.50 ± 0.08	6.44
12c	H	H	H	H	S	$CONH(CH_2)_2OH$	4.39 ± 0.15	0.20 ± 0.03	22.10
12d	H	H	Me	H	S	$CONH(CH_2)_2OH$	7.39 ± 0.22	1.13 ± 0.19	6.55
13a	H	H	CH_2OH	H	O	$CONHNH_2$	11.50 ± 1.21	0.42 ± 0.08	27.60
13b	H	H	H	H	O	$CONHNH_2$	46.60 ± 5.19	5.77 ± 0.27	8.01
13c	H	H	Me	H	O	$CONHNH_2$	49.10 ± 0.21	6.66 ± 0.96	7.38
13d	H	H	H	H	S	$CONHNH_2$	> 64.90 ± 2.35	0.50 ± 0.03	> 130.00
14	H	H	CH_2OH	H	O	CH_2OH	9.20 ± 0.39	4.14 ± 0.67	2.22
AZT[d])	–	–	–	–	–	–	500 ± 1.67	0.009 ± 0.001	55600

[a]) CC_{50} is concentration of drug that causes 50% reduction in total cell number. [b]) EC_{50} is concentration of drug that reduces syncytia formation by 50%. [c]) Therapeutic index (TI) is a ratio of the CC_{50} value/EC_{50} value. [d]) AZT was used as positive control.

compounds showed a significant anti-HIV activity. Among them, flazinamide (**9a**) displayed the most potent activity with an EC_{50} value of 0.38 μM and a TI value of 312.0. Further biological evaluations of **9a** are in progress in our laboratories. Moreover, the molecular-mechanism studies of these compounds are ongoing to further design and develop more potent compounds.

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Experimental Part

General. All reagents and solvents were commercially obtained, and were dried and purified when necessary. TLC: silica gel F_{254} plates, detection under UV light. Column chromatography (CC): silica gel

(200–300 mesh, *Qingdao Marine Chemical Inc.*, P. R. China). M.p.: X-type micro-melting point apparatus; uncorrected. ^{1}H- and ^{13}C-NMR spectra: in (D_6)DMSO or $CDCl_3$ with *Bruker AM-400* or *Bruker DRX-500* spectrometers; TMS as an internal standard (chemical shifts δ in ppm). FAB- and EI-MS: *VG Auto Spec-3000* spectrometer.

Synthesis of Compound **2**. To a stirred soln. of *tryptophan* **1** (10 mmol) in 50 ml of dry MeOH, under ice-cooling, was added $SOCl_2$ (2.18 ml, 30 mmol) dropwise over 10 min. After stirring the mixture for 3 h, MeOH was removed under reduced pressure, and H_2O (25 ml) was added. Then, the pH of the aq. soln. was adjusted to 9–10 with sat. aq. NaOH soln., the soln. was extracted with AcOEt, and the org. layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated to give the compound **2**.

(−)-L-Tryptophan Methyl Ester (**2a**). White solid. Yield: 2.13 g (98%). M.p. 87–90°. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.27 (br. *s*, 1 H); 7.61 (*d*, *J* = 7.8, 1 H); 7.35 (*d*, *J* = 8.0, 1 H); 7.19 (*t*, *J* = 7.4, 1 H); 7.12 (*t*, *J* = 7.4, 1 H); 7.05 (*s*, 1 H); 3.83–3.81 (*m*, 1 H); 3.71 (*s*, 3 H); 3.28 (*dd*, *J* = 4.7, 14.4, 1 H); 3.06 (*dd*, *J* = 7.7, 14.4, 1 H). EI-MS: 218 (15), 159 (10), 130 (100), 77 (13).

(−)-L-5-Fluorotryptophan Methyl Ester (**2d**). White solid. Yield: 2.26 g (96%). M.p. 85–89°. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.34 (br. *s*, 1 H); 7.82 (*d*, *J* = 7.8, 1 H); 7.70–7.68 (*m*, 1 H); 7.36 (*t*, *J* = 7.4, 1 H); 7.04 (*s*, 1 H); 3.88–3.84 (*m*, 1 H); 3.76 (*s*, 3 H); 3.22 (*dd*, *J* = 4.8, 14.2, 1 H); 3.06 (*dd*, *J* = 7.4, 14.2, 1 H). FAB-MS (pos.): 237 ($[M+1]^+$).

(−)-L-5-Methyltryptophan Methyl Ester (**2e**). White solid. Yield: 2.19 g (95%). M.p. 90–92°. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.28 (br. *s*, 1 H); 7.97 (*s*, 1 H); 7.72 (*d*, *J* = 7.8, 1 H); 7.22 (*t*, *J* = 7.4, 1 H); 7.10 (*s*, 1 H); 3.85 (*s*, 3 H); 3.86–3.83 (*m*, 1 H); 3.31 (*dd*, *J* = 4.7, 14.4, 1 H); 3.05 (*dd*, *J* = 7.7, 14.4, 1 H); 2.19 (*s*, 3 H). FAB-MS (pos.): 233 ($[M+1]^+$).

(−)-L-5-Methoxytryptophan Methyl Ester (**2f**). White solid. Yield: 2.44 g (96%). M.p. 92–95°. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.32 (br. *s*, 1 H); 7.63 (*d*, *J* = 7.8, 1 H); 7.59 (*s*, 1 H); 7.19 (*t*, *J* = 7.4, 1 H); 7.05 (*s*, 1 H); 4.01 (*s*, 3 H); 3.89–3.86 (*m*, 1 H); 3.76 (*s*, 3 H); 3.25 (*dd*, *J* = 4.7, 14.2, 1 H); 3.08 (*dd*, *J* = 7.7, 14.2, 1 H). FAB-MS (pos.): 249 ($[M+1]^+$).

(−)-L-6-Fluorotryptophan Methyl Ester (**2g**). White solid. Yield: 2.31g (98%). M.p. 96–98°. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.56 (br. *s*, 1 H); 8.11–7.99 (*m*, 1 H); 7.61 (*dd*, *J* = 2.1, 8.2, 1 H); 7.35 (*d*, *J* = 8.0, 1 H); 7.19 (*t*, *J* = 7.6, 1 H); 7.05 (*s*, 1 H); 3.92–3.88 (*m*, 1 H); 3.85 (*s*, 3 H); 3.31 (*dd*, *J* = 4.7, 14.4, 1 H); 3.05 (*dd*, *J* = 7.6, 14.4, 1 H). FAB-MS (pos.): 237 ($[M+1]^+$).

Synthesis of Compound **5**. Compound **3** (1 mmol) was added into a soln. of **2** (1 mmol) and CF_3COOH (TFA, 0.02 ml) in dry CH_2Cl_2 (10 ml) in the presence of 4-Å molecule sieves (M.S.; 200 mg), and the soln. was stirred for 2 d at r.t. After filtering and washing the flask with AcOEt, the combined org. soln. was evaporated under reduced pressure. The residue was taken up in 2 ml of DMF and neutralized with Et_3N (TEA). TEA (0.5 ml) was then added to the soln., and the mixture was cooled to −10°. Subsequently, trichlorocyanuric acid (TCCA; 232 mg, 1 mmol), dissolved in 1 ml of DMF, was slowly added keeping the temp. at −10°. After the addition was completed, the mixture was allowed to slowly warm to 0°, and stirred for 2 h at this temp. to complete the reaction. The resulting product was precipitated from ice water, filtered, washed with H_2O, and dried to give compound **5**.

*Methyl 1-[5-(Acetoxymethyl)furan-2-yl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylate* (**5a**). Yellow solid. Yield: 298 mg (82%). M.p. 153–156°. ^{1}H-NMR (400 MHz, $CDCl_3$): 10.24 (*s*, 1 H); 8.73 (*s*, 1 H); 8.12 (*d*, *J* = 8.0, 1 H); 7.67 (*d*, *J* = 8.2, 1 H); 7.56–7.52 (*m*, 1 H); 7.32–7.30 (*m*, 1 H); 7.30 (*d*, *J* = 3.4, 1 H); 6.58 (*d*, *J* = 3.4, 1 H); 5.23 (*s*, 2 H); 4.02 (*s*, 3 H); 2.15 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.0; 166.4; 153.7; 149.8; 141.0; 137.0; 133.0; 132.7; 130.0; 128.8; 121.5; 121.1; 120.7; 116.7; 112.9; 112.2; 109.7; 58.1; 52.5; 21.1. FAB-MS (pos.): 365 ($[M+1]^+$).

*Methyl 1-(Furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate* (**5b**). Yellow solid. Yield: 248 mg (85%). M.p. 144–147°. ^{1}H-NMR (400 MHz, $CDCl_3$): 9.61 (br. *s*, 1 H); 8.79 (*s*, 1 H); 8.18 (*d*, *J* = 8.0, 1 H); 7.72 (*d*, *J* = 8.0, 1 H); 7.63–7.59 (*m*, 2 H); 7.44 (*d*, *J* = 2.5, 1 H); 7.36 (*d*, *J* = 7.0, 1 H); 6.67 (*d*, *J* = 1.0, 1 H); 4.06 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.5; 153.6; 143.1; 140.5; 137.5; 133.2; 132.7; 130.2; 129.0; 121.8; 121.5; 121.0; 116.5; 112.4; 111.9; 110.1; 52.6. FAB-MS (pos.): 293 ($[M+1]^+$).

*Methyl 1-(5-Methylfuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate* (**5c**). Yellow solid. Yield: 269 mg (88%). M.p. 149–151°. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.63 (*s*, 1 H); 8.86 (*s*, 1 H); 8.29 (*d*, *J* = 7.6, 1 H); 7.73–7.70 (*m*, 2 H); 7.46 (*d*, *J* = 7.6, 1 H); 6.46 (*d*, *J* = 3.6, 1 H); 6.38 (*d*, *J* = 3.2, 1 H); 4.16 (*s*,

3 H); 2.54 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 166.6; 153.5; 151.8; 140.4; 137.4; 133.5; 132.4; 130.0; 128.9; 121.8; 121.6; 120.9; 116.0; 111.9; 111.4; 108.7; 52.6; 14.2. FAB-MS (pos.): 307 ($[M+1]^+$).

*Methyl 1-[5-(Acetoxymethyl)furan-2-yl]-6-fluoro-9*H-*pyrido[3,4-*b*]indole-3-carboxylate* (**5d**). Yellow solid. Yield: 324 mg (85%). M.p. 166–168°. ^{1}H-NMR (400 MHz, $CDCl_3$): 11.31 (*s*, 1 H); 8.75 (*s*, 1 H); 7.82 (*d*, *J* = 8.5, 1 H); 7.70–7.68 (*m*, 1 H); 7.38 (*t*, *J* = 8.5, 1 H); 7.34 (*d*, *J* = 2.5, 1 H); 6.65 (*d*, *J* = 2.5, 1 H); 5.28 (*s*, 2 H); 4.05 (*s*, 3 H); 2.19 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.7; 166.0; 158.7; 156.3; 149.9; 137.2; 136.6; 133.6; 132.9; 129.3; 121.4; 117.1; 116.6; 113.2; 112.7; 109.8; 106.7; 57.9; 52.3; 20.9. FAB-MS (pos.): 383 ($[M+1]^+$).

*Methyl 1-[5-(Acetoxymethyl)furan-2-yl]-6-methyl-9*H-*pyrido[3,4-*b*]indole-3-carboxylate* (**5e**). Yellow solid. Yield: 302 mg (80%). M.p. 155–158°. ^{1}H-NMR (500 MHz, $CDCl_3$): 10.15 (*s*, 1 H); 8.76 (*s*, 1 H); 7.95 (*s*, 1 H); 7.61 (*d*, *J* = 8.5, 1 H); 7.44 (*dd*, *J* = 1.0, 8.5, 1 H); 7.33 (*d*, *J* = 3.5, 1 H); 6.63 (*d*, *J* = 3.5, 1 H); 5.27 (*s*, 2 H); 4.05(*s*, 3 H); 2.55 (*s*, 3 H); 2.18 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 172.1; 166.5; 153.9; 149.8; 139.3; 136.8; 133.3; 132.7; 130.5; 130.3; 129.9; 121.4; 121.3; 116.8; 113.0; 111.9; 109.7; 58.8; 52.6; 21.4; 21.2. FAB-MS (pos.): 379 ($[M+1]^+$).

*Methyl 1-[5-(Acetoxymethyl)furan-2-yl]-6-methoxy-9*H-*pyrido[3,4-*b*]indole-3-carboxylate* (**5f**). Yellow solid. Yield: 338 mg (86%). M.p. 159–162°. ^{1}H-NMR (400 MHz, $CDCl_3$): 10.15 (*s*, 1 H); 8.76 (*s*, 1 H); 7.63 (*d*, *J* = 8.8, 1 H); 7.59 (*s*, 1 H); 7.33 (*t*, *J* = 7.2, 1 H); 7.26 (*d*, *J* = 3.2, 1 H); 6.63 (*d*, *J* = 3.2, 1 H); 5.27 (*s*, 2 H); 4.05 (*s*, 3 H); 3.78 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.1; 166.6; 154.7; 153.8; 149.8; 136.5; 135.9; 133.6; 132.9; 129.8; 121.6; 119.3; 116.9; 113.2; 113.2; 109.8; 102.9; 58.2; 55.8; 52.6; 21.2. FAB-MS (pos.): 395 ($[M+1]^+$).

*Methyl 1-[5-(Acetoxymethyl)furan-2-yl]-7-fluoro-9*H-*pyrido[3,4-*b*]indole-3-carboxylate* (**5g**). Yellow solid. Yield: 313 mg (82%). M.p. 163–165°. ^{1}H-NMR (400 MHz, $CDCl_3$): 10.37 (*s*, 1 H); 8.73 (*s*, 1 H); 8.10–8.08 (*m*, 1 H); 7.40 (*dd*, *J* = 2.1, 8.2, 1 H); 7.32 (*d*, *J* = 3.4, 1 H); 7.09 (*t*, *J* = 7.6, 1 H); 6.64 (*d*, *J* = 3.4, 1 H); 5.27 (*s*, 2 H); 4.05 (*s*, 3 H); 2.19 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.3; 166.3; 164.8; 162.4; 153.5; 149.8; 141.9; 137.6; 133.6; 132.7; 129.7; 122.8; 117.7; 116.3; 113.0; 109.6; 98.8; 58.2; 52.6; 21.2. FAB-MS (pos.): 383 ($[M+1]^+$).

*Methyl 1-(Thiophen-2-yl)-9*H-*pyrido[3,4-*b*]indole-3-carboxylate* (**5h**). Yellow solid. Yield: 261 mg (85%). M.p. 151–154°. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.75 (*s*, 1 H); 8.15 (*d*, *J* = 8.0, 1 H); 7.82 (*d*, *J* = 8.0, 1 H); 7.58–7.55 (*m*, 2 H); 7.47 (*d*, *J* = 4.0, 1 H); 7.33–7.30 (*m*, 1 H); 7.16 (*d*, *J* = 4.0, 1 H); 4.05 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.6; 141.6; 140.9; 136.9; 133.6; 130.0; 128.7; 127.8; 127.7; 127.6; 126.0; 121.6; 121.4; 120.8; 116.5; 112.2; 52.5. FAB-MS (pos.): 309 ($[M+1]^+$).

*Methyl 1-(5-Methylthiophen-2-yl)-9*H-*pyrido[3,4-*b*]indole-3-carboxylate* (**5i**). Yellow solid. Yield: 269 mg (85%). M.p. 155–158°. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.79 (*s*, 1 H); 8.17 (*d*, *J* = 7.6, 1 H); 7.82 (*d*, *J* = 7.6, 1 H); 7.54–7.51 (*m*, 2 H); 7.47 (*d*, *J* = 4.2, 1 H); 7.20 (*d*, *J* = 4.0, 1 H); 4.01 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 167.1; 145.2; 141.2; 136.8; 134.0; 130.3; 128.6; 127.7; 127.5; 127.2; 126.2; 121.5; 121.3; 121.0; 116.4; 112.8; 52.5; 14.5. FAB-MS (pos.): 323 ($[M+1]^+$).

*Methyl 1-Phenyl-9*H-*pyrido[3,4-*b*]indole-3-carboxylate* (**5j**). Yellow solid. Yield: 257 mg (85%). M.p. 151–153°. ^{1}H-NMR (500 MHz, $CDCl_3$): 10.48 (*s*, 1 H); 8.80 (*s*, 1 H); 8.14 (*d*, *J* = 7.5, 1 H); 7.93 (*d*, *J* = 7.0, 2 H); 7.57 (*d*, *J* = 7.5, 1 H); 7.51 (*t*, *J* = 7.5, 1 H); 7.30 (*t*, *J* = 7.2, 1 H); 7.30 (*t*, *J* = 7.2, 1 H); 7.30 (*t*, *J* = 7.2, 1 H); 7.30 (*t*, *J* = 7.2, 1 H); 3.97 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.9; 147.3; 140.6; 136.8; 135.6; 128.6; 128.4; 127.6; 126.5; 122.0; 121.7; 121.2; 120.7; 116.4; 112.1; 52.5. FAB-MS (pos.): 303 ($[M+1]^+$).

*Methyl 1-(4-Methylphenyl)-9*H-*pyrido[3,4-*b*]indole-3-carboxylate* (**5k**). Yellow solid. Yield: 265 mg (84%). M.p. 152–155°. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.75 (*s*, 1 H); 8.13 (*d*, *J* = 7.5, 1 H); 7.75 (*d*, *J* = 8.0, 2 H); 7.53–7.49 (*m*, 2 H); 7.25 (*d*, *J* = 7.5, 2 H); 7.24 (*d*, *J* = 7.5, 1 H); 3.96 (*s*, 3 H); 2.34 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.9; 143.1; 140.9; 138.8; 135.0; 134.5; 129.2; 127.8; 127.7; 127.6; 126.0; 121.6; 121.4; 120.5; 116.5; 112.0; 52.3; 21.0. FAB-MS (pos.): 317 ($[M+1]^+$).

*Methyl 1-(4-Fluorophenyl)-9*H-*pyrido[3,4-*b*]indole-3-carboxylate* (**5l**). Yellow solid. Yield: 268 mg (84%). M.p. 158–159°. ^{1}H-NMR (500 MHz, $CDCl_3$): 9.75 (*s*, 1 H); 8.83 (*s*, 1 H); 8.20 (*d*, *J* = 7.5, 1 H); 7.91 (*t*, *J* = 6.5, 2 H); 7.59–7.57 (*m*, 2 H); 7.35 (*t*, *J* = 6.5, 1 H); 7.18 (*t*, *J* = 7.5, 2 H); 3.96 (*s*, 3 H); 2.34 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 166.8; 164.4; 141.9; 141.1; 137.3; 135.0; 133.8; 130.4; 130.3; 129.7; 128.7; 121.7; 121.5; 120.7; 116.7; 115.7; 115.5; 112.0; 52.3. FAB-MS (pos.): 321 ($[M+1]^+$).

Synthesis of Compound **6**. To a soln. of compound **5** (0.2 mmol) in a 1:1.5 mixture with MeOH (5 ml) was added aq. NaOH (2 mol/l, 0.5 ml). After heating to reflux for 6–12 h, the medium was acidified to pH 5–6 with solid citric acid, diluted with distilled H_2O (20 ml), and extracted with AcOEt (4 × 10 ml). The org. layers were collected, washed with brine (2 × 10 ml), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give compound **6**.

*1-[5-(Hydroxymethyl)furan-2-yl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6a**). Yellow solid. Yield: 60.4 mg (98%). M.p. 238–244°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.61 (br. *s*, 1 H); 8.79 (*s*, 1 H); 8.36 (*d*, *J* = 7.6, 1 H); 7.81 (*d*, *J* = 8.1, 1 H); 7.60 (*t*, *J* = 7.5, 1 H); 7.40 (*d*, *J* = 2.5, 1 H); 7.31 (*t*, *J* = 7.5, 1 H); 6.60 (*d*, *J* = 2.5, 1 H); 4.66 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 167.0; 157.1; 151.2; 141.4; 132.1; 131.6; 129.8; 128.6; 121.8; 120.9; 120.3; 115.3; 112.8; 112.7; 110.7; 109.1; 55.9. FAB-MS (pos.): 309 ($[M+1]^+$).

*1-(Furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6b**). Yellow solid. Yield: 53.6 mg (96%). M.p. 234–237°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.87 (br. *s*, 1 H); 8.85 (*s*, 1 H); 8.39 (*d*, *J* = 8.0, 1 H); 8.01 (*t*, *J* = 7.5, 1 H); 7.80 (*d*, *J* = 8.0, 1 H); 7.61 (*t*, *J* = 7.0, 1 H); 7.56 (*d*, *J* = 3.5, 1 H); 7.32 (*t*, *J* = 7.5, 1 H); 6.82 (*d*, *J* = 1.5, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 166.4; 152.3; 144.2; 141.6; 136.8; 132.4; 132.0; 129.8; 128.8; 121.9; 120.8; 120.4; 115.8; 113.0; 112.3; 110.2. FAB-MS (pos.): 279 ($[M+1]^+$).

*1-(5-Methylfuran-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6c**). Yellow solid. Yield: 57.8 mg (99%). M.p. 237–240°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.61 (*s*, 1 H); 8.78 (*s*, 1 H); 8.36 (*d*, *J* = 8.0, 1 H); 7.82 (*d*, *J* = 8.0, 1 H); 7.61 (*t*, *J* = 7.5, 1 H); 7.36 (*d*, *J* = 1.6, 1 H); 7.31 (*t*, *J* = 7.5, 1 H); 6.40 (*s*, 1 H); 2.53 (*s*, 3 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 166.7; 153.9; 150.5; 141.5; 139.9; 132.7; 131.8; 129.7; 128.8; 121.9; 121.0; 120.5; 115.3; 113.0; 111.6; 108.6; 13.8. FAB-MS (pos.): 293 ($[M+1]^+$).

*6-Fluoro-1-[5-(hydroxymethyl)furan-2-yl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6d**). Yellow solid. Yield: 63.8 mg (98%). M.p. 253–256°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.65 (*s*, 1 H); 8.86 (*s*, 1 H); 8.29 (*d*, *J* = 8.5, 1 H); 7.80 (*dd*, *J* = 4.0, 8.5, 1 H); 7.38 (*t*, *J* = 9.0, 1 H); 7.40 (*d*, *J* = 3.0, 1 H); 6.61 (*d*, *J* = 3.0, 1 H); 5.50 (br. *s*, 1 H); 4.66 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 166.4; 158.3; 157.4; 156.0; 151.0; 137.8; 136.8; 132.8; 129.5; 121.5; 117.2; 116.3; 114.1; 111.2; 109.2; 107.6; 55.9. FAB-MS (pos.): 327 ($[M+1]^+$).

*1-[5-(Hydroxymethyl)furan-2-yl]-6-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6e**). Yellow solid. Yield: 63.2 mg (99%). M.p. 248–250°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.47 (br. *s*, 1 H); 8.76 (*s*, 1 H); 8.17 (*s*, 1 H); 7.69 (*d*, *J* = 8.0, 1 H); 7.45 (*d*, *J* = 8.0, 1 H); 7.40 (*d*, *J* = 3.5, 1 H); 6.61 (*d*, *J* = 3.5, 1 H); 4.66 (*s*, 2 H); 2.17 (*s*, 3 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 166.5; 157.2; 151.2; 139.6; 136.8; 132.3; 132.0; 130.4; 129.5; 121.4; 121.1; 115.6; 112.5; 111.0; 109.2; 55.9; 21.0. FAB-MS (pos.): 323 ($[M+1]^+$).

*1-[5-(Hydroxymethyl)furan-2-yl]-6-methoxyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6f**). Yellow solid. Yield: 64.8 mg (96%). M.p. 252–254°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.47 (*s*, 1 H); 8.85 (*s*, 1 H); 8.00 (*s*, 1 H); 7.70 (*d*, *J* = 8.8, 1 H); 7.40 (*s*, 1 H); 7.26 (*d*, *J* = 8.4, 1 H); 6.60 (*s*, 1 H); 4.66 (*s*, 2 H); 3.78 (*s*, 3 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 166.5; 157.2; 154.2; 151.3; 136.3; 136.1; 132.5; 132.3; 129.6; 121.5; 119.0; 116.1; 113.7; 110.9; 109.2; 103.7; 55.9; 55.6. FAB-MS (pos.): 339 ($[M+1]^+$).

*7-Fluoro-1-[5-(hydroxymethyl)furan-2-yl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6g**). Yellow solid. Yield: 62.4 mg (96%). M.p. 253–256°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.75 (*s*, 1 H); 8.81 (*s*, 1 H); 8.44–8.42 (*m*, 1 H); 7.53 (*d*, *J* = 9.2, 1 H); 7.38 (*d*, *J* = 3.8, 1 H); 7.18 (*t*, *J* = 7.6, 1 H); 6.61 (*d*, *J* = 3.8, 1 H); 4.66 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 164.1; 161.7; 157.3; 151.2; 142.4; 142.2; 132.5; 132.4; 129.7; 124.1; 123.9; 117.8; 115.6; 111.3; 109.3; 99.2; 56.0. FAB-MS (pos.): 327 ($[M+1]^+$).

*1-(Thiophen-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6h**). Yellow solid. Yield: 56.1 mg (95%). M.p. 252–254°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.02 (*s*, 1 H); 8.84 (*s*, 1 H); 8.39 (*d*, *J* = 7.6, 1 H); 7.82 (*d*, *J* = 8.0, 1 H); 7.53 (*m*, 2 H); 7.45 (*t*, *J* = 7.2, 1 H); 7.32 (*m*, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 166.8; 141.7; 140.6; 136.2; 133.4; 130.2; 128.9; 127.2; 127.5; 127.2; 126.2; 121.1; 121.8; 120.3; 116.6; 112.4. FAB-MS (pos.): 295 ($[M+1]^+$).

*1-(5-Methylthiophen-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6i**). Yellow solid. Yield: 57.8 mg (94%). M.p. 253–258°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.02 (*s*, 1 H); 8.84 (*s*, 1 H); 8.39 (*d*, *J* = 7.6, 1 H); 7.82 (*d*, *J* = 8.0, 1 H); 7.53–7.50 (*m*, 2 H); 7.45 (*t*, *J* = 7.2, 1 H); 7.32–7.28 (*m*, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 167.1; 142.5; 141.9; 140.3; 137.2; 133.4; 130.5; 128.8; 127.3; 127.5; 127.2; 126.2; 121.8; 120.3; 116.6; 112.4; 14.2. FAB-MS (pos.): 309 ($[M+1]^+$).

*1-Phenyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6j**). Yellow solid. Yield: 56.4 mg (98%). M.p. 258–260°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 10.48 (*s*, 1 H); 8.80 (*s*, 1 H); 8.14 (*d*, *J* = 7.5, 1 H); 7.93 (*d*, *J* = 7.0, 2 H); 7.57 (*d*, *J* = 7.5, 1 H); 7.51 (*t*, *J* = 7.5, 1 H); 7.30 (*t*, *J* = 7.2, 1 H); 7.30 (*t*, *J* = 7.2, 1 H); 7.30 (*t*, *J* = 7.2, 1 H); 7.30 (*t*, *J* = 7.2, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 166.9; 147.3; 140.6; 136.8; 135.6; 128.6; 128.4; 127.6; 126.5; 122.0; 121.7; 121.2; 120.7; 116.4; 112.1. FAB-MS (pos.): 289 ($[M+1]^+$).

*1-(4-Methylphenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6k**). Yellow solid. Yield: 60.0 mg (99%). M.p. 262–264°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.12 (br. *s*, 1 H); 8.97 (*s*, 1 H); 8.44 (*d*, *J* = 7.6, 1 H); 7.93 (*d*, *J* = 6.8, 2 H); 7.71 (*d*, *J* = 7.6, 1 H); 7.62 (*t*, *J* = 7.6, 1 H); 7.44 (*d*, *J* = 6.8, 2 H); 7.62 (*t*, *J* = 7.6, 1 H); 2.44 (*s*, 3 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 165.9; 142.1; 141.5; 139.2; 135.7; 134.5; 132.9; 129.9; 129.4; 129.3; 190.0; 122.4; 121.0; 120.8; 116.6; 113.0; 21.1. FAB-MS (pos.): 303 ($[M+1]^+$).

*1-(4-Fluorophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**6l**). Yellow solid. Yield: 60.2 mg (98%). M.p. 266–269°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.93 (br. *s*, 1 H); 8.90 (*s*, 1 H); 8.41 (*d*, *J* = 7.5, 1 H); 8.12 (*t*, *J* = 6.0, 2 H); 7.68 (*d*, *J* = 8.0, 1 H); 7.59 (*t*, *J* = 7.5, 1 H); 7.45 (*t*, *J* = 7.5, 2 H); 7.32 (*t*, *J* = 7.5, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 166.7; 163.5; 141.5; 140.6; 137.2; 134.4; 133.9; 130.9; 130.8; 129.5; 128.7; 122.0; 121.8; 120.4; 116.3; 115.6; 115.5; 112.7. FAB-MS (pos.): 307 ($[M+1]^+$).

Synthesis of Compound **7**. A mixture of **5a** (0.5 mmol) and anh. DMF (5 ml) was stirred at r.t. until clear, and then 60% NaH (2 mmol) and MeI/EtBr (1 mmol) were added. The mixture was stirred at r.t. for 1 h. The resulting mixture was poured into H_2O (10 ml) and extracted with AcOEt. The org. phase was washed with H_2O and brine, then dried (Na_2SO_4), filtered, and evaporated. The oil obtained was purified by silica CC to give compound **7**.

*Methyl 1-[5-(Acetoxymethyl)furan-2-yl]-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate* (**7a**). Yellow solid. Yield: 150.2 mg (80%). M.p. 126–129°. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.75 (*s*, 1 H); 8.18 (*d*, *J* = 8.0, 1 H); 7.72 (*d*, *J* = 8.2, 1 H); 7.56–7.54 (*m*, 1 H); 7.32–7.29 (*m*, 1 H); 7.31 (*d*, *J* = 3.2, 1 H); 6.62 (*d*, *J* = 3.2, 1 H); 5.23 (*s*, 2 H); 4.08 (*s*, 3 H); 4.01 (*s*, 3 H); 2.16 (*s*, 3 H). FAB-MS (pos.): 379 ($[M+1]^+$).

*Methyl 1-[5-(Acetoxymethyl)furan-2-yl]-9-ethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate* (**7b**). Yellow solid. Yield: 160.7 mg (82%). M.p. 137–140°. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.73 (*s*, 1 H); 8.12 (*d*, *J* = 8.0, 1 H); 7.69 (*d*, *J* = 8.2, 1 H); 7.62–7.59 (*m*, 1 H); 7.38–7.36 (*m*, 1 H); 7.30 (*d*, *J* = 3.4, 1 H); 6.58 (*d*, *J* = 3.4, 1 H); 5.26 (*s*, 2 H); 4.12–4.09 (*m*, 2 H); 2.18 (*s*, 3 H); 1.38–1.36 (*m*, 3 H). FAB-MS (pos.): 393 ($[M+1]^+$).

Synthesis of Compound **8**. To a soln. of compound **7** (0.2 mmol) in a 1 : 1.5 mixture with MeOH (5 ml) was added aq. NaOH (2 mol/l, 0.5 ml). After heating to reflux for 6 h, the medium was acidified to pH 5–6 with solid citric acid, diluted with distilled H_2O (20 ml), and extracted with AcOEt (4 × 10 ml). The org. layers were collected, washed with brine (2 × 10 ml), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give compound **8**.

*1-(Furan-2-yl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**8a**). Yellow solid. Yield: 34.9 mg (96%). M.p. 206–209. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.66 (br. *s*, 1 H); 8.82 (*s*, 1 H); 8.37 (*d*, *J* = 8.0, 1 H); 7.92 (*d*, *J* = 8.0, 1 H); 7.60 (*t*, *J* = 7.5, 1 H); 7.40 (*d*, *J* = 3.2, 1 H); 7.31 (*t*, *J* = 7.5, 1 H); 6.96 (*d*, *J* = 3.2, 1 H); 4.68 (*s*, 2 H); 4.02 (*s*, 3 H). FAB-MS (pos.): 365 ($[M+1]^+$).

*9-Ethyl-1-[5-(Hydroxymethyl)furan-2-yl]-9*H*-pyrido[3,4-*b*]indole-3-carboxylic Acid* (**8b**). Yellow solid. Yield: 37.0 mg (98%). M.p. 212–214. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.61 (br. *s*, 1 H); 8.79 (*s*, 1 H); 8.36 (*d*, *J* = 7.6, 1 H); 7.81 (*d*, *J* = 8.1, 1 H); 7.64 (*t*, *J* = 7.5, 1 H); 7.45 (*d*, *J* = 2.5, 1 H); 7.37 (*t*, *J* = 7.5, 1 H); 6.82 (*d*, *J* = 2.5, 1 H); 4.72 (*s*, 2 H); 4.06–4.05 (*m*, 2 H); 1.32–1.30 (*m*, 3 H). FAB-MS (pos.): 379 ($[M+1]^+$).

Synthesis of Compound **9**. To a soln. of compound **5** (0.2 mmol) in 5 ml MeOH was added aq. NH_3 (25%, 1 ml). After stirring for 3 d at r.t., the medium was concentrated under reduced pressure. The residue was purified by CC to give compound **9**.

*1-[5-(Hydroxymethyl)furan-2-yl]-9*H*-pyrido[3,4-*b*]indole-3-carboxamide* (**9a**). Yellow solid. Yield: 39.3 mg (64%). M.p. 194–198. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.13 (*s*, 1 H); 8.76 (*s*, 1 H); 8.18 (*d*, *J* = 8.0, 1 H); 7.76 (*d*, *J* = 8.0, 1 H); 7.60 (*t*, *J* = 7.5, 1 H); 7.34 (*t*, *J* = 7.5, 1 H); 7.30 (*d*, *J* = 3.3, 1 H); 6.50 (*d*, *J* = 3.0, 1 H); 4.73 (*s*, 2 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 166.7; 157.2; 151.7; 141.4; 139.7; 131.5; 131.4; 130.2; 128.8; 122.0; 121.1; 120.4; 112.7; 112.6; 111.0; 109.2; 55.0. FAB-MS (pos.): 308 ($[M+1]^+$).

*1-(Furan-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carboxamide* (**9b**). Yellow solid. Yield: 34.3 mg (62%). M.p. 164–167°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.42 (*s*, 1 H); 8.83 (*s*, 1 H); 8.25 (*d*, *J* = 8.0, 1 H); 7.81 (*d*, *J* = 8.0, 1 H); 7.65 (*t*, *J* = 7.5, 1 H); 7.39 (*t*, *J* = 7.5, 1 H); 7.30 (*d*, *J* = 3.3, 1 H); 7.22 (*t*, *J* = 7.5, 1 H); 6.50

(d, J = 3.0, 1 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 167.2; 157.8; 152.1; 142.4; 131.5; 131.4; 130.2; 128.8; 122.0; 121.7; 121.1; 120.4; 112.7; 112.6; 111.2; 109.5. FAB-MS (pos.): 278 ($[M+1]^+$).

*1-(5-Methylfuran-2-yl)-9*H-*pyrido[3,4-*b*]indole-3-carboxamide* (**9c**). Yellow solid. Yield: 39.5 mg (68%). M.p. 168–171°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.50 (s, 1 H); 8.70 (s, 1 H); 8.34 (d, J = 8.0, 1 H); 8.20 (s, 1 H); 7.80 (d, J = 8.0, 1 H); 7.59 (t, J = 7.5, 1 H); 7.51 (d, J = 3.0, 1 H); 7.29 (t, J = 7.5, 1 H); 6.39 (d, J = 3.0, 1 H); 2.54 (s, 3 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 166.7; 153.8; 150.9; 141.4; 139.6; 131.7; 131.3; 130.0; 128.6; 121.8; 121.0; 120.2; 112.8; 112.1; 111.3; 108.5; 13.8. FAB-MS (pos.): 292 ($[M+1]^+$).

*7-Fluoro-1-[5-(hydroxymethyl)furan-2-yl]-9*H-*pyrido[3,4-*b*]indole-3-carboxamide* (**9d**). Yellow solid. Yield: 49.4 mg (76%). M.p. 243–246°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.75 (s, 1 H); 8.81 (s, 1 H); 8.44–8.42 (m, 1 H); 7.53 (d, J = 9.2, 1 H); 7.38 (d, J = 3.8, 1 H); 7.18 (t, J = 7.6, 1 H); 6.61 (d, J = 3.8, 1 H); 4.66 (s, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 166.5; 161.5; 157.3; 151.5; 142.2; 140.2; 131.9; 131.3; 130.0; 124.0; 117.9; 112.4; 111.1; 109.2; 108.7; 99.8; 55.9. FAB-MS (pos.): 326 ($[M+1]^+$).

*1-(Thiophen-2-yl)-9*H-*pyrido[3,4-*b*]indole-3-carboxamide* (**9e**). Yellow solid. Yield: 41.0 mg (69%). M.p. 188–191°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.81 (s, 1 H); 8.77 (s, 1 H); 8.37 (d, J = 7.6, 1 H); 8.18 (d, J = 8.1, 1 H); 7.77–7.75 (m, 2 H); 7.62 (t, J = 7.2, 1 H); 7.53 (d, J = 4.0, 1 H); 7.33 (d, J = 3.2, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 166.3; 142.1; 141.6; 139.3; 134.8; 132.0; 130.4; 128.7; 128.6; 128.5; 126.6; 121.8; 121.1; 120.5; 112.9; 112.8. FAB-MS (pos.): 294 ($[M+1]^+$).

Synthesis of Compound **10**. To a soln. of compound **5** (0.2 mmol) in 5 ml MeOH was added $HONH_2$ (33% in EtOH, 0.5 ml). After stirring for 24 h at r.t., the soln. was concentrated under reduced pressure. The residue was purified by CC to give compound **10**.

1-(Furan-2-yl)-N-*hydroxy-9*H-*pyrido[3,4-*b*]indole-3-carboxamide* (**10a**). Yellow solid. Yield: 35.0 mg (60%). M.p. 241–244°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.82 (br. s, 1 H); 8.79 (s, 1 H); 8.17 (d, J = 8.0, 1 H); 8.08 (t, J = 8.4, 1 H); 7.79 (t, J = 8.4, 1 H); 7.66 (d, J = 8.0, 1 H); 7.50 (d, J = 4.4, 1 H); 7.41 (t, J = 7.6, 1 H); 7.21 (d, J = 4.8, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 165.4; 145.5; 143.2; 141.2; 134.5; 132.6; 130.9; 129.6; 128.2; 128.0; 126.6; 122.0; 121.1; 120.8; 112.9; 112.4. FAB-MS (pos.): 293 ($[M+1]^+$).

N-*Hydroxy-1-(thiophen-2-yl)-9*H-*pyrido[3,4-*b*]indole-3-carboxamide* (**10b**). Yellow solid. Yield: 37.9 mg (60%). M.p. 248–250°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.76 (br. s, 1 H); 8.73 (s, 1 H); 8.19 (d, J = 8.0, 1 H); 8.05 (t, J = 8.4, 1 H); 7.75 (t, J = 8.4, 1 H); 7.60 (d, J = 8.0, 1 H); 7.56 (d, J = 4.4, 1 H); 7.34 (t, J = 7.6, 1 H); 7.29 (d, J = 4.8, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 164.8; 145.7; 142.2; 140.5; 134.4; 132.8; 131.4; 129.7; 128.4; 128.2; 126.9; 121.9; 121.1; 120.7; 112.8; 112.6. FAB-MS (pos.): 309 ($[M+1]^+$).

N-*Hydroxy-1-[5-(Hydroxymethyl)furan-2-yl]pyrido[3,4-*b*]indole-3-carboxamide* (**10c**). Yellow solid. Yield: 39.9 mg (62%). M.p. 246–248°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.86 (br. s, 1 H); 8.72 (s, 1 H); 8.32 (d, J = 8.0, 1 H); 8.12 (t, J = 8.0, 1 H); 7.82 (t, J = 8.0, 1 H); 7.64 (d, J = 8.0, 1 H); 7.41 (d, J = 3.4, 1 H); 6.64 (d, J = 3.4, 1 H); 4.59 (s, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 165.8; 145.5; 143.2; 141.2; 134.5; 132.6; 130.9; 129.6; 128.8; 128.5; 128.1; 122.2; 121.4; 120.8; 112.8; 112.4; 55.6. FAB-MS (pos.): 323 ($[M+1]^+$).

Synthesis of Compound **11**. To a soln. of compound **5** (0.2 mmol) in 5 ml MeOH was added $MeNH_2$ (33% in EtOH; 0.5 ml). After stirring for 24 h at r.t., the soln. was concentrated under reduced pressure. The residue was purified by CC to give compound **11**.

1-(Furan-2-yl)-N-*methyl-9*H-*pyrido[3,4-*b*]indole-3-carboxamide* (**11a**). Yellow solid. Yield: 37.2 mg (64%). M.p. 248–252°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.79 (s, 1 H); 8.81 (s, 1 H); 8.75 (d, J = 8.0, 1 H); 8.37 (d, J = 8.0, 1 H); 7.79 (d, J = 8.0, 1 H); 7.69 (d, J = 3.0, 1 H); 7.59 (t, J = 7.5, 1 H); 7.38 (t, J = 4.0, 1 H); 7.29 (t, J = 7.5, 1 H); 2.92 (s, 3 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 165.0; 152.7; 144.2; 141.6; 139.5; 131.5; 131.4; 130.2; 128.7; 121.9; 120.9; 120.2; 112.9; 112.4; 112.3; 110.2; 26.1. FAB-MS (pos.): 292 ($[M+1]^+$).

N-*Methyl-1-(thiophen-2-yl)-9*H-*pyrido[3,4-*b*]indole-3-carboxamide* (**11b**). Yellow solid. Yield: 38.6 mg (66%). M.p. 255–257°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.76 (s, 1 H); 8.76 (s, 1 H); 8.39 (d, J = 8.0, 1 H); 8.35 (d, J = 5.0, 1 H); 8.15 (d, J = 3.4, 1 H); 7.81 (d, J = 5.0, 1 H); 7.75 (d, J = 7.5, 1 H); 7.60 (t, J = 7.5, 1 H); 7.36 (t, J = 4.0, 1 H); 7.31 (t, J = 7.5, 1 H); 2.93 (s, 3 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 164.9; 142.0; 141.6; 139.5; 134.9; 132.1; 130.4; 128.7; 128.6; 128.5; 126.7; 121.9; 121.1; 120.5; 112.8; 112.7; 26.1. FAB-MS (pos.): 308 ($[M+1]^+$).

1-[5-(Hydroxymethyl)furan-2-yl]-N-*methyl-9*H-*pyrido[3,4*-b*]indole-3-carboxamide* (**11c**). Yellow solid. Yield: 41.7 mg (65%). M.p. 212–214°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.72 (*s*, 1 H); 8.84 (*s*, 1 H); 8.72 (*d*, *J* = 8.0, 1 H); 8.38 (*d*, *J* = 8.0, 1 H); 7.76 (*t*, *J* = 7.6, 1 H); 7.60 (*t*, *J* = 7.6, 1 H); 7.38 (*d*, *J* = 3.2, 1 H); 6.59 (*d*, *J* = 3.2, 1 H); 4.68 (*s*, 2 H); 2.94 (*s*, 3 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 165.4; 152.8; 144.4; 141.6; 139.5; 131.5; 131.4; 130.2; 128.7; 128.2; 120.8; 120.5; 112.8; 112.3; 112.2; 110.4; 55.8; 26.1. FAB-MS (pos.): 322 ($[M+1]^+$).

Synthesis of Compound **12**. To a soln. of compound **5** (0.2 mmol) in 5 ml MeOH was added $NH_2CH_2CH_2OH$ (0.5 ml). After stirring for 3 d at r.t., the medium was concentrated under reduced pressure. The residue was purified by CC to give the compound **12**.

N-*(2-Hydroxyethyl)-1-[5-(hydroxymethyl)furan-2-yl]-9*H-*pyrido[3,4*-b*]indole-3-carboxamide* (**12a**). Yellow solid. Yield: 49.8 mg (71%) M.p. 269–272°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.50 (*s*, 1 H); 8.71 (*s*, 1 H); 8.37 (*d*, *J* = 8.0, 1 H); 7.81 (*d*, *J* = 8.5, 1 H); 7.61 (*t*, *J* = 8.0, 1 H); 7.48 (*d*, *J* = 3.0, 1 H); 7.30 (*t*, *J* = 7.5, 1 H); 6.43 (*d*, *J* = 3.0, 1 H); 4.86 (*s*, 2 H); 3.62 (*d*, *J* = 5.0, 2 H); 3.48–3.44 (*m*, 2 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 164.4; 153.8; 150.7; 141.4; 139.3; 131.6; 131.3; 130.0; 128.6; 121.8; 121.0; 120.2; 112.8; 112.0; 111.3; 108.5; 59.9; 56.6; 41.3. FAB-MS (pos.): 352 ($[M+1]^+$).

1-(Furan-2-yl)-N-*(2-hydroxyethyl)-9*H-*pyrido[3,4*-b*]indole-3-carboxamide* (**12b**). Yellow solid. Yield: 50.0 mg (78%). M.p. 266–269°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.93 (*s*, 1 H); 8.90 (*s*, 1 H); 8.41 (*d*, *J* = 7.5, 1 H); 8.12 (*t*, *J* = 6.0, 2 H); 7.68 (*d*, *J* = 8.0, 1 H); 7.59 (*t*, *J* = 7.5, 1 H); 7.45 (*t*, *J* = 7.5, 1 H); 7.32 (*t*, *J* = 7.5, 1 H); 3.66 (*d*, *J* = 5.0, 2 H); 3.53–3.51 (*m*, 2 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 166.7; 151.5; 150.6; 141.2; 137.2; 133.9; 130.9; 130.8; 129.5; 128.7; 122.0; 121.8; 120.4; 116.3; 115.5; 112.7; 56.6; 42.5. FAB-MS (pos.): 322 ($[M+1]^+$).

N-*(2-Hydroxyethyl)-1-(thiophen-2-yl)-9*H-*pyrido[3,4*-b*]indole-3-carboxamide* (**12c**). Yellow solid. Yield: 50.4 mg (75%). M.p. 278–280°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 12.10 (*s*, 1 H); 8.98 (*s*, 1 H); 8.46 (*d*, *J* = 8.8, 1 H); 7.85 (*d*, *J* = 8.8, 1 H); 7.69 (*t*, *J* = 7.2, 1 H); 7.63 (*t*, *J* = 7.2, 1 H); 7.43 (*t*, *J* = 7.6, 1 H); 7.34 (*t*, *J* = 7.2, 1 H); 6.45 (*t*, *J* = 3.0, 1 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 164.4; 153.8; 150.7; 141.4; 139.3; 131.6; 131.3; 130.0; 128.6; 121.8; 121.0; 120.2; 112.8; 112.0; 111.3; 108.5; 59.9; 41.6; 13.8. FAB-MS (pos.): 338 ($[M+1]^+$).

N-*(2-Hydroxyethyl)-1-(5-methylthiophen-2-yl)-9*H-*pyrido[3,4*-b*]indole-3-carboxamide* (**12d**). Yellow solid. Yield: 50.5 mg (72%). M.p. 284–286°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.51 (*s*, 1 H); 8.72 (*s*, 1 H); 8.38 (*d*, *J* = 8.0, 1 H); 7.81 (*d*, *J* = 8.5, 1 H); 7.61 (*t*, *J* = 8.0, 1 H); 7.48 (*d*, *J* = 3.0, 1 H); 7.30 (*t*, *J* = 7.5, 1 H); 6.45 (*t*, *J* = 3.0, 1 H); 4.88 (*s*, 1 H); 3.63 (*d*, *J* = 5.0, 2 H); 3.49–3.47 (*m*, 2 H); 2.46 (*s*, 3 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 164.2; 142.0; 141.6; 139.1; 134.9; 132.1; 130.5; 128.9; 128.7; 128.6; 126.7; 122.1; 121.1; 120.5; 112.8; 112.8; 59.9; 41.5. FAB-MS (pos.): 352 ($[M+1]^+$).

Synthesis of Compound **13**. To a soln. of compound **5** (0.2 mmol) in 5 ml MeOH was added aq. $NH_2NH_2 \cdot H_2O$ (85%, 0.5 ml). After stirring for 24 h at r.t., the medium was concentrated under reduced pressure. The residue was purified by CC to give compound **13**.

*1-[5-(Hydroxymethyl)furan-2-yl]-9*H-*pyrido[3,4*-b*]indole-3-carbohydrazide* (**13a**). Yellow solid. Yield: 42.5 mg (66%). M.p. 253–256°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.56 (*s*, 1 H); 9.87 (*s*, 1 H); 8.72 (*d*, *J* = 1.4, 1 H); 7.40 (*d*, *J* = 7.8, 1 H); 7.79 (*d*, *J* = 8.2, 1 H); 7.69 (*d*, *J* = 1.6, 1 H); 7.62 (*t*, *J* = 7.2, 1 H); 7.31 (*t*, *J* = 7.4, 1 H); 6.61 (*d*, *J* = 2.8, 1 H); 5.47 (*t*, *J* = 5.6, 1 H); 4.68 (*d*, *J* = 5.6, 2 H); 4.59 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 163.7; 157.2; 151.7; 141.3; 139.1; 131.7; 131.3; 130.1; 128.8; 122.1; 121.0; 120.3; 112.6; 112.2; 111.3; 109.2; 56.0. FAB-MS (pos.): 323 ($[M+1]^+$).

*1-(Furan-2-yl)-9*H-*pyrido[3,4*-b*]indole-3-carbohydrazide* (**13b**). Yellow solid. Yield: 35.6 mg (61%). M.p. 238–241°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.81 (*s*, 1 H); 9.90 (*s*, 1 H); 8.71 (*s*, 1 H); 8.37 (*d*, *J* = 7.6, 1 H); 7.99 (*d*, *J* = 7.6, 1 H); 7.76–7.74 (*m*, 2 H); 7.59 (*t*, *J* = 7.2, 1 H); 7.32 (*t*, *J* = 7.5, 1 H); 7.29 (*t*, *J* = 7.2, 1 H); 4.80 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 163.8; 152.8; 144.3; 141.6; 131.7; 131.6; 130.2; 129.0; 128.8; 122.0; 120.9; 120.3; 112.9; 112.6; 112.5; 110.5. FAB-MS (pos.): 293 ($[M+1]^+$).

*1-(5-Methylfuran-2-yl)-9*H-*pyrido[3,4*-b*]indole-3-carbohydrazide* (**13c**). Yellow solid. Yield: 40.4 mg (65%). M.p. 240–244°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 11.51 (*s*, 1 H); 9.82 (*s*, 1 H); 8.66 (*s*, 1 H); 8.36 (*d*, *J* = 8.0, 1 H); 7.81 (*d*, *J* = 8.0, 1 H); 7.60–7.58 (*m*, 2 H); 7.30 (*t*, *J* = 7.5, 1 H); 6.40 (*s*, 1 H); 4.58 (*s*, 2 H); 2.07 (*s*, 3 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 168.7; 153.8; 150.9; 141.4; 139.0; 131.9; 131.2; 129.9; 128.6; 121.8; 121.0; 120.2; 112.8; 111.8; 111.7; 108.6; 13.8. FAB-MS (pos.): 307 ($[M+1]^+$).

*1-(Thiophen-2-yl)-9*H*-pyrido[3,4-*b*]indole-3-carbohydrazide* (**13d**). Yellow solid. Yield: 46.8 mg (76%). M.p. 268–271°. ^{1}H-NMR (400 MHz, (D_6)DMSO): 11.80 (*s*, 1 H); 9.31 (*s*, 1 H); 8.73 (*s*, 1 H); 8.37 (*d*, *J* = 8.0, 1 H); 8.16 (*d*, *J* = 8.0, 1 H); 7.77–7.74 (*m*, 2 H); 7.60 (*t*, *J* = 7.2, 1 H); 7.33 (*d*, *J* = 4.0, 1 H); 7.29 (*d*, *J* = 3.2, 1 H); 4.46 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D_6)DMSO): 163.7; 142.1; 141.6; 138.9; 135.2; 132.1; 130.4; 129.0; 128.8; 128.7; 126.9; 122.1; 121.1; 120.9; 112.9; 112.8. FAB-MS (pos.): 309 ([*M* + 1]$^+$).

Synthesis of Compound **14**. To a fine suspension of compound **5a** (0.2 mmol) in 5 ml of dry THF and dry DMF, $NaBH_4$ (0.4 mmol) was added. After stirring for 24 h at r.t., the mixture was cooled, treated with H_2O (1 ml), and stirred for 1 h. The solvent was concentrated under reduced pressure, and H_2O (10 ml) was added. The aq. suspension was extracted with AcOEt (4 × 10 ml). The org. layers were collected, washed with brine (2 × 10 ml), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by CC to give compound **14**.

*3-(Hydroxymethyl)-1-[5-hydroxymethyl)furan-2-yl]-9*H*-pyrido[3,4-*b*]indole* (**14**). Yellow solid. Yield: 42.2 mg (76%). M.p. 221–223°. ^{1}H-NMR (500 MHz, (D_6)DMSO): 10.86 (*s*, 1 H); 8.12 (*d*, *J* = 7.6, 1 H); 8.03 (*s*, 1 H); 7.66 (*d*, *J* = 8.0, 1 H); 7.54 (*t*, *J* = 8.5, 2 H); 7.28 (*d*, *J* = 3.2, 1 H); 6.52 (*d*, *J* = 3.2, 1 H); 4.91 (*s*, 2 H); 4.74(*s*, 2 H). ^{13}C-NMR (125 MHz, (D_6)DMSO): 155.6; 154.1; 149.6; 142.3; 132.8; 132.0; 131.0; 129.1; 121.9; 121.5; 120.3; 112.5; 111.3; 110.5; 110.1; 65.4; 57.1. FAB-MS (neg.): 277 ([*M* – 1]$^-$).

Anti-*HIV Assays* in vitro. *Reagents, Cells, and Virus.* AZT (3′-azido-3′-deoxythymidine) and MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) were purchased from *Sigma*. SDS (sodium dodecyl sulfate) was from *Serva*, and DMF from *Shanghai Chemical Reagents Company* (P. R. China). Complete *RPMI-1640* medium was supplemented with 10% heat-inactivated fetal calf serum (*Gibco*), 2 mM L-glutamine, 10 mM HEPES, 50 μM 2-sulfanylethanol, 100,000 IU/ml penicilline, and 100 μg/ml streptomycin sulfate. The laboratory-derived virus HIV-1_{IIIB} and T lymphocyte cell line C8166 were donated by the *Medical Research Council* (*MRC*), *AIDS Research Project* (UK). Cells and virus were stored and resuscitated by common methods.

MTT-Based Cytotoxicity Assay of Flazin Analogues. Cellular toxicity of compounds was assessed by MTT method as described previously. Briefly, on a microtiter plate, 100 μl of 4×10^5 cells/ml were seeded. Then, 100 μl of various concentrations (400, 80, 16, 3.2, 0.64, and 0.128 μg/ml, resp.) of flazin analogues diluted in *RPMI-1640* were added and incubated at 37° in a humidified atmosphere of 5% CO_2 for 72 h. The supernatants were discarded and 20 μl of MTT reagent (5 mg/ml in PBS) was added to each well, then incubated at 37° for 4 h, 100 μl of 50% DMF/20% SDS was added. After the formazan was dissolved completely, the plates were read on *Bio-Tek ELx800 ELISA* reader at 595 nm/630 nm, and the cytotoxic concentration that caused the reduction of viable cells by 50% (CC_{50}) was calculated from dose-response curve.

Cytopathic-Effect Inhibition Assay of Flazin Analogues. In the presence or absence of various concentrations of flazin analogues, C8166 cells (4×10^5/ml) were infected with HIV-1_{IIIB} at a multiplicity of infection (M.O.I.) of 0.06. The final volume was 200 μl. The plates were incubated in humidified incubator at 37° and 5% CO_2. AZT was used for drug control. After 3 d of culture, the cytopathic effect was measured by counting the number of syncytia (multinucleated giant cell) in each well under an inverted microscope. Percentage inhibition of syncytia formation was calculated from the percentage of syncytial cell number in treated culture to that in infected control culture and, 50% effective concentration (EC_{50}) was calculated according to the *Reed & Muench* method. The concentrations of flazin analogues in the experimental part was 400, 80, 16, 3.2, 0.64, and 0.128 μg/ml.

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