SYNTHESIS AND ANTITUMOR ACTIVITY OF JAVACARBOLINE DERIVATIVES

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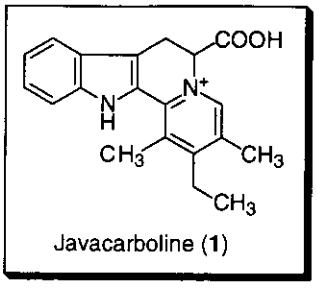
Abstracts- Syntheses of 12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromides (**15-27**) and 11*H*-pyrrolo[2,1-*a*]-β-carbolines (**32-35**), structurally related to the tetracyclic alkaloid javacarboline (**1**) have been achieved *via* 2 steps routes starting from the respective β-carbolines. Their synthetic compounds showed potent antitumor activities against P-388 murine leukemia cells and PC-6 human lung carcinoma cells.

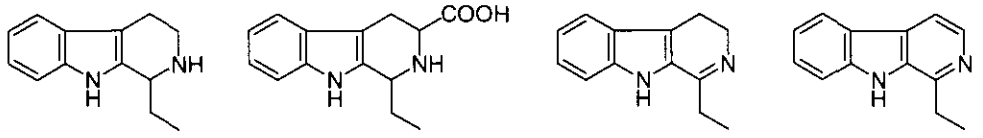
Javacarboline (**1**) is a tetracyclic β-carboline alkaloid isolated by us[1] from the Indonesian medicinal plant *Picrasma javanica* Bl. The structure was determined by spectroscopic techniques and X-Ray crystallographic analysis. The alkaloid has weak antitumor activity against P-388 murine leukemia cells and PC-6 human lung carcinoma cells *in vitro* with 50% cell growth inhibition (GI_{50}) values 32.5 and 35.9 μg/mL, respectively. In search for compounds with potent antitumor activity, we were interested in the design, synthesis and structure-activity relationships of 12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromides (**15-27**) and 11*H*-pyrrolo[2,1-*a*]-β-carbolines (**32-35**), structurally related to javacarboline (**1**). In this paper, we describe the synthesis and antitumor activity testing *in vitro* of novel javacarboline analogues.



Javacarboline (**1**)

We felt that in order to select javacarboline analogues with potent antitumor activity for synthesis, the first task will be to find out a lead structure as high an antitumor activity as possible. With this aim, the β-carbolines (**2-5**) were prepared by Pictet-Spengler reaction.[2] The results of antitumor activities testing (Table 1) showed that aromatization of the C-ring and the elimination of carboxy group were

essential for increasing the antitumor activity against the two systems. We then decided to prepared several 1-ethyl-β-carboline (**5**) analogues in order to optimize the activity further.



2 **3** **4** **5**

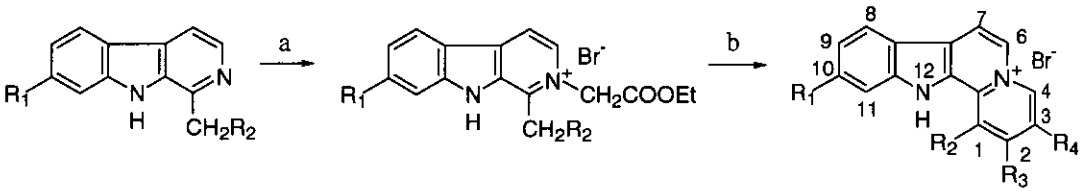
Figure 1

Table 1. Antitumor activities against P-388 and PC-6 cell lines (GI_{50}: μg/mL)

compound	P-388	PC-6
2	16.5	19.4
3	>50	>50
4	9.2	18.3
5	6.1	6.2

Synthesis of 12*H*-Pyrido[2,1-*a*]-β-carbolin-5-ium Bromides

12*H*-Pyrido[2,1-*a*]-β-carbolin-5-iums were synthesized by the routes shown in Scheme 1. The treatment of β-carbolines (**5-9**) with bromoacetate in refluxing acetone gave the key compounds, 2-ethoxycarbonylmethyl-β-carbolin-2-ium bromides (**10-14**). Westphal reaction[2] with the dione reagents thereafter led to the corresponding 12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromides (**15-27**). However, treatment of compound (**11**) with 2,3-pentanedione and 2,3-hexanedione yields a mixture of C-2 and C-3 positional isomers (**17** and **18**, **19** and **20** respectively) in the ratio 2:1 or 3:1 as determined by HPLC analysis. The mixtures were separated by preparative HPLC to yield pure compounds (**17-20**). The structures of compounds (**15-27**) were established using spectroscopic methodology (^{1}H-NMR, difference NOE, 2D-COSY and HMBC experiments). Especially significant in ^{1}H-NMR spectra of **15-27** was the chemical shift of H-4 near *ca.* 9 ppm due to deshielding by adjacent to N_b atom. We also carried out an X-Ray crystallographic analysis of **24** to confirm the formation of the javacarboline skeleton (Figure 2).



	R_1	R_2		R_1	R_2		R_1	R_2	R_3	R_4
5	H	Me	**10**	H	Me	**15**	H	Me	Me	Me
6	H	H	**11**	H	H	**16**	H	Me	Et	Et
7	H	Et	**12**	H	Et	**17**	H	Me	Me	Et
8	H	OMe	**13**	H	OMe	**18**	H	Me	Et	Me
9	OMe	H	**14**	OMe	H	**19**	H	Me	Me	*n*-Pr
						20	H	Me	*n*-Pr	Me
						21	H	H	Me	Me
						22	H	H	Et	Et
						23	H	Et	Me	Me
						24	H	OMe	Me	Me
						25	H	OMe	Et	Et
						26	OMe	H	Me	Me
						27	OMe	H	Et	Et

Reagent and conditions: (a) $BrCH_2COOCH_2CH_3$ in dry acetone, reflux, (b) R_2COCOR_3 in dry acetone, reflux

Scheme 1

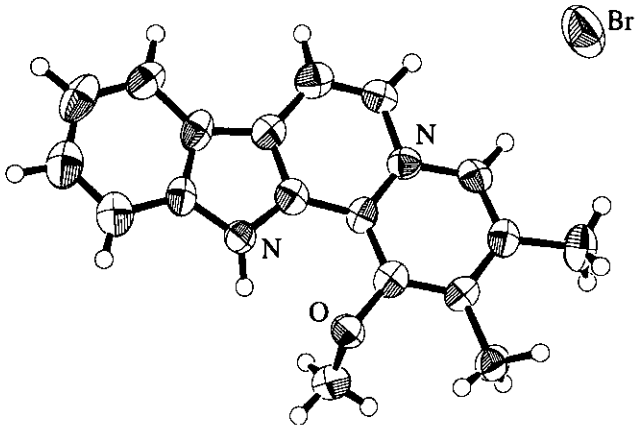
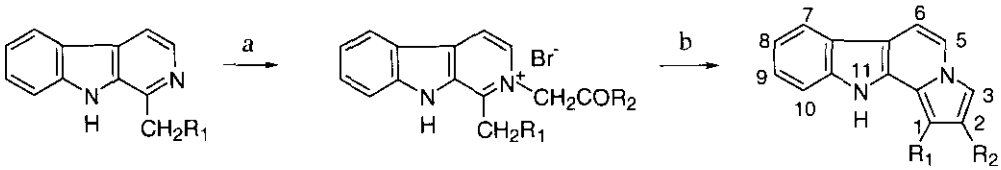


Figure 2. An ORTEP drawing of **24**

Synthesis of 11*H*-Pyrrolo[2,1-*a*]-β-carbolines

11*H*-Pyrrolo[2,1-*a*]-β-carbolines were synthesized by the routes shown in Scheme 2. Thus, treatment of β-carbolines (**5** and **6**) with bromoacetone or bromoacetophenone in acetone under reflux condition furnish the 2-acetonyl- and 2-phenacyl-β-carbolin-2-ium bromides (**28-31**). Cyclization by refluxing with aq. sodium carbonate solution led to the formation of corresponding 11*H*-pyrrolo[2,1-*a*]-β-carbolines (**32-35**).



	R_1
5	Me
6	H

	R_1	R_2
28	H	Me
29	H	Ph
30	Me	Me
31	Me	Ph

	R_1	R_2
32	H	Me
33	H	Ph
34	Me	Me
35	Me	Ph

Reagent and conditions: (a) $BrCH_2COC_6H_5$, $BrCH_2COCH_3$ in dry acetone, reflux, (b) aq.Na_2CO_3, reflux

Scheme 2

Biological Results

A study of biological properties of thirteen 12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromides (**15-27**) and four 11*H*-pyrrolo[2,1-*a*]-β-carbolines (**32-35**) were carried out in P-388 murine leukemia cells and PC-6 human lung carcinoma cells *in vitro*. The most cytotoxic compound was **15** which was about 160-180 fold more potent against PC-6 cells than javacarboline (**1**) and about as active as cisplatin. However, in the test against P-388 cells, compound (**15**) is about 10 fold less potent than cisplatin. Further synthetic work aimed at structural modification is in progress to find out compounds with more potent antitumor activity than cisplatin.

Table 3. Antitumor activities against P-388 and PC-6 cell lines (GI_{50}: μg/mL)

compound	P-388	PC-6	compound	P-388	PC-6
1	32.5	35.9	**24**	0.3	0.6
15	0.2	0.2	**25**	0.8	4.2
16	0.7	1.1	**26**	1.6	1.9
17	0.9	1.6	**27**	1.3	1.2
18	1.0	1.1	**32**	0.3	0.5
19	0.5	0.7	**33**	>50	22.9
20	0.9	1.1	**34**	0.3	0.3
21	1.5	1.4	**35**	>50	18.9
22	2.0	1.2	cisplatin	0.02	0.3
23	0.5	0.8			

EXPERIMENTAL

General Procedures

All melting points were measured on a Yanagimoto micromelting point hot-stage type apparatus without uncorrected. IR spectra as KBr pellets were recorded with a JASCO 300E FT-IR spectrophotometer, respectively. The ^{1}H-NMR, difference NOE, 2D COSY, and HMBC spectra were recorded with a JEOL EX-400 (^{1}H: 400 MHz) spectrometer. Chemical shifts are given on the δ scale (ppm) with tetramethylsilane as an internal standard, and coupling constants are given in Hz. EIMS and FABMS spectra were conducted using JEOL D-300 and DX-303 mass spectrometers, respectively. HRMS were measured on a JEOL DX-303 mass spectrometers. Column chromatography was performed on silica gel (Merck). Analytical and preparative HPLC were performed using a silica gel column (Senshu Pak, silica-3251-N, 8φ x 250 mm).

General Procedure of Preparation for β-Carbolines

Compounds (**2-8**) were prepared from tryptamine or *L*-tryptophan by the Pictet-Spengler reaction with the appropriate aldehyde in an acidic medium, according to the literature procedure.[3] 7-Methoxy-1-methyl-β-carboline (**9**) was purchased from Sigma.

1-Ethyl-1,2,3,4-tetrahydro-β-carboline (2)[4]

Yield 87.6%, powder, mp 225-228°C. $[\alpha]_D$ 0° (*c*=1.38, MeOH). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.08 (3H, t, *J*=7.6 Hz, $CH_2C\underline{H}_3$), 1.93, 2.20 (each 1H, m, $C\underline{H}_2CH_3$), 2.96 (2H, m, H-4), 3.35, 3.58 (each 1H, m, H-3), 4.58 (1H, br s, H-1), 7.02 (1H, t, *J*=7.9 Hz, H-6), 7.11 (1H, t, *J*=7.9 Hz, H-7), 7.36 (1H, d, *J*=7.9 Hz, H-8), 7.45 (1H, d, *J*=7.9 Hz, H-5), 9.12 (1H, br s, NH). MS *m/z* : 200 (M^+). HRMS *m/z*: Calcd for $C_{13}H_{16}N_2$, 200.1310. Found, 200.1326 (M^+).

1-Ethyl-1,2,3,4-tetrahydro-β-carboline 3-carboxylic acid (3)

Yield 56.9%, powder, mp 271-273°C. $[\alpha]_D$ -146.4° (*c*=1.04, pyridine). ^{1}H-NMR (DMSO-d_6, 323K) δ: 0.99 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$), 1.81, 2.12 (each 1H, m, $C\underline{H}_2CH_3$), 2.71 (1H, ddd, *J*=2.4, 11.6, 15.6 Hz, H-4β), 3.04 (1H, ddd, *J*=1.2, 4.3, 15.6 Hz, H-4α), 3.55 (1H, dd, *J*=4.3, 11.6 Hz, H-3α), 4.23 (1H, br s, H-1), 6.97 (1H, t, *J*=7.9 Hz, H-6), 7.05 (1H, t, *J*=7.9 Hz, H-7), 7.30 (1H, d, *J*=7.9 Hz, H-8), 7.40 (1H, d, *J*=7.9 Hz, H-5), 10.71 (1H, br s, NH). MS *m/z*: 244 (M^+). HRMS *m/z*: Calcd for $C_{14}H_{16}N_2O_2$, 244.1208. Found, 244.1217 (M^+).

1-Ethyl-3,4-dihydro-β-carboline (4)

Yield 97.9%, powder, mp 225-228°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.15 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$), 2.67 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$), 2.74 (2H, t, *J*=8.1 Hz, H-4), 3.72 (2H, *J*=8.1 Hz, H-3), 7.04 (1H, t, *J*=8.1 Hz, H-6), 7.19 (1H, t, *J*=8.1 Hz, H-7), 7.40 (1H, d, *J*=8.1 Hz, H-8), 7.54 (1H, d, *J*=8.1 Hz, H-5), 11.26 (1H, br s, NH). MS *m/z* : 198 (M^+). HRMS *m/z*: Calcd for $C_{13}H_{14}N_2$, 198.1154 Found, 198.1170 (M^+).

1-Ethyl-β-carboline (5)[4]
Yield 89.6%, colorless needles, mp 195-197°C (acetone). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.42 (3H, t, *J*=7.7 Hz, $CH_2C\underline{H}_3$), 3.19 (2H, q, *J*=7.7 Hz, $C\underline{H}_2CH_3$), 7.24 (1H, t, *J*=8.1 Hz, H-6), 7.55 (1H, t, *J*=8.1 Hz, H-7), 7.65 (1H, d, *J*=8.1 Hz, H-8), 7.91 (1H, d, *J*=5.5 Hz, H-4), 8.18 (1H, d, *J*=8.1 Hz, H-5), 8.29 (1H, d, *J*=5.5 Hz, H-3), 11.53 (1H, br s, NH). MS *m/z*: 198 (M^+). HRMS *m/z*: Calcd for $C_{13}H_{12}N_2$, 198.0998. Found, 198.1001 (M^+).

1-Methyl-β-carboline (6)[4]
Yield 88.7%, colorless needles, mp 202°C (acetone). ^{1}H-NMR (DMSO-d_6, 323K) δ: 2.76 (3H, s, CH_3), 7.23 (1H, t, *J*=8.2 Hz, H-6), 7.53 (1H, t, *J*=8.2 Hz, H-7), 7.60 (1H, d, *J*=8.2 Hz, H-8), 7.92 (1H, d, *J*=5.3 Hz, H-4), 8.19 (1H, d, *J*=8.2 Hz, H-5), 8.20 (1H, d, *J*=5.3 Hz, H-3), 11.53 (1H, br s, NH). MS *m/z*: 182 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2$: C 79.10, H 5.53, N 15.37, Found: C 79.30, H 5.89, N 15.66.

1-Propyl-β-carboline (7)[4]
Yield 87.6%, colorless needles, mp 218-220°C (acetone). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.00 (3H, t, *J*=7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.86 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.08 (2H, m, $C\underline{H}_2CH_2CH_3$), 7.22 (1H, t, *J*=8.1 Hz, H-6), 7.52 (1H, t, *J*=8.1 Hz, H-7), 7.59 (1H, d, *J*=8.1 Hz, H-8), 7.89 (1H, d, *J*=5.1 Hz, H-4), 8.17 (1H, d, *J*=8.1 Hz, H-5), 8.25 (1H, d, *J*=5.1 Hz, H-3), 11.43 (1H, br s, NH). MS *m/z* : 210 (M^+). *Anal.* Calcd for $C_{14}H_{14}N_2$: C 79.97, H 6.71, N 13.32, Found: C 79.90, H 6.84, N 13.11.

1-Methoxymethyl-β-carboline (8)[5]
Yield 65.3%, colorless needles, mp 123-125°C (acetone). ^{1}H-NMR ($CDCl_3$) δ: 3.49 (3H, s, $CH_2OC\underline{H}_3$), 5.04 (2H, s, $C\underline{H}_2OCH_3$), 7.23 (1H, t, *J*=7.2 Hz, H-6), 7.45 (1H, t, *J*=7.2 Hz, H-7), 7.64 (1H, d, *J*=7.2 Hz, H-8), 8.05 (1H, d, *J*=6.6 Hz, H-4), 8.08 (1H, d, *J*=6.6 Hz, H-3), 8.12 (1H, d, *J*=7.2 Hz, H-5), 11.33 (1H, br s, NH). MS *m/z*: 212 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O$: C 73.56, H 5.70, N 13.20, Found: C 73.79, H 5.56, N 13.19.

General Procedure for the Preparation of 2-Ethoxycarbonylmethyl-β-carbolin-2-ium Bromides. A mixture of ethyl bromoacetate (5 mL, 28.4 mmol) and β-carboline derivative (10.0 mmol) in anhydrous acetone (100 mL) was refluxed for 6 h. After being cooled, the precipitate was filterated, washed with anhydrous acetone, and then recrystallized from acetone-methanol (1:3) to yield 2-ethoxycarbonylmethyl-β-carbolin-2-ium bromide.

1-Ethyl-2-ethoxycarbonylmethyl-β-carbolin-2-ium bromide (10)
Yield 98.4%, yellow needles, mp 198-202°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.27 (3H, t, *J*=7.0 Hz, $COOCH_2C\underline{H}_3$), 1.35 (3H, t, *J*=7.7 Hz, $CH_2C\underline{H}_3$-1), 3.49 (2H, t, *J*=7.7 Hz, $C\underline{H}_2CH_3$-1), 4.27 (2H, q, *J*=7.0 Hz, $COOC\underline{H}_2CH_3$), 5.81 (2H, s, CH_2-N), 7.47 (1H, t, *J*=8.1 Hz, H-6), 7.83 (1H, m, H-7, 8), 8.47 (1H, d, *J*=8.1 Hz, H-5), 8.62 (1H, d, *J*=6.6 Hz, H-4), 8.71 (1H, d, *J*=6.6 Hz, H-3). IR ν max KBr cm^{-1}: 3570, 3330, 3080, 1730, 1630. MS *m/z*: 283 (M^+). HRMS *m/z*: Calcd for $C_{17}H_{19}N_2O_2$, 283.1442. Found, 283.1427 (M^+).

1-Methyl-2-ethoxycarbonylmethyl-β-carbolin-2-ium bromide (11)

Yield 97.2%, yellow needles, mp 243-245°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.27 (3H, t, *J*=7.0 Hz, $CH_2C\underline{H}_3$), 3.06 (3H, s, CH_3-1), 4.28 (2H, q, *J*=7.0 Hz, $C\underline{H}_2CH_3$), 5.79 (2H, s, CH_2COO), 7.45 (1H, m, H-6), 7.81 (2H, m, H-7, 8), 8.46 (1H, d, *J*=8.1 Hz, H-5), 8.60 (1H, d, *J*=6.6 Hz, H-4), 8.68 (1H, d, *J*=6.6 Hz, H-3), 12.80 (1H, br s, NH). IR ν max KBr cm^{-1}: 3030, 3000, 1740, 1640. MS *m/z*: 269 (M^+). *Anal.* Calcd for $C_{16}H_{17}N_2O_2Br$: C 55.03, H 4.91, N 8.02, Found: C 54.92, H 5.05, N 8.28.

1-Propyl-2-ethoxycarbonylmethyl-β-carbolin-2-ium bromide (12)

Yield 92.4%, yellow needles, mp 225-227°C. ^{1}H-NMR (DMSO-d_6, 323K): 1.07 (3H, t, *J*=7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.27 (3H, t, *J*=7.0 Hz, $COOCH_2C\underline{H}_3$), 1.75 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.44 (2H, m, $C\underline{H}_2CH_2CH_3$), 4.27 (2H, q, *J*=7.3 Hz, $COOC\underline{H}_2CH_3$), 5.78 (2H, s, CH_2-N), 7.46 (1H, m, H-6), 7.82 (1H, m, H-7, 8), 8.46 (1H, d, *J*=8.1 Hz, H-5), 8.58 (1H, d, *J*=6.6 Hz, H-4), 8.69 (1H, d, *J*=6.6 Hz, H-3). IR ν max KBr cm^{-1}: 3588, 3325, 3080, 3037, 1730, 1632. MS *m/z*: 297 (M^+). HRMS *m/z*: Calcd for $C_{18}H_{21}N_2O_2$, 297.1598. Found, 297.1565 (M^+).

1-Methoxymethyl-2-ethoxycarbonylmethyl-β-carbolin-2-ium bromide (13)

Yield 94.7%, yellow needles, mp 215-222°C. ^{1}H-NMR (DMSO-d_6, 323K): 1.24 (3H, t, *J*=7.0 Hz, $COOCH_2C\underline{H}_3$), 3.36 (3H, s, $CH_2OC\underline{H}_3$), 4.23 (2H, q, *J*=7.0 Hz, $COOC\underline{H}_2CH_3$), 5.30 (2H, s, $C\underline{H}_2OCH_3$), 5.75 (2H, s, CH_2-N), 7.51 (1H, t, *J*=8.1 Hz, H-6), 7.87 (1H, m, H-7, 8), 8.52 (1H, d, *J*=8.1 Hz, H-5), 8.73 (1H, d, *J*=6.2 Hz, H-4), 8.87 (1H, d, *J*=6.2 Hz, H-3), 12.90 (1H, s, NH). IR ν max KBr cm^{-1}: 3060, 3000, 1750, 1630. MS *m/z*: 299 (M^+). *Anal.* Calcd for $C_{17}H_{19}N_2O_3Br$: C 53.84, H 5.05, N 7.39, Found: C 53.32, H 5.20, N 7.12.

1-Methyl-7-methoxy-2-ethoxycarbonylmethyl-β-carbolin-2-ium bromide (14)

Yield 97.3%, yellow needles, mp 230-232°C. ^{1}H-NMR (DMSO-d_6, 323K): 1.27 (3H, t, *J*=7.0 Hz, $COOCH_2C\underline{H}_3$), 2.99 (3H, s, CH_3), 3.96 (3H, s, OCH_3-7), 4.27 (2H, q, *J*=7.0 Hz, $COOC\underline{H}_2CH_3$), 5.74 (2H, s, CH_2-N), 7.09 (1H, dd, *J*=2.6, 8.8 Hz, H-6), 7.15 (1H, d, *J*=2.2 Hz, H-8), 8.34 (1H, d, *J*=8.8 Hz, H-5), 8.52 (1H, d, *J*=6.6 Hz, H-4), 8.54 (1H, d, *J*=6.6 Hz, H-3), 12.80 (1H, br s, NH). IR ν max KBr cm^{-1}: 3000, 1730, 1620. MS *m/z*: 299 (M^+). *Anal.* Calcd for $C_{17}H_{19}N_2O_3Br$: C 53.84, H 5.05, N 7.39, Found: C 53.32, H 5.20, N 7.12.

General Procedure for the Synthesis of 12*H*-Pyrido[2,1-*a*]-β-carbolin-5-ium Bromides

A mixture of 2-ethoxycarbonylmethyl-β-carbolin-2-ium bromide (2.0 g, 5.5 mmol), the dione reagent (34.2 mmol) and anhydrous sodium acetate (1.0 g, 12.2 mmol) in anhydrous acetone (120 mL) was refluxed for 6 h. After being cooled, the precipitate was filterated, washed with anhydrous acetone, and then recrystallized from acetone-methanol (1:3) to yield 12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide. The same procedure was followed for **15**-**27**. The precipitate of **17**-**20** was subjected to preparative HPLC (Senshu Pak, Silica-3251-N, 8 ϕ x 250 mm, detector UV 254 nm, solvent system *n*-hexane-dichloroethane-ethanol-trifluoroacetic acid (1800 : 600 : 600 : 3.6), flow rate 2.5 mL/min) was used .

1,2,3-Trimethyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (15)

Yield 66.5%, yellow needles, mp >300°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 2.37 (3H, s, CH_3-3), 2.40 (3H, s, CH_3-2), 3.50 (3H, s, CH_3-1), 7.09 (1H, t, *J*=8.1 Hz, H-9), 7.37 (1H, t, *J*=8.1 Hz, H-10), 7.78 (1H, d, *J*=8.1 Hz, H-11), 8.18 (1H, d, *J*=8.1 Hz, H-8), 8.30 (1H, d, *J*=6.6 Hz, H-7), 8.35 (1H, d, *J*=6.6 Hz, H-6), 8.82 (1H, s, H-4). IR ν max KBr cm^{-1}: 3400, 3040, 2960, 2320, 1630. MS *m/z*: 261 (M^+). *Anal.* Calcd for $C_{18}H_{17}N_2Br$: C 63.35, H 5.02, N 8.21, Found: C 63.52, H 5.15, N 8.33.

1-Methyl-2,3-diethyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (16)

Yield 36.5%, yellow needles, mp >300°C (methanol). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.24 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-2), 1.36 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-3), 2.86 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-2), 2.96 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-2), 3.59 (3H, s, CH_3-1), 7.08 (1H,. t, *J*=8.1 Hz, H-9), 7.35 (1H, t, *J*=8.1 Hz, H-10), 7.78 (1H, d, *J*=8.1 Hz, H-11), 8.19 (1H, d, *J*=8.1 Hz, H-8), 8.40 (1H, d, *J*=6.6 Hz, H-7), 8.44 (1H, d, *J*=6.6 Hz, H-6), 8.87 (1H, s, H-4). IR ν max KBr cm^{-1}: 2950, 2340, 1630. MS *m/z*: 289 (M^+). *Anal.* Calcd for $C_{20}H_{21}N_2Br$: C 65.05, H 5.73, N 7.59, Found: C 65.06, H 5.69, N 7.55.

1,2-Dimethyl-3-ethyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (17)

Yield 33.9%, yellow needles, mp >300°C (methanol). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.37 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-3), 2.64 (3H, s, CH_3-2), 2.95 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-3), 3.15 (3H, s, CH_3-1), 7.47 (1H, t, *J*=8.1 Hz, H-9), 7.70 (1H, t, *J*=8.1 Hz, H-10), 8.00 (1H, d, *J*=8.1 Hz, H-11), 8.40 (1H, d, *J*=8.1 Hz, H-8), 8.70 (1H, d, *J*=7.0 Hz, H-7), 8.98 (1H, d, *J*=7.0 Hz, H-6), 9.16 (1H, s, H-4), 12.17 (1H, br s, NH). Difference NOE spectra: irradiated Hδ→observed Hδ (enhancement NOE %): δ 9.16 (H-4)→ δ 1.37 (CH_2CH_3-3, 12 %), δ 8.98 (H-6, 17 %). IR ν max KBr cm^{-1}: 3421, 3167, 1639. MS *m/z*: 275 (M^+). *Anal.* Calcd for $C_{19}H_{19}N_2Br$: C 64.23, H 5.39, N 7.89, Found: C 64.23, H 5.35, N 7.71.

1,3-Dimethyl-2-ethyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (18)

Yield 15.8%, yellow needles, mp >300°C (methanol). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.28 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-2), 2.59 (3H, s, CH_3-3), 3.07 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-2), 3.22 (3H, s, CH_3-1), 7.47 (1H, t, *J*=8.1 Hz, H-9), 7.71 (1H, t, *J*=8.1 Hz, H-10), 8.03(1H, d, *J*=8.1 Hz, H-11), 8.41(1H, d, *J*=8.1 Hz, H-8), 8.70 (1H, d, *J*=7.0 Hz, H-7), 8.90 (1H, d, *J*=7.0 Hz, H-6), 9.21 (1H, s, H-4), 12.21 (1H, br s, NH). Difference NOE spectra: irradiated Hδ→observed Hδ (enhancement NOE %): δ 9.21 (H-4)→ δ 2.59 (CH_3-3, 15 %), δ 8.90 (H-6, 16 %). IR ν max KBr cm^{-1}: 3419, 3194, 1645. MS *m/z*: 275 (M^+). *Anal.* Calcd for $C_{19}H_{19}N_2Br$: C 64.23, H 5.39, N 7.89, Found: C 64.28, H 6.10, N 7.11.

1,2-Dimethyl-3-propyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (19)

Yield 38.8%, yellow needles, mp >300°C (methanol). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.07 (3H, t, *J*=7.3 Hz, $CH_2CH_2C\underline{H}_3$-3), 1.76 (2H, sextet, *J*=7.3 Hz, $CH_2C\underline{H}_2CH_3$-3), 2.65 (3H, s, CH_3-2), 2.91 (2H, t, *J*=7.3 Hz, $C\underline{H}_2CH_2CH_3$-3), 3.18 (3H, s, CH_3-2), 7.47 (1H, t, *J*=8.1 Hz, H-9), 7.71 (1H, t, *J*=8.1 Hz, H-10), 7.99 (1H, d, *J*=8.1 Hz, H-11), 8.41 (1H, d, *J*=8.1 Hz, H-8), 8.71 (1H, d, *J*=7.0 Hz, H-7), 8.94 (1H, d, *J*=7.0 Hz, H-6), 9.16 (1H, s, H-4), 12.15 (1H, br s, NH). IR ν max KBr cm^{-1}: 3419,1645. MS *m/z*: 289 (M^+). *Anal.* Calcd for $C_{20}H_{21}N_2Br$: C 65.05, H 5.73, N 7.59,Found: C 65.40, H 6.02, N 7.44.

1,3-Dimethyl-2-propyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (20)

Yield 12%, yellow needles, mp >300°C (methanol). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.11 (3H, t, *J*=7.3 Hz, $CH_2CH_2C\underline{H}_3$-2), 1.66 (2H, sextet, *J*=7.3 Hz, $CH_2C\underline{H}_2CH_3$-3), 2.57 (3H, s, CH_3-3), 3.02 (2H, t, *J*=7.3 Hz, $C\underline{H}_2CH_2CH_3$-2), 3.22 (3H, s, CH_3-1), 7.45 (1H, t, *J*=8.1 Hz, H-9), 7.69 (1H, t, *J*=8.1 Hz, H-10), 7.99 (1H, d, *J*=8.1 Hz, H-11), 8.41 (1H, d, *J*=8.1 Hz, H-8), 8.70 (1H, d, *J*=7.0 Hz, H-7), 8.85 (1H, d, *J*=7.0 Hz, H-6), 9.18 (1H, s, H-4), 12.13 (1H, br s, NH). Difference NOE spectra: irradiated Hδ→observed Hδ (enhancement NOE %): δ 9.18 (H-4)→δ 2.57 (CH_3-3, 15 %), δ 8.85 (H-6, 15 %). *Anal.* Calcd for $C_{20}H_{21}N_2Br$: C 65.05, H 5.73, N 7.59, Found: C 65.32, H 5.95, N 7.68.

2,3-Dimethyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (21)

Yield 53.6%, yellow needles, mp 300°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 2.53 (3H, s, CH_3-3), 2.67 (3H, s, CH_3-2), 7.45 (1H, t, *J*=8.1 Hz, H-9), 7.72 (1H, t, *J*=8.1 Hz, H-10), 7.86 (1H, d, *J*=8.1 Hz, H-11), 8.42 (1H, d, *J*=8.1 Hz, H-8), 8.71 (1H, d, *J*=7.0 Hz, H-7), 8.76 (1H, s, H-1), 8.88 (1H, d, *J*=7.0 Hz, H-6), 9.23 (1H, s, H-4). IR ν max KBr cm^{-1}: 2950, 2300, 1630. MS *m/z* : 247 (M^+). HRMS *m/z*: Calcd for $C_{17}H_{15}N_2$, 247.1232. Found, 247.1225 (M^+).

2,3-Diethyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (22)[6]

Yield 74.6%, yellow needles, mp >300°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.38 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-2), 1.47 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-3), 2.93 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-3), 3.02 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-2), 7.43 (1H, t, *J*=8.1 Hz, H-9), 7.67 (1H, t, *J*=8.1 Hz, H-10), 7.85 (1H, d, *J*=8.1 Hz, H-11), 8.38 (1H, d, *J*=8.1 Hz, H-8), 8.68 (1H, d, *J*=7.0 Hz, H-6), 8.80 (1H, s, H-1), 8.91 (1H, d, *J*=7.0 Hz, H-7), 9.19 (1H, s, H-4). IR ν max KBr cm^{-1}: 2900, 2340, 1670, 1630. MS *m/z* : 275 (M^+). *Anal.* Calcd for $C_{19}H_{19}N_2Br$: C 64.23, H 5.39, N 7.89, Found: C 64.23, H 5.49, N 7.68.

1-Ethyl-2,3-dimethyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (23)

Yield 36.8%, yellow needles, mp >300°C (methanol). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.39 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-1), 2.54 (3H, s, CH_3-3), 2.64 (3H, s, CH_3-2), 3.60 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-1), 7.56 (1H, t, *J*=8.1 Hz, H-9), 7.70 (1H, t, *J*=8.1 Hz, H-10), 8.05 (1H, d, *J*=8.1 Hz, H-11), 8.39 (1H, d, *J*=8.1 Hz, H-8), 8.71 (1H, d, *J*=7.0 Hz, H-7), 8.92 (1H, d, *J*=7.0 Hz, H-6), 9.24 (1H, s, H-4), 11.96 (1H, br s, NH). IR ν max KBr cm^{-1}: 3416, 3208, 1624. MS *m/z*: 275 (M^+). *Anal.* Calcd for $C_{19}H_{19}N_2Br$: C 64.23, H 5.39, N 7.89, Found: C 64.22, H 5.43, N 7.90.

1-Methoxy-2,3-dimethyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (24)

Yield 85.6%, yellow needles, mp >300°C (methanol). ^{1}H-NMR (DMSO-d_6, 323K) δ: 2.49 (3H, s, CH_3-3), 2.50 (3H, s, CH_3-2), 4.11 (3H, s, OCH_3-1), 7.46 (1H, t, *J*=8.1 Hz, H-9), 7.71 (1H, t, *J*=8.1 Hz, H-10), 8.00 (1H, d, *J*=8.1 Hz, H-11), 8.41 (1H, d, *J*=8.1 Hz, H-8), 8.75 (1H, d, *J*=7.0 Hz, H-7), 8.93 (1H, d, *J*=7.0 Hz, H-6), 9.18 (1H, s, H-4). IR ν max KBr cm^{-1}: 3400, 3000, 1630. MS *m/z*: 277 (M^+). *Anal.* Calcd for $C_{18}H_{17}N_2OBr$: C 60.52, H 4.80, N 7.84, Found: C 60.48, H 4.79, N 7.88.

1-Methoxy-2,3-diethyl-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (25)

Yield 66.9%, yellow needles, mp 238-240°C (methanol). ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.29 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-2), 1.38 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-3), 2.89 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-3), 2.97 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-2), 4.15 (3H, s, OCH_3-1), 7.19 (1H, t, *J*=8.1 Hz, H-9), 7.46 (1H, t, *J*=8.1Hz, H-10), 7.84 (1H, d, *J*=8.1 Hz, H-11), 8.26 (1H, d, *J*=8.1 Hz, H-8), 8.53 (1H, d, *J*=6.6 Hz, H-7), 8.63 (1H, d, *J*=6.6 Hz, H-6), 8.91 (1H, s, H-4). IR ν max KBr cm^{-1}: 2950, 1640. MS *m/z*: 290 ([M-CH_3]$^+$). FAB-MS *m/z*: 305 (M^+). *Anal.* Calcd for $C_{20}H_{21}N_2OBr$: C 62.35, H 5.49, N 7.27, Found: C 62.19, H 5.54, N 7.20.

2,3-Dimethyl-10-methoxy-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (26)

Yield 31.6%, yellow needles, mp >300°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 2.50 (3H, s, H-1-CH_3-2), 2.64 (3H, s, CH_3-2), 3.96 (3H, s, OCH_3-10), 7.07 (1H, dd, *J*=2.2, 8.8 Hz, H-9), 7.23 (1H, d, *J*=2.2 Hz, H-11), 8.26 (1H, d, *J*=8.8 Hz, H-8), 8.56 (1H, d, *J*=7.0 Hz, H-7), 8.67 (1H, s, H-1), 8.80 (1H, d, *J*=7.0 Hz, H-6), 9.15 (1H, s, H-4). IR ν max KBr cm^{-1}: 3449, 3367, 3066, 1625. MS *m/z*: 277 (M^+). *Anal.* Calcd for $C_{18}H_{17}N_2OBr$: C 60.52, H 4.80, N 7.84, Found: C 60.34, H 5.06, N 7.68.

2,3-Diethyl-10-methoxy-12*H*-pyrido[2,1-*a*]-β-carbolin-5-ium bromide (27)

Yield 75.1%, yellow needles, mp >300°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.37 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-2), 1.45 (3H, t, *J*=7.33 Hz, $CH_2C\underline{H}_3$-3), 2.90 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-3), 3.00 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-2), 3.94 (3H,s, OCH_3-10), 7.03 (1H, dd, *J*=2.2, 8.8 Hz, H-9), 7.23 (1H, d, *J*=2.2 Hz, H-11), 8.24 (1H, d, *J*=8.8 Hz, H-8), 8.56 (1H, d, *J*=7.0 Hz, H-7), 8.69 (1H, s, H-1), 8.83 (1H, d, *J*=7.0 Hz, H-6), 9.09 (1H,s, H-4). IR ν max KBr cm^{-1}: 2950, 2340, 1630. MS *m/z*: 305 (M^+). HRMS *m/z*: Calcd for $C_{20}H_{21}N_2O$, 305.1649. Found, 305.1630 (M^+).

Preparation of 2-Acetonyl-β-carbolin-2-ium Bromides (28 and 30)

A mixture of bromoacetone (3.5 mL, 20.5 mmol) and β-carboline derivative (15.3 mmol) in anhydrous acetone (50 mL) was refluxed for 30 min. After being cooled, the precipitate was filterated, washed with anhydrous acetone, and then recrystallized from methanol to afford 2-acetonyl-β-carbolin-2-ium bromide.

1-Methyl-2-acetonyl-β-carbolin-2-ium bromide (28)

Yield 95.4%, yellow needles, mp 268-270°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 2.42 (3H, s, CH_3-1), 2.98 (3H, s, $CH_2COC\underline{H}_3$-2), 5.97 (2H, s, $C\underline{H}_2COCH_3$-2), 7.46 (1H, m , H-6), 7.80-7.82 (2H, m, H-7, 8), 8.45 (1H, d, *J*=8.1 Hz, H-5), 8.50 (1H, d, *J*=6.6 Hz, H-4), 8.67 (1H, d, *J*=6.6 Hz, H-3), 12.94 (1H, br s, NH). IR ν max KBr cm^{-1}: 3444, 3064, 3010, 1735, 1639. FAB-MS *m/z*: 239 (M^+). *Anal.* Calcd for $C_{15}H_{15}N_2OBr$: C 56.44, H 4.74, N 8.78, Found: C 56.87, H 4.98, N 8.85.

1-Ethyl-2-acetonyl-β-carbolin-2-ium-β-carbolinium bromide (30)

Yield 94.7%, yellow needles, mp 277°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.30 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$-1), 2.42 (3H, s, CH_2COCH_3-2), 3.36 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$-1), 5.94 (2H, s,

C<u>H</u>$_2$COCH$_3$-2), 7.45-7.49 (1H, m, H-6), 7.82 (2H, d like, H-7, 8), 8.42 (1H, d, *J*=6.6 Hz, H-4), 8.47 (1H, d, *J*=8.1 Hz, H-5), 8.67 (1H, d, *J*=6.6 Hz, H-3), 12.90 (1H, br s, NH). IR ν max KBr cm^{-1}: 3444, 3079, 1731, 1633. FAB-MS *m/z*: 253 (M^+). *Anal.* Calcd for $C_{16}H_{17}N_2OBr$: C 57.67, H 5.14, N 8.41, Found: C 57.95, H 5.43, N 8.76.

Preparation of 2-Phenacyl-β-carbolin-2-ium Bromides (29 and 31)

A mixture of phenylbromoacetone (4.0 g, 20.1 mmol) and β-carboline (3.0 g, 15.3 mmol) in anhydrous acetone (50 mL) was refluxed for 30 min. After being cooled, the precipitate was filterated, washed with anhydrous acetone, and then recrystallized from methanol to afford 2-phenacyl-β-carbolin-2-ium bromide.

1-Methyl-2-phenacyl-β-carbolin-2-ium Bromide (29)

Yield 78.26%, yellow needles, mp 189-190°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 3.01 (3H, s, CH$_3$-1), 6.64 (2H, s, C<u>H</u>$_2$COC$_6$H$_5$-2), 7.44-7.53 (1H, m, H-6), 7.68 (2H, t, *J*=7.7 Hz, H-3', 5'), 7.78-7.87 (3H, m, H-7, 8, 4'), 8.15 (2H, d, *J*=7.1 Hz, H-2', 6'), 8.48 (1H, d, *J*=8.1 Hz, H-5), 8.59 (1H, d, *J*=6.6 Hz, H-4), 8.71 (1H, d, *J*=6.6 Hz, H-3), 12.91 (1H, br s, NH). IR ν max KBr cm^{-1}: 3423, 3075, 1695, 1635. FAB-MS *m/z*: 301 (M^+). *Anal.* Calcd for $C_{20}H_{17}N_2OBr$: C 63.00, H 4.49, N 7.35, Found: C 63.32, H 4.98, N 7.78.

1-Ethyl-2-phenacyl-β-carbolin-2-ium Bromide (31)

Yield 86.1%, yellow needles, mp 164-166°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 1.31(3H, t, *J*=7.7 Hz, CH$_2$C<u>H</u>$_3$-1), 3.44 (2H, q, *J*=7.7 Hz, C<u>H</u>$_2$CH$_3$-1), 6.64 (2H, s, C<u>H</u>$_2$COC$_6$H$_5$), 7.45-7.53 (1H, m, H-6), 7.69 (2H, t, *J*=7.7 Hz, H-3' 5'), 7.78-7.87 (3H, m, H-7, 8, 4'), 8.17 (2H, d, *J*=7.7 Hz, H-2', 6'), 8.49 (1H, d, *J*=8.1 Hz, H-5), 8.60 (1H, d, *J*=6.6 Hz, H-4), 8.73 (1H, d, *J*=6.6 Hz, H-3), 12.95 (1H, br s, NH). IR ν max KBr cm^{-1}: 3405, 3068, 1645, 1631. FAB-MS *m/z*: 315 (M^+). *Anal.* Calcd for $C_{21}H_{19}N_2OBr$: C 63.81, H 4.84, N 7.09, Found: C 63.88, H 5.02, N 7.28.

General Procedure for the Synthesis of 11*H*-Pyrrolo[2,1-*a*]-β-carbolines.

2-Acetonyl- or 2-phenacyl-β-carbolin-2-ium bromide (1.0 g, 3.0 mmol) was stirred with sodium carbonate (1.2 g, 11.3 mmol) in H$_2$O (100 mL). The reaction mixture was heated at 100°C for 15 min. After being cooled, the mixture was extracted with CHCl$_3$ (50 mL x 3) and then the extract was washed with water (20 mL x 2). After drying with sodium sulfate, the solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel with CHCl$_3$ as eluent to give a residue which was recrystallized from chloroform-methanol (5:1) to yield 11*H*-pyrrolo[2,1-*a*]-β-carboline.

2-Methyl-11*H*-pyrrolo[2,1-*a*]-β-carboline (32)

Yield 49.6%, yellow needles, mp; 201-204°C (decomp). ^{1}H-NMR (DMSO-d_6, 323K) δ: 2.29 (3H, s, CH$_3$-2), 6.51 (1H, s, H-1), 7.11 (1H, t, *J*=8.1 Hz, H-8), 7.13 (1H, d, *J*=7.1 Hz, H-6), 7.21 (1H, t, *J*=8.1 Hz, H-9), 7.39 (1H, quartet like, *J*=0.7 Hz, H-3), 7.47 (1H, d, *J*=8.1 Hz, H-10), 7.87 (1H, d, *J*=8.1 Hz, H-7), 7.89 (1H, dd, *J*=0.7, 7.1 Hz, H-5), 11.63 (1H, br s, NH). IR ν max KBr cm^{-1}: 3394, 3052, 1644.

MS *m/z*: 220 (M^+). HRMS *m/z*: Calcd for $C_{15}H_{12}N_2$, 220.0998. Found: 220.0999 (M^+).

2-Phenyl-11*H*-pyrrolo[2,1-*a*]-β-carboline (33)

Yield 58.3 %, yellow needles, mp 215°C. ^{1}H-NMR (DMSO-d_6, 323K) δ: 7.04 (1H, s, H-1), 7.16 (1H, t, *J*=7.7 Hz, H-8), 7.21-7.30 (3H, m, H-6, 7, 4'), 7.42 (2H, t, *J*=7.3 Hz, H-3', 5'), 7.52 (1H, d, *J*=7.7 Hz, H-10), 7.72 (2H, d, *J*=7.3 Hz, H-2', 6'), 7.91 (1H, d, *J*=7.7 Hz, H-9), 8.00 (1H, d, *J*=7.0 Hz, H-5), 8.04 (1H, d, *J*=1.5 Hz, H-3), 11.83 (1H, br s, NH). IR ν max KBr cm^{-1}: 3400, 3054, 1643. MS *m/z*: 282 (M^+). HRMS *m/z*: Calcd for $C_{20}H_{14}N_2$, 282.1154. Found: 282.1167 (M^+).

1,2-Dimethyl-11*H*-pyrrolo[2,1-*a*]-β-carboline (34)

Yield 36.4%, yellow needles, mp 215°C (decomp). ^{1}H-NMR (DMSO-d_6, 323K) δ: 2.18 (3H, s, CH_3-2), 2.53 (3H, s, CH_3-1), 7.03 (1H, d, *J*=7.1 Hz, H-6), 7.11 (1H, t, *J*=8.1 Hz, H-8), 7.20 (1H, t, *J*=8.1 Hz, H-9), 7.34 (1H, s, H-3), 7.54 (1H, d, *J*=8.1 Hz, H-10), 7.80 (1H, d, *J*=7.2 Hz, H-5), 7.82 (1H, d, *J*=8.1 Hz, H-7), 11.18 (1H, br s, NH). IR ν max KBr cm^{-1}: 3434, 2911, 1637. MS *m/z*: 234 (M^+). HRMS *m/z*: Calcd for $C_{16}H_{14}N_2$, 234.1154. Found: 234.1156 (M^+).

1-Methyl-2-Phenyl-11*H*-pyrrolo[2,1-*a*]-β-carboline (35)

Yield 58.4%, yellow needles, mp 205°C (decomp). ^{1}H-NMR (DMSO-d_6, 323K) δ: 2.70 (3H, s, CH_3-1), 7.14 (1H, t, *J*=8.1 Hz, H-8), 7.10-7.29 (3H, m, H-6, 7, 4'), 7.43 (2H, t, *J*=7.3 Hz, H-3', 5'), 7.52 (1H, d, *J*=8.1 Hz, H-10), 7.72 (2H, d, *J*=7.3 Hz, H-2', 6'), 7.91 (1H, d, *J*=7.7 Hz, H-9), 8.01 (1H, d, *J*=7.0 Hz, H-5), 8.04 (1H, d, *J*=1.5 Hz, H-3), 11.82 (1H, br s, NH). IR ν max KBr cm^{-1}: 3399, 3054, 1637. MS *m/z*: 296 (M^+). HRMS *m/z*: Calcd for $C_{21}H_{16}N_2$, 296.1310. Found: 296.1306 (M^+).

Crystal Data of 24

Crystallized from methanol and belonging to monoclinic space group $P2_1/n$. Lattice constants and intensity data were measured on a Rigaku AFC-7R diffractometer with a device for graphite-monochromated CuKα radiation. Crystal data: $C_{19}H_{18}N_2OBr$, a=10.680(2), b=13.408(2), c=11.301(1) Å, Z=4, D_{calc}=1.553 g/cm^3, CuKα (λ=1.54178 Å), β=101.84°. A total of 1876 independent reflections with I>3σ(I) were used for structure analysis. The structure was solved by the direct method (MITHRIL84)[7] and expanded using Fourier techniques.[8] The structure was then refined by full-matrix least squares with anisotropic temperature factors for non-hydrogen and isotropic atoms for hydrogen atoms to an *R* factor of 0.095.

***In Vitro* Cytotoxity**

To examine the direct growth-inhibitory effects of test compounds against P-388 against murine leukemia cells and PC-6 human lung carcinoma cells, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed and the concentration giving a growth inhibition of 50% (GI_{50}) was calculated according to a published procedure.[9]

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