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Syntheses and Cytotoxicity Evaluation of Bis(indolyl)thiazole, Bis(indolyl)pyrazinone and Bis(indolyl)pyrazine: Analogues of Cytotoxic Marine Bis(indole) Alkaloid

Biao Jiang* and Xiao-Hui Gu

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P.R. China

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Abstract—2,4-Bis(3′-indolyl)thiazoles, 3,5-bis(3′-indolyl)-2(1*H*)pyrazinone and 3,6-bis(3′-indolyl)pyrazine were synthesized and evaluated for cytotoxic activity against diverse human cancer cell lines by the National Cancer Institute. These compounds demonstrated significant inhibitory effects in the growth of a range of cancer cell lines. 2,4-Bis(3′-indolyl)thiazole displayed selective cytotoxicity against certain leukemia cell lines with GI_{50} values in the low micromolar range while the substituted derivatives showed a broad spectrum of cytotoxic activity. 3,5-Bis(3′-indolyl)-2(1*H*)pyrazinone and 3,6-bis[3′-(*N*-methyl-indolyl)]pyrazine possessed strong inhibitory activity against a wide range of human tumor cell lines. The mechanism of action remained unknown. The results suggested that 2,4-bis(3′-indolyl)thiazoles, 3,5-bis(3′-indolyl)-2(1*H*)pyrazinone and 3,6-bis[3′-(*N*-methyl-indolyl)] pyrazine offer potential as lead compounds for the discovery of anticancer agents.

Introduction

Cancer remains a major threat to the public health. Natural products, especially marine natural products, continue to be an important source of novel bio-active chemotypes for anticancer drug development. A number of bis(indole)alkaloids have been isolated from the marine environment over the past decade, which exhibit various biological activities including antibacterial, antiviral and cytotoxic activities.[1,2] Nortopsentins **A**–**C**, having a characteristic 2,4-bis(3-indolyl)imidazole skeleton, were isolated from the deep-water marine sponge *spongsorites ruetzleri* (Fig. 1). Nortopsentins **A**–**C** exhibited in vitro cytotoxicity against P388 cell: IC_{50}(μg/mL), 7.6, 7.8 and 1.7 respectively.[3–6] Due to the interesting biological activities and unique chemical structures of marine indolealkaloids and its low availability, marine indolealkaloids as lead compounds for discovery of new drugs have become an attractive field in medicinal chemistry. In our effort to search for novel antitumor compounds, we designed and synthesized bis(indolyl) alkaloids in which the imidazole moiety of the cytotoxic marine bis(indole) alkaloid nortopsentins was replaced with a thiazole, pyrazinone or pyrazine ring. When evaluated for cytotoxicity in the NCI's in vitro disease-oriented antitumor screen, the bis(indole)alkaloids analogues were found to possess significant cytotoxic activities against human cancer cell lines with GI_{50} values in the low micro-molar concentration range.

Results and Discussion

A general synthesis of 2,4-bis(3′-indolyl)thiazoles is shown in Scheme 1. Indole-3-carboxaldehydes (**1**), prepared from the corresponding indole by the Vilsmeier reaction, were transformed into indole-3-carbonitriles (**2**) in good yields by treatment with diammonium hydrogen phosphate, 1-nitropropane and acetic acid.[7] Treatment of indole-3-carbonitrile (**2**) with H_2S in pyridine in the presence of triethylamine yielded indole-3-carbothioamides (**3**) in good yields.[8,9] 3-Acetylindoles (**5**) were prepared from *N*-toluenesulphonylindoles[10] by Friedel–Crafts acylation in excellent yields.[11] Bromination of **5** with copper(II) bromide in refluxing $CHCl_3$/EtOAc[12,13] afforded the α-bromoketones **6** in moderate yield. The centeral thiazole ring between the indolyl groups was constructed by reaction of the corresponding thioamide **3** and α-bromoketone **6** in refluxing absolute ethanol for 0.5–1 h. The *N*-tosylated bis(3-indolyl)thiazoles deposited from the reaction solution. After filtration, the products were obtained in excellent yields. Deprotection of the toluenesulfonyl group with

Keywords: alkaloiods; antitumor compounds; cytotoxins; substituent effects.

*Corresponding author. Tel.: +86-21-6416-3300; fax: +86-21-6416-6128; e-mail: jiangb@pub.sioc.ac.cn

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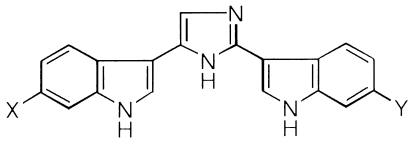


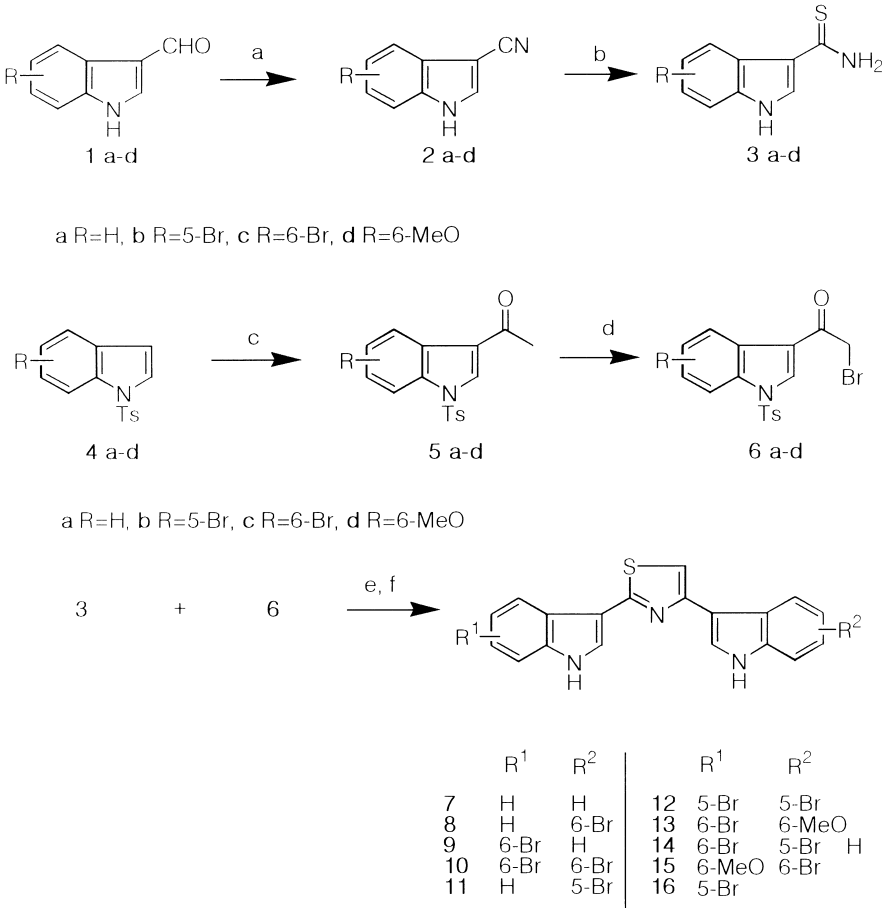
Nortopsentin A X= Y=Br
Nortopsentin B X=Br, Y=H
Nortopsentin C X =H, Y=Br

Figure 1.

NaOH in refluxing methanol afforded the 2,4-bis(3-indolyl)thiazoles **7**–**16**.

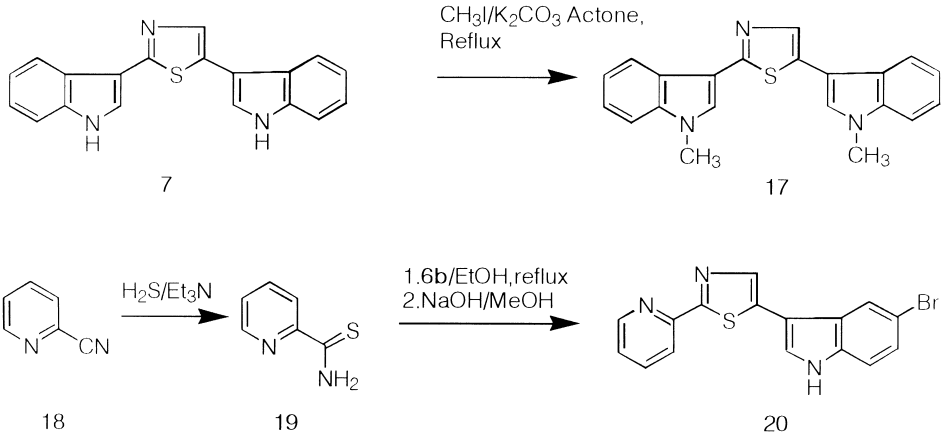
2,4-Bis[3′-(*N*-methylindolyl)]thiazole (**17**) was synthesized from **7** in 83% yield by reaction with an excess of iodomethane in acetone in the presence of anhydrous potassium carbonate. 2-(2′-Pyridinyl)-4-[3′-(5′-bromonoindolyl)] thiazole **20** was synthesized as shown in Scheme 2. Commercially available 2-cyanopyridine (**18**) was converted to 2-thioamide (**19**) with H_2S and triethylamine in methanol. Carbothioamide (**19**) was condensed with 3-(α-bromoacetyl)-5-bromo-indole **6b** in refluxing ethanol and subsequent *N*-detosylation with NaOH, **20** was obtained in 86% yield (Scheme 2).

The prepared indolylthiazole compounds were evaluated for cytotoxicity in the NCI's in vitro disease-oriented antitumor screen[14–16] against approximately a panel of 60 human tumor cell lines derived from leukemia, non-small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. The results are shown in Table 1 as GI_{50} values. All compounds exhibited cytotoxic activities against a variety of human cancer cell lines. The compound **7** selectively exhibited in vitro cytotoxicities against leukemia and ovarian cancer cell lines, affording GI_{50} of 3.27 μM in K562, 5.31 μM in Molt-4 and 8.14 μM in IGROV1 assay. In the other human tumor cell line assay, the GI_{50} of compound **7** exceeded 100 μM. To test the possibility that substitutes in the indole ring might result in a potency increase, most of the 2,4-bis(3-substituted-indolyl)thiazoles showed broad effects on tumor cell lines from the leukemia, colon cancer, CNS cancer and breast cancer panels while unsubstituted counterpart **7** brought out highly selective activity against leukemia cell lines and IGROV1 ovarian cancer cell lines. The position of bromine in the indole ring plays an important role in cytotoxicity. Dibrominated compound **16** effectively exhibited MCF 7 of breast cancer, affording the GI_{50} of 0.888 μM. The compound **17**, masked the NH in indolyl ring with methyl group, resulted in decreased activity against leukemia cell lines. Changing one indolyl ring for pyridinyl ring, **20** has detrimental effect on activities against certain colon cancer, ovarian cancer, prostate cancer,



	R^1	R^2		R^1	R^2
7	H	H	12	5-Br	5-Br
8	H	6-Br	13	6-Br	6-MeO
9	6-Br	H	14	6-Br	5-Br H
10	6-Br	6-Br	15	6-MeO	6-Br
11	H	5-Br	16	5-Br	

Scheme 1. Conditions and reagents: (a) $(NH_4)_2HPO_4$, $CH_3CH_2CH_2NO_2$, HOAc, reflux; (b) H_2S, Et_3N; (c) Ac_2O, $AlCl_3$, CH_2Cl_2, 0 °C-rt; (d) $CuBr_2$, $CHCl_3$–EtOAc (1:1), reflux; (e) EtOH, reflux; (f) NaOH, MeOH, reflux.



Scheme 2.

Table 1. Inhibition of in vitro tumor cell growth by prepared indolyl thiazoles

Cell line	Cytotoxicity (GI_{50} in μM)[a]											
	7	8	9	10	11	12	13	14	15	16	17	20
Leukemia												
CCRF-CEM	ND[b]	14.6	10.9	10.1	2.11	2.40	27.7	2.58	2.66	2.99	>100	5.35
HL-60(TB)	ND	ND	ND	0.95	2.43	2.76	ND	3.76	4.13	3.86	>100	1.96
K-562	3.27	18.8	5.61	4.69	1.96	1.94	15.2	2.13	1.74	2.15	11.2	2.98
MOLT-4	5.31	19.9	31.2	5.80	1.41	1.75	23.0	1.55	2.95	2.26	14.1	3.56
RPMI8226	ND	19.4	12.2	11.4	1.97	1.95	27.1	2.24	2.03	1.84	20.8	5.04
Non-small cell lung cancer												
NCI-226	>100	14.4	24.4	3.3	2.10	3.14	45.4	2.48	2.24	7.23	32.2	8.91
NCIH322M	>100	16.7	18.9	18.4	2.01	1.99	70.8	2.51	3.09	2.99	24.5	13.0
NCI-H460	>100	16.1	7.31	16.4	2.55	1.93	23.2	2.31	1.58	2.00	26.5	4.05
EKVX	>100	15.6	29.5	28.6	ND	ND	32.1	0.48	0.29	0.55	ND	3.99
Colon cancer												
HCT-15	>100	15.2	17.8	8.50	1.81	2.51	7.54	2.70	0.81	2.84	>100	8.05
SW-620	>100	16.5	25.6	12.5	1.52	2.14	7.00	3.57	5.50	2.89	59.4	14.6
CNS cancer												
SF-295	33.6	14.6	9.23	4.81	1.98	2.71	73.5	4.56	ND	ND	23.5	2.57
SF-268	ND	18.3	32.1	ND	1.52	2.44	26.0	2.69	13.8	1.80	58.2	13.7
SNB-19	>100	17.8	41.87	17.2	2.11	3.75	>100	2.60	10.5	3.34	42.6	4.03
U21	>100	17.9	28.1	15.3	2.10	2.30	25.0	3.34	5.07	3.00	32.4	10.4
Ovarian cancer												
IGROV1	8.14	13.0	30.5	14.4	1.85	1.70	81.5	2.96	4.61	2.43	27.0	19.9
OVCAR-5	>100	16.1	37.1	23.6	1.96	2.14	42.7	2.16	3.44	2.35	95.9	26.1
Renal cancer												
786-0	>100	18.0	19.9	15.9	2.28	1.95	27.4	1.50	3.89	2.21	17.2	6.04
A498	>100	17.0	25.7	23.2	1.92	2.48	89.4	2.19	7.43	2.40	12.6	3.99
RXF 393	ND	22.4	7.62	18.4	1.81	1.69	11.9	2.42	2.03	1.66	14.1	2.31
Prostate cancer												
PC-3	>100	15.6	16.9	15.3	2.02	2.57	10.4	4.16	3.49	2.81	21.9	8.53
DU-145	>100	18.8	14.9	18.4	2.29	2.61	>100	3.74	5.46	2.03	42.9	14.1
Breast cancer												
MCF7	>100	16.7	27.2	6.46	2.13	2.70	54.1	0.88	4.36	3.82	45.5	10.3
MDAMB435	33.1	14.9	25.6	4.34	2.53	2.27	7.70	4.54	14.6	3.97	26.4	46.3
MDA-N	83.0	19.2	31.5	2.94	1.88	2.09	8.27	2.86	6.84	3.77	24.9	23.7
T-47D	>100	24.8	23.9	16.2	3.27	2.90	59.3	3.33	4.12	1.76	28.1	5.54
BT-549	>100	18.3	73.8	41.1	2.71	10.6	67.3	1.24	1.46	1.41	56.3	>100
Melanoma												
LOX IWVI	21.8	15.5	6.55	11.3	1.97	1.69	64.1	2.32	2.41	1.87	36.4	5.52
MALME-3M	>100	16.9	>100	ND	1.28	1.72	17.5	1.45	1.50	2.83	19.0	19.1
M14	>100	14.2	32.4	10.6	1.61	1.63	>100	2.86	5.49	2.77	26.7	13.5
SK-MEL-2	>100	ND	37.5	68.8	1.81	1.98	19.1	3.25	7.30	2.91	38.8	21.7
SK-MEL-28	>100	14.2	7.74	32.0	3.02	3.05	>100	9.84	1.36	4.96	61.5	64.2
SK-MEL-5	ND	14.9	23.7	28.5	1.76	1.63	>100	2.82	5.13	3.36	26.9	12.9

[a]Data obtained from NCI's in vitro disease-oriented tumor cells screen.
[b]Not determined.

melanoma and breast cancer cell lines, but it has little effect on activities against certain leukemia, and renal cancer cell lines.

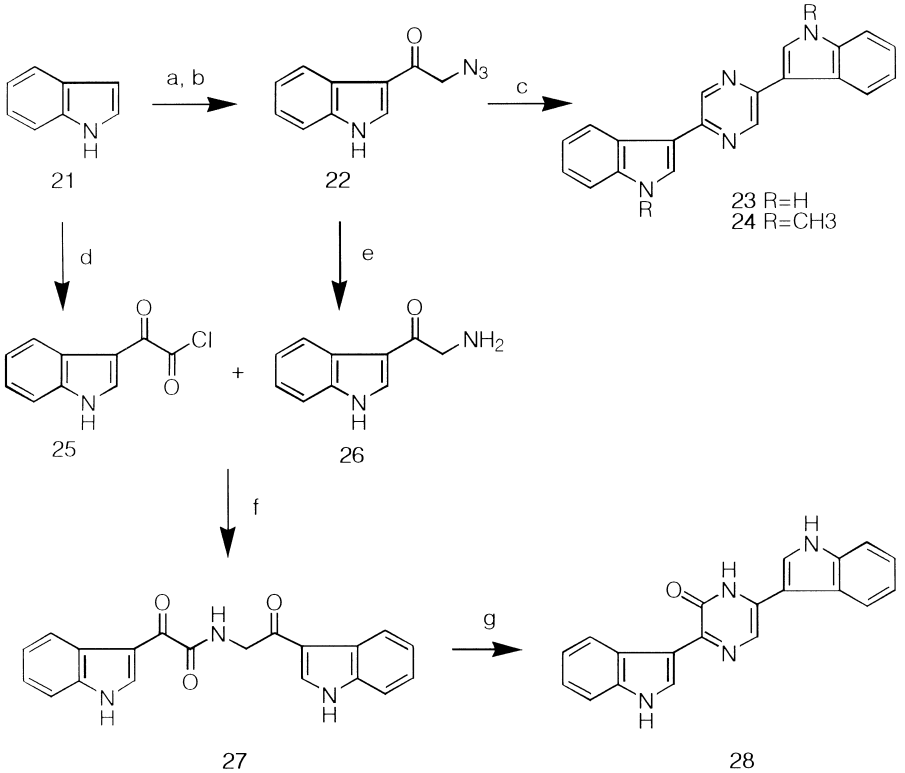
Compound **7** was then evaluated in a hollow fiber cell assay,[17] recently developed at the National Cancer Institute, wherein tumor cells are cultivated in hollow fibers through encapsulation/implantation technology. This assay is intended to provide a preliminary indication of the potential for compounds to exhibit in vivo antineoplastic activity in xenograft models. The cell lines used in the assay were LOX, UACC-62, MDA-MB-435, MDA-MB-231, COLO205, SW620, SF-295, U251, OVCAR-3, OVCAR-5, NCI-H23 and NCI-H522. The test doses were 150 and 100 mg/kg/ingestion given IP once daily for 4 days. The results suggested that compound **7** was inactive in vivo.

Nortopsentins have a structure of five-member ring of imidazole attached by two indolyl groups. The thiazole analogues of nortopsentin prepared above, also showed the cytotoxic activities. Several pyrazine compounds has been proved to be potent antitumor agents.[18,19] In the family of marine bisindole alokoilds, antitumor active dragmacidin d isolated from *spongosorites* sp. has a chemical structure of a central six-membered ring of pyrazinone linked with two indolyl groups and show antiviral activities.[20,21] We planned to synthesize the pyrazine and pyrazinone analogues bearing bisindole. Thus, 3,6-bis(3′-indolyl)pyrazine and 3,5-bis(3′-indolyl)-2(1*H*)pyrazinone were designed and synthesized as shown in Scheme 3. Reaction of indole with chloroacetyl chloride in toluene containing pyridine,[22] followed by treatment with sodium azide in refluxing aqueous acetone[23] afforded the azidoketone **22** in 34% overall yield. α-Azidoketone **22** was hydrogenated over 10%Pd/C in methanol containing a few drops of glacial acetic acid at room temperature for 24 h to offer 3,5-bisindolyl pyrazine **23** in 74% yield.[24] Attempting to synthesize **23** by treatment of α-azidoketone **22** with triphenylphosphine or tributylphosphine[25] resulted in recovery of the starting material.

Azidoketone **22** was hydrogenated over 10% Pd/C in methanol containing concentration hydrochloric acid to afford 3-(α-aminoacetyl)indole hydrochloride salt **26**. Reaction of **26** with 3-indolylglyoxylic chloride **25**[26] in CH_2Cl_2 and Et_3N yielded compound **27** in 67% yield.

In accordance with reported methods applying for synthesis of the central pyrazinone ring, such as, treatment of **27** with ammonium acetate in refluxing ethanol,[27] or in refluxing acetic acid[9] failed to give compound **28**. Tried to search other synthetic process, finally, central pyrazinone ring was successfully constructed by treatment of **27** in excess of ammonia at 60–80 °C under 50 psi pressure for three days. The desired product **28** was obtained in the form of a brown solid in 62% yield.

As shown in Table 2, in spite of the fact that compound **23** showed weakness of cytotoxicity, its *N*-methylated derivative **24** possessed very strong inhibitory activity against all cell lines with GI_{50} values below 10 μM. The GI_{50} values of **24** were respectively 0.72, 0.248, 0.058, 0.287, and 0.29 μM against NCI-H322M lung, HCT-15 and KM12 colon, SK-MEL-5 melanoma, and MCF 7



Scheme 3. Reagents and conditions: (a) ($ClCH_2COCl$, pyridine, toluene, 60 °C, 36%; (b) NaN_3, acetone/H_2O, reflux, 98%; (c) H_2, 5%Pd/C, EtOH, AcOH (trace) rt; (d) $(COCl)_2$, CH_2Cl_2 rt; (e) H_2, 10% Pd/C, MeOH, 35%HCl, 87%; (f) Et_3N, CH_2Cl_2, rt, 67%; (g) liq. NH_3, MeOH, 60–80 °C, 62%.

Table 2. Inhibition of tumor cell growth in vitro by compound **23**, **24** and **28** (GI_{50} in μM)[a,b]

Cells/compounds	23	28	24
Leukemia			
K-562	2.97	18.8	7.19
SR	3.99	30.0	3.14
Non-small cell lung cancer			
NCI-H522	6.79	28.5	1.94
NCI-H322M	15.5	41.7	0.72
Colon cancer			
HCT-15	11.1	58.6	0.248
KM 12	4.96	74.2	0.058
SW-620	4.90	18.9	2.07
CNS cancer			
SF-295	4.53	20.2	1.87
SF-539	8.62	23.5	ND[c]
Melanoma			
SK-MEL-5	13.4	50.1	0.287
Ovarian cancer			
IGROV1	12.93	30.9	5.66
OVCAR-4	6.57	> 100	2.81
Renal cancer			
RXF 393	2.73	26.7	2.17
CAKI-1	3.28	74.8	5.77
Breast cancer			
MCF7	10.2	6.60	0.29
MDA-MB-435	3.29	25.0	1.16
MDA-N	2.47	19.1	1.21

[a]Data obtained from NCI's in vitro disease-oriented tumor cells screen.
[b]GI_{50} is the molar concentration causing 50% growth inhibition of tumor cells. Compounds with $GI_{50} > 100$ μM are considered inactive.
[c]ND = not determined.

breast cancer cell line. Compound **28** demonstrated strong inhibitory effects against a variety of tumor cell lines, including leukemia, non-small cell lung cancer, colon cancer, CNS cancer, ovarian cancer, renal cancer, and breast cancer cell lines with GI_{50} values between 1 and 10 μM, but it displayed inhibitory effects weaker than that of melanoma cell lines.

COMPARE computations[28] were performed on the NCI screening data for all of the synthesized bis(indole) alkaloid compounds, and all were negative (Pearson correlation coefficients <0.6) against the NCI "Standard Agent" database. This suggested that these compounds probably act a mechanism differentiating those of the Standard Agents.

In conclusion, we have synthesized a series of novel 2,4-bis(3′-indolyl)thiazoles, 3,6-bis(3′-indolyl)pyrazine and 3,5-bis(3′-indolyl)-2(1*H*)pyrazinone. The compounds demonstrated powerful inhibitory effects in vitro in the growth of a wide variety of human tumor cell lines and would promise as lead compounds for further development of indole alkaloid anticancer agents.

Experimental

Mp was uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer with Me_4Si as an internal standard. *J* values were given in Hz. Infrared spectra were taken on a Shimadzu IR-440 spectrometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were run respectively on a Finnigan 4021 GC MS/DC and Varian MAT 21 instrument with an ionising voltage of 70eV.

General procedure for synthesis of indole-3-carbonitrile (2). A mixture of indole-3-carbaldehyde (10 mmol), diammonium hydrogen phosphate (7.0 g, 53 mmol), 1-nitropropane (30 mL, 340 mmol) and acetic acid (10 mL) was refluxed for 16 h. The reaction mixture was turned to dark red from pale-yellow. The solvent was removed under reduced pressure, and water (200 mL) was added to the dark residue. After a short time, crude indole-3-carbonitrile precipitated rapidly. The solid was filtered and recrystallized from acetone–hexane to yield fairly pure indole-3-carbonitrile (**2**).

Indole-3-carbonitrile (2a). Yield 68%; mp 178.8–179.4 °C; UV (95%EtOH) λ_{max} 217, 270, 278, 285 nm; IR (KBr) ν_{max} 3224 (NH), 2228 (C≡N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.32 (s, 1H), 7.91 (m, 1H), 7.83 (m, 1H), 7.56–7.47 (m, 2H); MS (EI) *m*/*z* 142 (M^+).

5-Bromoindole-3-carbonitrile (2b). Yield 67%; mp 191.1–191.7 °C; UV (MeOH) λ_{max} 218, 234, 278 nm; IR (KBr) ν_{max} 3289 (NH), 2218 (C≡N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.39 (br, 1H), 8.31 (d, *J* = 1.9 Hz, 1H), 7.79 (d, *J* = 2.5 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.41 (dd, *J* = 1.8 and 8.6 Hz, 1H); MS (EI) *m*/*z* 222/220 (M^+).

6-Bromoindole-3-carbonitrile (2c). Yield 81%; mp 186.2–186.5 °C; IR (KBr) ν_{max} 3255 (NH), 2221 (C≡N) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.31 (br, 1H), 8.28 (s, 1H), 7.75 (m, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.36 (dd, *J* = 1.7 and 8.5 Hz, 1H); MS (EI) *m*/*z* 222/220 (M^+).

6-Methoxyindole-3-carbonitrile (2d). Yield 72%; mp 173.6–174.2 °C dec; UV (MeOH) λ_{max} 220, 270, 290 nm; IR (KBr) ν_{max} 3256 (NH), 2837, 2223 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.98 (br, 1H, NH), 8.10 (d, *J* = 2.6 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.89 (dd, *J* = 2.3 and 8.7 Hz, 1H), 3.80 (s, 3H, OCH_3); MS (EI) *m*/*z* 172 (M^+).

General procedure for synthesis of indole-3-thioamide (3). H_2S gas was bubbled into a mixture of indole-3-carbonitrile **2** (10 mmol), pyridine (20 mL) and triethylamine (2 mL, 14 mmol) for 1 h. The resultant reaction mixture was sealed and stirred for two days at room temperature. The mixture was poured onto ice-cooled water (100 mL). The orange–yellow precipitate was collected by filtration, washed with water and dried under reduce pressure to afford **3**.

Indole-3-carbothioamide (3a). Yield 68%; mp 148.6–152.2 °C; UV (MeOH) λ_{max} 212, 252, 276, 324 nm; IR (KBr) ν_{max} 3386, 3276, 3180, 1623, 1529, 1442, 1365, 1133 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.79 (br, 1H), 8.96 (br, 1H), 8.82 (br, 1H,), 8.62 (m, 1H), 8.09 (d, *J* = 2.9 Hz, 1H), 7.43 (m, 1H), 7.15 (m, 2H); MS (EI) *m*/*z* 176 (M^+).

5-Bromoindole-3-carbothioamide (3b). Yield 58%; mp 240.8–241.2 °C; UV (MeOH) λ_{max} 218, 234, 278 nm. IR (KBr) ν_{max} 3381, 3190, 1623, 1525, 1435, 1295, 1191, 1117 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.95 (br, 1H), 9.01 (br, 1H), 8.94–8.90 (m, 2H), 8.14 (d, $J=2.1$ Hz, 1H), 7.42 (d, $J=8.6$ Hz, 1H), 7.3 (dd, $J=2.0$ and 8.6 Hz); MS (EI) m/z 254/256 (M^+).

6-Bromoindole-3-carbothioamide (3c). Yield 58%; mp 193.2–193.6 °C dec; IR (KBr) ν_{max} 3348, 3176, 1627, 1447, 1408, 1365, 1204, 1147 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.87 (br, 1H), 9.05 (brs, 1H), 8.92 (br, 1H), 8.61 (d, $J=8.7$ Hz, 1H), 8.10 (d, $J=2.3$ Hz, 1H), 7.64 (d, $J=1.5$ Hz, 1H), 7.28 (dd, $J=8.7$ and 1.5 Hz, 1H); MS (EI) m/z 256/254 (M^+).

6-Methoxyindole-3-carbothioamide (3d). Yield 72%; mp 240 °C dec; UV (MeOH) ν_{max}, 220, 270, 290 nm; IR (KBr) ν_{max} 3256 (NH), 3200, 2837, 1630, 1510, 1435, 1133 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.18 (br, 1H), 9.01 (br, 2H), 8.08 (d, $J=2.6$ Hz, 1H), 7.49 (d, $J=8.6$ Hz, 1H), 7.23 (d, $J=2.3$ Hz, 1H), 7.01 (dd, $J=2.3$ and 8.7 Hz, 1H), 3.80 (s, 3H, OCH_3); MS (EI) m/z 172 (M^+).

Pyridinyl-2-thioamide (19). Compound **19** was prepared in same procedure as **3** in yield 69%; mp 137.2–137.4 °C; IR (KBr) ν_{max} 3349, 3149, 1602, 1581, 1441, 1275, 1146 cm^{-1}; ^1H NMR (DMSO-d_6) δ 10.16 (br, 1H), 9.92 (br, 1H), 8.61 (m, 1H), 8.53 (m, 1H), 7.98 (m, 1H), 7.60 (m, 1H); MS (EI) m/z 138 (M^+).

General procedure for synthesis of 3-acetyl-*N*-(toluenesulfonyl) indoles (5a–d). To a solution of indole (80 mmol) in toluene (80 mL) was added Bu_4NHSO_4 (1.88 g, 5.55 mmol), 50% aqueous KOH (100 mL) and p-$CH_3C_6H_4SO_2Cl$ (20.4 g in 200 mL toluene) and the mixture stirred at ambient temperature for 3 h. The organic layer was separated, washed with H_2O, dried over Na_2SO_4, concentrated under reduced pressure, and the crude product was crystallized form 95% ethanol.

To a suspension solution of $AlCl_3$ (20.5 g, 154 mmol) in CH_2Cl_2 (300 mL) was added acetic anhydride (8.0 mL, 85 mmol) at ambient temperature for 30 min. A solution of *N*-(toluenesulfonyl) indole (6.8 g, 25 mmol) in CH_2Cl_2 (40 mL) was added dropwise. The mixture was stirred at ambient temperature for 16 h and poured into ice (200 g). The aqueous layer was extracted with CH_2Cl_2. The organic extracts were washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. After removal of the solvent, the crude product was recrystallized with MeOH to give pure 3-acetyl-*N*-(toluenesulfonyl)indole **5**.

3-Acetyl-*N*-(toluenesulfonyl)indole (5a). Yield 94%; mp 148.1–150.3 °C; UV (MeOH) ν_{max} 206, 2588 nm; IR (KBr) ν_{max} 1670, 1595, 1540, 1478, 1445, 1381, 1192 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.33 (m, 1H), 8.22 (s, 1H), 7.95–7.83 (m, 3H), 7.38–7.32 (m, 4H), 2.58 (s, 3H), 2.38 (s, 3H); MS (EI) m/z 313 (M^+).

3-Acetyl-5-bromo-*N*-(toluenesulfonyl)indole (5b). Yield 91%; mp 166.8–167.3 °C; UV (MeOH) λ_{max}, 216, 276 nm; IR (KBr) ν_{max} 1671, 1595, 1537, 1437, 1380, 1294, 1191 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.49 (d, $J=1.9$ Hz, 1H), 8.18 (s, 1H), 7.81 (d, $J=8.3$ Hz, 2H), 7.79 (d, $J=8.7$ Hz, 1H), 7.46 (dd, $J=1.9$ and 8.8 Hz, 1H), 7.29 (d, $J=8.3$ Hz, 2H), 2.55 (s, 3H), 2.37 (s, 3H); MS (EI) m/z 392/390 (M^+).

3-Acetyl-6-bromo-*N*-(toluenesulfonyl)indole (5c). Yield 85%; mp 166.0–166.9 °C; UV (MeOH) λ_{max} 210, 276 nm; IR (KBr) ν_{max} 1674, 1598, 1536, 1477, 1378, 1361, 1196, 1183 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (d, $J=8.5$ Hz, 1H), 8.16 (s, 1H), 8.11 (d, $J=1.6$ Hz, 1H), 7.84 (d, $J=8.5$ Hz, 2H), 7.45 (dd, $J=1.6$ and 8.6 Hz, 1H), 7.33 (d, $J=8.3$ Hz, 2H), 2.56 (s, 3H), 2.40 (s, 3H); MS (EI) m/z 393/391 (M^+).

3-Acetyl-6-methoxy-*N*-(toluenesulfonyl)indole (5d). Yield 87%; mp 128.2–128.9 °C; UV (MeOH) λ_{max} 230 nm; IR (KBr) ν_{max} 1668, 1615, 1492, 1382, 1279, 1249, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (d, $J=8.8$ Hz, 1H), 8.10 (s, 1H), 7.82 (d, $J=8.4$ Hz, 2H), 7.43 (d, $J=2.3$ Hz, 1H), 7.28 (d, $J=8.8$ Hz, 2H), 6.95 (dd, $J=2.3$ and 8.8 Hz, 1H), 3.87 (s, 3H), 2.54 (s, 3H), 2.37 (s, 3H); MS (EI) m/z 343 (M^+).

General procedure for synthesis of *N*-(toluenesulfonyl)-3-(2-bromoacetyl) indole (6). To a suspension solution of copper (II) bromide (1.92 g, 8.57 mmol) in ethyl acetate (25 ml) was added a solution of 3-acetyl-*N*-(toluenesulfonyl)indoles (7 mmol) in chloroform (25 mL). The mixture was refluxed with vigorous stirring for 10 h. When the reaction was cooled to room temperature, the solid was filtered. After removal of solvent under reduced pressure, the crude product was purified by column chromatography to give (**6**).

***N*-(Toluenesulfonyl)-3-(2-bromoacetyl)indole (6a).** Yield 55%; mp 126.6–127.4 °C; UV (MeOH) λ_{max} 206, 234, 294 nm; IR (KBr) ν_{max} 1669, 1535, 1479, 1446, 1390, 1337, 1294, 1191 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35 (s, 1H), 8.31 (m, 1H), 7.96–7.93 (m, 1H), 7.86 (d, $J=8.4$ Hz, 2H), 7.44–7.34 (m, 2H), 7.31 (d, $J=8.3$ Hz, 2H), 4.36 (s, 2H, CH_2Br), 2.38 (s, 3H, CH_3); MS (EI) m/z 393/391 (M^+).

***N*-Toluenesulphonyl-5-bromo-3-(2-bromoacetyl)indole (6b).** Yield 56%; mp 164–164 °C; UV (MeOH) λ_{max} 214, 292 nm; IR (KBr) ν_{max} 1691, 1593, 1493, 1391, 1294, 1193 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.45 (d, $J=2.0$ Hz, 1H), 8.33 (s, 1H), 7.82 (d, $J=8.4$ Hz, 1H), 7.80 (d, $J=8.7$ Hz, 1H), 7.48 (dd, $J=2.0$ and 8.8 Hz, 1H), 7.30 (d, $J=8.3$ Hz, 2H), 4.32 (s, 2H), 2.38 (s, 3H); MS (EI) m/z 473/469 (M^+).

***N*-Toluenesulphonyl-6-bromo-3-(2-bromoacetyl)indole (6c).** Yield 63%; mp 159–160 °C. UV (MeOH) λ_{max} 240, 290 nm; IR (KBr) ν_{max} 1687, 1537, 1378, 1292, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (s, 1H), 8.17 (d, $J=8.5$ Hz, 1H), 8.13 (d, $J=1.6$ Hz, 1H), 7.86 (d, $J=8.5$ Hz, 2H), 7.50 (m, 1H), 7.40–7.34 (m, 3H), 4.36 (s, 2H, CH_2Br), 2.41 (s, 3H, CH_3); MS (EI) m/z 473/469 (M^+).

***N*-Toluenesulphonyl-6-methoxy-3-(2-bromoacetyl)indole (6d).** Yield 58%; mp 156.4–156.8 °C; UV (MeOH) λ_{max}

236 nm; IR (KBr) ν_{max} 1688, 1540, 1390, 1292, 1190 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.68 (s, 1H), 8.09–7.97 (m, 3H), 7.49–7.39 (m, 3H), 7.00 (m, 1H), 4.67 (s, 2H), 3.84 (s, 3H), 2.34 (s, 3H); MS (EI) *m*/*z* 423/421 (M^+).

General procedure for preparation of 2,4-bis(3′-indolyl)-thiazoles (7–16). A suspension of the indole-3-thioamide **3** (5 mmol) and 3-(2-bromoacetyl)-*N*-(toluenesulphonyl) indole **6** (5 mmol) in absolute ethanol (25 mL) was refluxed at 80–90 °C for about 30 min. A precipitate deposited from the reaction mixture. The solid was filtered and treated with 10% sodium hydroxide in methanol. The resulting mixture was refluxed for 3 h. After removal of solvent, the mixture was extracted with ether and washing with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography to afford corresponding 2,4-bis(3′-indolyl)thiazole.

2,4-Bis(3′-indolyl)thiazole (7). Yield 88%; mp 289.2–289.8 °C; UV (95%EtOH) λ_{max} 226, 274 nm; IR (KBr) ν_{max} 3388, 3123 (NH), 1675, 1616, 1575, 1475, 1427, 1333, 1259, 1097 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.74 (br, 1H, NH), 11.39 (br, 1H, NH), 8.37 (m, 1H), 8.22 (m, 1H), 8.14 (m, 1H), 7.6 (m, 1H), 7.53–7.47 (m, 2H), 7.26–7.16 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 161.76, 150.54, 136.65, 136.5, 126.39, 126.22, 124.66, 124.39, 122.36, 121.55, 120.71, 120.45, 120.18, 119.7, 112.16, 111.35, 110.84, 105.95; MS (EI) *m*/*z* 315 (M^+); HRMS calcd. for $C_{19}H_{13}N_3S$ 315.0831, found 315.0829.

2(3′-Indolyl)-4-[3′-(6′-bromoindolyl)]thiazole (8). Yield 82%; mp 256.7–257.4 °C; UV (95% EtOH) λ_{max} 210, 260 nm; IR (KBr) ν_{max} 3442, 3215, 1617, 1578, 1474, 1232, 1134 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.78 (br, 1H, NH), 11.56 (br, 1H, NH), 8.35 (m, 1H), 8.21 (d, J = 8.6 Hz, 1H), 8.16 (d, J = 2.5 Hz, 1H), 8.03 (d, J = 2.1 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.65 (s, 1H), 7.52 (m, 1H), 7.37 (s, 1H), 7.31 (d, J = 1.8 Hz, 1H), 7.28–7.22 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 162.06, 149.78, 137.51, 136.63, 126.57, 125.73, 124.90, 124.52, 122.42, 122.03, 120.79, 120.38, 114.46, 114.33, 112.24, 111.47, 110.66, 106.63; MS (EI) *m*/*z* 395/393 (M^+); HRMS calcd. for $C_{19}H_{12}BrN_3S$ 393.9837, found 393.9799.

2-[3′-(6′-Bromoindolyl)]-4-(3′-indolyl)thiazole (9). Yield 76%; mp 261.0–262.3 °C (dec.); UV (95%EtOH) λ_{max} 228, 280 nm; IR (KBr) ν_{max} 3390, 3122 (NH), 1670, 1544, 1456, 1423, 1333, 1292, 1235, 1147, 1021 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.87 (br, 1H, NH), 11.42 (br, 1H, NH), 8.34 (d, J = 8.56 Hz, 1H), 8.21–8.17 (m, 2H), 8.00 (s, 1H), 7.7 (s, 1H), 7.63 (s, 1H), 7.48 (m, 1H), 7.39 (dd, 1H), 7.20–7.16 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 161.11, 150.59, 137.41, 136.62, 127.23, 124.81, 124.64, 123.53, 122.24, 121.48, 120.03, 119.65, 114.97, 114.67, 111.82, 111.19, 110.95, 106.22; MS (EI) *m*/*z* 395/393 (M^+); HRMS calcd. for $C_{19}H_{12}BrN_3S$ 395.9993, found 395.9953.

2,4-Bis[3′-(6′-bromoindolyl)]thiazole (10). Yield 78%; mp >300 °C; UV (95%EtOH) λ_{max} 232, 270 nm; IR (KBr) ν_{max} 3539, 3206 (NH), 1615, 1579, 1473, 1331, 1294, 1120, 1098, 1055 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.87 (br, 1H, NH), 11.55 (br, 1H, NH), 8.31 (d, J = 8.5 Hz, 1H), 8.18 (m, 2H), 8.03 (s, 1H), 7.68 (m, 25H), 7.40–7.27 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 162.40, 150.94, 138.43, 134.55, 130.27, 128.64, 128.41, 126.73, 124.64, 124.37, 123.52, 123.23, 122.93, 116.02, 115.72, 115.41, 112.39, 111.85, 107.91; MS (EI) *m*/*z* 475/471 (M^+); HRMS calcd. for $C_{19}H_{11}Br_2N_3S$ 470.9041, found 470.9052.

2-(3′-Indolyl)-4-[3′-(5′-bromoindolyl)]thiazole (11). Yield 84%, mp 213.2–214.4 °C (dec.); UV (MeOH) λ_{max} 220, 266 nm; ^1H NMR (DMSO-d_6) δ 11.73 (br, 1H, NH), 11.60 (br, 1H, NH), 8.52 (d, J = 1.7 Hz, 1H), 8.41 (m, 1H), 8.13 (d, J = 2.3 Hz, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.65 (s, 1H), 7.53 (m, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.33–7.23 (m, 2H); MS (EI) *m*/*z* 394/392 (M^+).

2,4-Bis[3′-(5′-bromoindolyl)]thiazole (12). Yield 72%; mp 238.7–239.5 °C; UV (MeOH) λ_{max} 218, 266 nm; ^1H NMR (DMSO-d_6) δ 11.85 (br, 1H, NH), 11.57 (br, 1H, NH), 8.57 (d, J = 1.9 Hz, 1H), 8.48 (d, J = 1.8 Hz, 1H), 8.35 (d, J = 2.4 Hz, 1H), 8.02 (d, J = 1.9 Hz, 1H), 7.67 (s, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.38 (dd, J = 1.9 and 8.6 Hz, 1H), 7.31 (dd, J = 1.91 and 8.6 Hz, 1H); MS (EI) *m*/*z* 475/471 (M^+); HRMS calcd. for $C_{19}H_{11}Br_2N_3S$ 470.9040, found 470.9036.

2-[3′-(6′-Bromoindolyl)]-4-[3′-(6′-methoxylindoly)]thiazole (13). Yield 73%; mp 275.8–276.7 °C (dec.); UV (MeOH) λ_{max} 228, 282 nm; IR (KBr) ν_{max} 3401, 3120, 1629, 1567, 1503, 1450, 1404, 1330, 1248, 1158 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.84 (br, 1H, NH), 11.18 (br, 1H, NH), 8.33 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 1.5 Hz, 1H), 7.72 (d, J = 1.51 Hz, 1H), 7.56 (s, 1H), 7.39 (dd, J = 1.8 and 8.5 Hz, 1H), 6.99 (d, J = 2.2 Hz, 1H), 6.83 (dd, J = 2.3 and 8.7 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 161.09, 155.69, 150.69, 137.44, 137.27, 127.22, 127.05, 123.56, 123.34, 122.23, 120.67, 119.04, 115.00, 114.71, 111.21, 110.99, 106.01, 94.87, 55.16; MS (EI) *m*/*z* 425/423 (M^+); HRMS calcd. for $C_{20}H_{14}BrN_3OS$ 423.0219, found 423.0206.

2-[3′-(6′-Bromoindolyl)]-4-[3′-(5′-bromoindolyl)]thiazole (14). Yield 75%; mp 253.4–235.9 °C (dec.); UV (MeOH) λ_{max} 218, 268 nm; ^1H NMR (DMSO-d_6) δ 11.80 (br, 1H, NH), 11.57 (br, 1H, NH), 8.47 (d, J = 1.4 Hz, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 8.04 (d, J = 1.8 Hz, 1H), 7.73 (d, J = 1.5 Hz, 1H), 7.66 (s, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.37 (dd, J = 1.7 and 8.5 Hz, 1H), 7.32 (dd, J = 1.8 and 8.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 164.44, 149.94, 137.45, 135.24, 127.33, 126.53, 126.06, 125.88, 124.00, 123.44, 123.38, 122.58, 122.17, 115.03, 114.78, 113.82, 112.39, 110.91, 110.86; MS (EI) *m*/*z* 475/471 (M^+); HRMS calcd. for $C_{19}H_{11}Br_2N_3S$ 474.8999, found 474.8964.

2-[3′-(6′-methoxylindolyl)]-4-(3′-indolyl)thiazole (15). Yield 75%; mp 241.6–242.3 °C (dec.); UV (MeOH) λ_{max} 226, 284 nm; IR (KBr) ν_{max} 3388, 3121, 1633, 1544, 1456, 1301, 1250 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.73 (s, 1H, NH), 11.18 (s, 1H, NH), 8.36 (m, 1H), 8.13 (d,

$J=2.5$ Hz, 1H), 8.04 (d, $J=8.8$ Hz, 1H), 7.85 (d, 1H), 7.55 (s, 1H), 7.52 (m, 1H), 7.25 (m, 2H), 6.98 (d, $J=2.3$ Hz, 1H), 6.82 (dd, $J=8.7$ and 2.3 Hz, 1H); MS (EI) m/z 345 (M^+); HRMS calcd. for $C_{20}H_{15}N_3OS$ 345.0936, found 345.0920.

2-[3′-(5′-Bromoindolyl)]-4-[3′-(6′-bromoindolyl)]thiazole (16). Yield 74%; mp 240.5–241.4 °C; UV (MeOH) λ_{max} 232, 268 nm; IR (KBr) ν_{max} 3429, 3205, 1616, 1542, 1416, 1329, 1287, 1242 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.89 (br, 1H, NH), 11.48 (br, 1H, NH), 8.56 (d, $J=1.9$ Hz, 1H), 8.23 (d, $J=8.6$ Hz, 1H), 8.18 (d, $J=2.3$ Hz, 1H), 7.98 (d, $J=1.7$ Hz, 1H), 7.69 (d, $J=1.7$ Hz, 1H), 7.63 (s, 1H), 7.50 (d, $J=8.6$ Hz, 1H), 7.37 (dd, $J=1.9$ and 8.6 Hz, 1H), 7.27 (dd, $J=1.8$ and 8.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 161.43, 149.98, 137.42, 137.25, 135.28, 135.12, 127.87, 127.70, 126.06, 125.45, 124.89, 123.83, 122.78, 122.34, 121.95, 114.47, 114.20, 113.30, 110.30; MS (EI) m/z 475/471 (M^+); HRMS calcd. for $C_{19}H_{11}Br_2N_3S$ 470.9040, found 470.9049.

2-(2′-Pyridinyl)-4-[3′-(5′-bromoindolyl)]thiazole (20). Yield 86%; mp 229.3–230.4 °C; UV (MeOH) λ_{max} 232, 266 nm; IR (KBr) ν_{max} 1567, 1479, 1453, 1433, 1278, 1228 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.67 (br, 1H, NH), 8.67 (m, 1H), 8.42 (d, $J=1.5$ Hz, 1H), 8.27 (d, $J=7.9$ Hz, 1H), 8.07 (d, $J=2.2$ Hz, 1H), 8.04 (dd, $J=1.5$ and 7.8 Hz, 1H), 7.99 (s, 1H), 7.54–7.46 (m, 2H), 7.32 (dd, $J=1.8$ and 8.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 167.42, 151.73, 150.58, 149.7, 137.75, 135.23, 126.40, 126.24, 126.07, 124.96, 124.18, 122.43, 118.99, 113.86, 113.14, 112.52, 110.48; MS (EI) m/z 354/356 (M^+).

2,4-Bis(3′-*N*-methylindolyl)thiazole (17). A mixture of 2,4-bis(3′-indolyl)thiazole **7** (149 mg, 0.473 mmol), iodomethane (1 mL) and anhydrous potassium carbonate (354 mg, 2.5 mmol) in dry acetone (10 mL) was refluxed for 16 h. Additional iodomethane (1 mL) and potassium carbonate (354 mg, 2.5 mmol) were added and then refluxed for overnight. After evaporation of the solvent, water (10 mL) added. The mixture was extracted with ether. The extracts were washed with saturated brine, dried over sodium sulfate. After working up, the crude product was purified by flash chromatography to give **17** (135 mg, 83%). Mp 174.2–174.6 °C; UV (MeOH) λ_{max} 228, 298 nm; IR (KBr) ν_{max} 1612, 1566, 1477, 1417, 1330, 1240 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.39 (m, 1H), 8.22 (d, 1H), 8.16 (s, 1H), 7.8 (s, 1H), 7.58 (s, 1H), 7.57–7.51 (m, 2H), 7.34–7.18 (m, 4H), 3.90 (s, 3H), 3.89 (s, 3H); MS (EI) m/z 343 (M^+); HRMS cald. for $C_{21}H_{17}N_3S$ 343.1144, found 343.1145.

3,6-Bis(3′-indolyl)pyrazine (23). 3-(α-Aza-acetyl)indole (400 mg, 2 mmol) in methanol (20 mL) containing acetic acid (0.5 mol) was hydrogenated over 5% Pd/C (100 mg) at 50 psi for over night. The catalyst was filtered. After removing the solvent, the crude product was subject to flash chromatography to afford **23** (420 mg, 68%). Mp 271–274 °C; UV (MeOH) λ_{max} 210, 244, 304 nm; ^1H NMR (DMSO-d_6) δ 11.21 (s, 1H), 8.33 (s, 1H), 8.19 (d, $J=7.5$ Hz, 1H), 7.48 (d, $J=7.5$ Hz, 1H), 7.23–7.17 (m, 3H); MS (EI), m/z 310 (M^+).

2-(3′-Indolyl)-*N*-[2-(3′-indolyl)-2-oxo-ethyl]-2-oxo-acetomide (27). To a solution of 3-(2-amino-acetyl)-indole (90 mg, 0.71 mmol) and triethyl amine (0.4 mL, 2.85 mmol) in CH_2Cl_2 (20 mL) was added indolyl glyoxylic chloride (190 mg, 0.91 mmol) at 0 °C. The mixture was stirred over night. After work up as usual, the crude product was purified by chromatography on silica gel to afford **27** (165 mg, 67%). Mp. 264–265 °C; UV (95%EtOH) λ_{max} 208, 242, 396 nm; IR (KBr) ν_{max} 3386, 3337, 2927, 2675, 2645, 1583, 1497, 1336 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.47 (t, $J=5.75$, 5.92 Hz, 1H, NH), 8.38 (d, $J=1.95$ Hz, 1H), 8.04 (d, $J=2.37$ Hz, 1H), 7.82 (m, 1H), 7.737 (m, 1H), 7.12–7.04 (m, 2H), 6.85 (m, 2H), 6.79 (m, 2H), 4.19 (d, $J=3.77$ Hz, 2H); MS (EI) m/z: 345 (M^+).

3,5-Bis(3′-indolyl)-2(1*H*)pyrazinone (28). Compound **27** (150 mg, 0.43 mmol) in methanol (5 mL) was added to liquid ammonia (10 mL) in autoclave. The mixture was heated at 80 °C for 3 days. After evaporation of ammonia, the crude product was chromatography on silica gel to afford **28** (65 mg, 63%). Mp >300 °C; UV (95%EtOH) λ_{max} 274, 402 nm; IR (KBr) ν_{max} 3555, 3410, 2920, 1640, 1619, 1531, 1499, 1455, 1418, 1332, 1237, 1161 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.27 (s, 1H, CONH), 11.64 (s, 1H, NH), 11.35 (s, 1H, NH), 8.90 (s, 1H), 8.79 (d, $J=7.69$ Hz, 1H), 8.04 (d, $J=7.87$ Hz, 1H), 7.85 (s, 1H), 7.52–7.47 (m, 3H), 7.24–7.08 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 153.62, 150.31, 136.82, 136.67, 136.25, 131.31, 131.14, 129.97, 125.98, 124.50, 123.20, 122.56, 122.15, 121.40, 120.43, 119.89, 119.89, 119.33, 116.24, 113.33, 111.83; HRMS calcd. for $C_{20}H_{14}N_4O$ 326.1167, found 326.1178.

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