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Brønsted Acid Catalyzed Bisindolization of α-Amido Acetals: Synthesis and Anticancer Activity of Bis(indolyl)ethanamino Derivatives

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A Brønsted acid catalyzed bisindolization reaction with suitable α-amido acetals that tolerates a wide range of indoles is reported. The method allows rapid access to the biologically relevant bisindolyl ethanamine scaffold in good to excellent yields upon mild amide basic hydrolysis. In preliminary pharmacological studies, some of these compounds display cytotoxic activity in U937 cancer cells. The marine natural alkaloid 2,2-di(6′-bromo-3′-indolyl)-ethylamine was the most active compound and could be a lead candidate for further optimization. For the first time, the biological role of this brominated bisindole marine alkaloid is presented.

Introduction

Marine organisms such as corals, sponges, ascidians, and tunicates are rich sources of biologically active molecules.[1] The unprecedented structures of these compounds and their potent activity against a broad number of pharmacological targets make them excellent synthetic targets and very good lead candidates. Among the various structural classes, the marine indole alkaloids have received much attention due to the significant activity that they have elicited in cancer and cytotoxicity assays and also for their unexplored potential on neurological targets and behavioral diseases.[2] In the early 1990s, compounds containing brominated indole rings, such as 2,2-bis(6-bromo-3-indolyl) ethylamine (**1**), were isolated from the Californian tunicate *Didemnum candidum* and the New Caledonian sponge *Orina* sp.[3] However, no biological studies have been reported with this brominated bisindole alkaloid.[4] On the other hand, several natural products with anticancer activity (vibrindole A, streptindole, etc. Figure 1) share a common 3,3′-diindolylmethane (DIM) molecular unit.[5] DIM itself is known to exhibit antiproliferative as well as apoptotic activities against various cancer cells,[6] and it is presently in clinical trials for the treatment of prostate and breast cancer.[7] However, the widespread pharmacological use of DIM is limited owing to its poor efficacy and unacceptable pharmacokinetic profile. DIM has a low oral bioavailability due to its highly lipophilic nature and chemical instability in the stomach. The presence of the alkylamino side chain in the marine alkaloid **1** could play a pivotal role not only for possible enhancement of therapeutic activities, but it could improve its solubility in water and impart acid resistance. It should also be pointed out that the side chain allows the possibility of further synthetic transformations by amino derivatization and/or conjugation. Moreover, given the high cytotoxicity typical of bromine-containing derivatives,[8] the presence of two bromoindole units in compound **1** warrants its investigation as an anticancer agent.

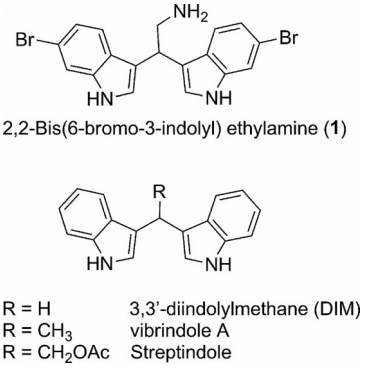

Figure 1. The marine natural product **1** and some natural anticancer agents having the DIM molecular unit.

Various protocols for the synthesis of bisindolylethylamine derivatives have been reported. The majority of the synthetic methods involve Friedel–Crafts alkylation of indoles with nitrogen-protected glycinaldehydes[9] or their synthetic equivalents such as nitrones.[10] Although the protection of nitrogen prevents undesired inter- and intramolecu-

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lar self-condensation reactions, it can also have a detrimental effect on the final deprotection step of sensitive bis-indole substrates. An alternative method to obtain bisindolyl ethylamine derivatives could be the selective reduction of bis(indol-3-yl)nitroethane prepared by the Michael addition of indoles on nitrovinylindole.[11] However, the reduction of the nitro group to the corresponding free amine was found to be difficult, and in situ acylation derivatization was needed. Yet, although all of these synthetic strategies are useful, they have some limitations in terms of the requirement for stoichiometric amounts of promoters or activators (e.g., Lewis or Brønsted acids), and/or the deprotection step is low yielding and limited by poor functional-group tolerance.[12] Consequently, the development of new, catalytic and efficient methods to broaden the substrate scope and enhance the selective construction of such molecules is highly desirable. As part of our ongoing research program to develop new methodologies for the synthesis of bisindolyl derivatives[13] and to determine the mechanism by which these molecules exhibit their anticancer activity,[14] herein we report a practical and versatile organocatalytic synthetic procedure for the synthesis of bisindolylethylamine derivatives. The in vitro cytotoxicity was also evaluated for some of these derivatives.

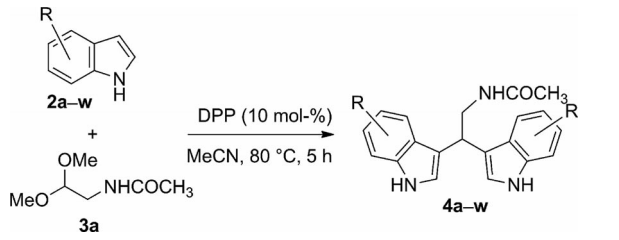
Results and Discussion

For the synthesis of the bisindolylethylamine derivatives, we explored a novel double indolization protocol with the readily available (acetylamino)acetaldehyde dimethyl acetal **3a**[15] as a suitable two-carbon, nitrogen-containing electrophile in the presence of diphenyl phosphate (DPP) as the organocatalyst.[16] To optimize the reaction conditions, we initially examined the effects of a range of parameters, including catalyst loading, concentration, reaction temperature, time, and solvent. Regarding the amount of catalyst, it was observed that as little as 5 mol-% DPP was sufficient to promote the formation of *N*-[2,2-di(1*H*-indol-3-yl)]acetamide (**4a**) in excellent yield, although long reaction times (usually 72 h) were needed for full conversion. However, we found that the reaction performed in acetonitrile (5 h, 1 M solution) in the presence of 10 mol-% DPP provided the best results in terms of reaction time and yield (Table 1, entry 1). Notably, the newly designed reaction did not proceed in the absence of catalyst, and the presence of water had a detrimental effect. After establishing suitable conditions for the reaction, we demonstrated the generality of this catalytic process for the synthesis of various *N*-acetyl bisindolyethylamines (Table 1).

A range of commercially available indoles with either electron-donating or -withdrawing functional groups on the benzo ring as well as alkyl and aryl substituents at the C-2 position were highly compatible with the procedure described above (Table 1). In contrast, no reactivity was observed with indoles bearing an electron-withdrawing group in the C-2 position, such as 2-indole-carboxylic acid or its ester (Table 1, entries 4 and 5), probably due to a combination of steric hindrance and electron deficiency. In particular, the reaction proceeded smoothly and the products were obtained in very good yields by using methyl- (**2b**, **2c**, **2t**, and **2v**) or methoxy- (**2i** and **2m**) indoles. Furthermore, various halogens, such as fluoro- (**2j**), chloro- (**2k** and **2r**) and bromo- (**2h**, **2l**, **2s** and **2u**) groups were well tolerated in different indole positions, and afforded the corresponding products **4j**, **4k**, **4r**, **4h**, **4l**, **4s**, and **4u** in 48–98% yield (Table 1, entries 10, 11, 19, 8, 12, 20, and 22). High catalytic activities were also found in the coupling of indoles bearing strong electron-withdrawing nitro and methoxycarbonyl groups (Table 1, entries 16 and 17). When 1*H*-pyrrolo-[2,3-*b*]pyridine (**2w**) was used as an alternative nucleophile, the desired product **4w** was not obtained (Table 1, entry 24). It is noteworthy that the formation of polymerization products as byproducts was not observed in any of these transformations. Furthermore, the outstanding compatibility of the functional groups, OMe, Br, Cl, COOMe, B (pinacolate), I, and NO_2, is remarkable. Among them, the carbon-OMe, -boron, and -halogen bonds should be useful for further elaboration as a carbon–carbon bond.

We then applied this reaction strategy for the total synthesis of the marine natural product **1**. For this purpose, we first examined the reaction of 6-bromoindole with N-unprotected aminoacetaldehyde dimethyl acetal by using

Table 1. Substrate scope.

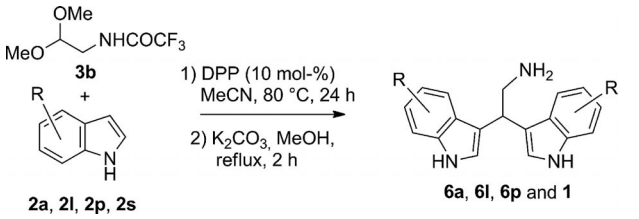


Entry	Indole	R	Product[c]	Yield [%][a]
1	**2a**	H	**4a**	99
2	**2b**	*N*-Me	**4b**	98
3	**2c**	2-Me	**4c**	88
4	**2d**	2-COOH	**4d**	n.r.[b]
5	**2e**	2-COOMe	**4e**	n.r.[b]
6	**2f**	2-Ph	**4f**	94
7	**2g**	2-Me, 5-Cl	**4g**	89
8	**2h**	4-Br	**4h**	75
9	**2i**	4-OMe	**4i**	42
10	**2j**	5-F	**4j**	98
11	**2k**	5-Cl	**4k**	48
12	**2l**	5-Br	**4l**	98
13	**2m**	5-OMe	**4m**	99
14	**2n**	5-OH	**4n**	29
15	**2o**	5-Bpin	**4o**	67
16	**2p**	5-COOMe	**4p**	53
17	**2q**	5-NO_2	**4q**	45
19	**2r**	6-Cl	**4r**	65
20	**2s**	6-Br	**4s**	90
21	**2t**	6-Me	**4t**	87
22	**2u**	7-Br	**4u**	68
23	**2v**	7-Me	**4v**	98
24	**2w**	7-aza	**4w**	n.r.[b]

[a] Isolated yield. [b] n.r.: no reaction.

the reaction conditions described above, but the desired product was not obtained. On the other hand, the acetamido moiety in **3a** is well-known for its resistance to hydrolysis even at low pH values, as well as its relative stability in alkaline media. This characteristic was confirmed in failed attempts to hydrolyze compound **4s**, and a complex mixture of dimeric and oligomeric products was observed. It is known that bis-indolylmethanes are substantially more stable in both weakly acidic and neutral aqueous solutions than at very low pH. In seeking an alternative strategy to protect the amino functional group, we opted for the trifluoroacetyl group, not only because it is reputed to be one of the most labile N-protective amides available[17] but also because it was expected to increase the electrophilicity of the acetals, thus allowing for even milder bisindolization reaction conditions. Moreover, the trifluoroacetyl group can be conveniently removed under very mild basic conditions, which is orthogonal to most standard substituents, and is compatible with the sensitive bisindole scaffold. These reports led us to test the reactivity and selectivity of acetal **3b**, containing a trifluoroacetyl group, in the bisindolization of α-amino acetals. The bisindolization reaction with *N*-trifluoroacetylamino acetal **3b** proceeded well in all cases (Table 2, entries 1–4), albeit more slowly than with **3a**.

Table 2. Bisindolization reaction with **3b** and subsequent mild hydrolysis.



Entry	Indole	R	Product	Yield [%][a]
1	**2a**	H	**6a**	55
2	**2l**	5-Br	**6l**	88
3	**2p**	5-COOMe	**6p**	68
4	**2s**	5-Br	**1**	82

[a] Isolated yield.

Interestingly, the *N*-trifluoroacetyl protecting group proved to be stable under the reaction conditions and was easily removed by simple basic hydrolysis, which was performed directly on the crude trifluoroacetamido derivatives, to give bis-indolylethanamine derivatives **6** in very high yield. This reaction sequence was successfully applied to the synthesis of the natural marine bisindole alkaloid **1**. The overall yield of this synthesis was found to be very high (82%) in comparison to reported methods.[9b,10b] An area of major concern in considering the production and utilization of bisindoles as pharmaceuticals is their instability at normal gastric pH (pH 1–2). However, the incorporation of an alkylamino side chain in these compounds can counteract the instability under acidic conditions. Stability studies in acidic medium revealed that compound **1** was surprisingly stable in aqueous HCl solution. For example, heating a solution of **1** in deuterated dimethyl sulfoxide ([D_6]-DMSO) with DCl at 50 °C for 2 h caused no change in the ^{1}H NMR spectrum, suggesting that the undesired acid-catalyzed elimination of the indole molecule and consequent formation of indoleninium cations (generally observed with other bisindolemethanes) did not occur.

We tested some of our compounds for cytotoxicity, including **1**, **4s**, **8**, the reference parent compound DIM, and two other representative 3,3′-bisindoles: 6,6′-dibromo,3,3′-diindolylmethane (**9**)[18] and the natural product 2,2-bis(3,3′-indolyl)propionic acid (**10**) (Figure 2).[13]

Potential anticancer activity was evaluated on immortalized promonocytic leukemia cells (U937). Cellular viability was evaluated by a trypan blue dye exclusion assay after treatment for 48 h at final compound concentrations of 1 and 5 μM (Figure 3, Panel A).[19] Moreover, to evaluate more accurately the biological response, dose–response experiments were performed by treating U937 cells with the most effective compounds for 48 h (Figure 3, Panel B). Some of the tested compounds, including **1** and **8**, were found to reduce cell count in comparison to the DMSO control. Interestingly, the natural compound **1**, exhibited the highest anticancer potency, with 50% growth inhibition (GI50) values in the 1–1.3 μM range. The results of the present study indicated the importance of incorporating the alkylamino side chain into the bioactive parent DIM. There was also evidence that locating a bromine atom at position

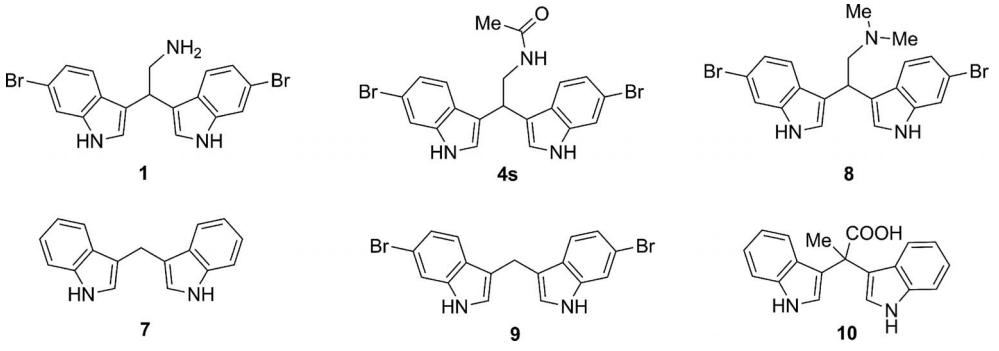


Figure 2. Compounds tested for anticancer activity.

6 of the indole favored antiproliferative activity, whereas N-acetylation strongly decreased the antiproliferative activity. The biological activity of these compounds was further investigated by analyzing their effects on cell cycle progression.[20] Cell treatments with **1** and **8**, each at 1 and 5 μM, for 48 h induced cell cycle perturbation. We monitored a progressive accumulation of cells in the G1 phase concomitantly with a decrease of cells in the G2/M phase (Figure S1, in the Supporting Information). Cytotoxicity was also monitored and quantified by evaluating the increase of hypodiploid cells. Both compounds **1** and **8** induced strong accumulation of hypodiploid cells (Figure S2, in the Supporting Information). As observed in the cell survival studies, the other compounds tested did not coherently induce cell cycle alterations or hypodyploid cell accumulation.

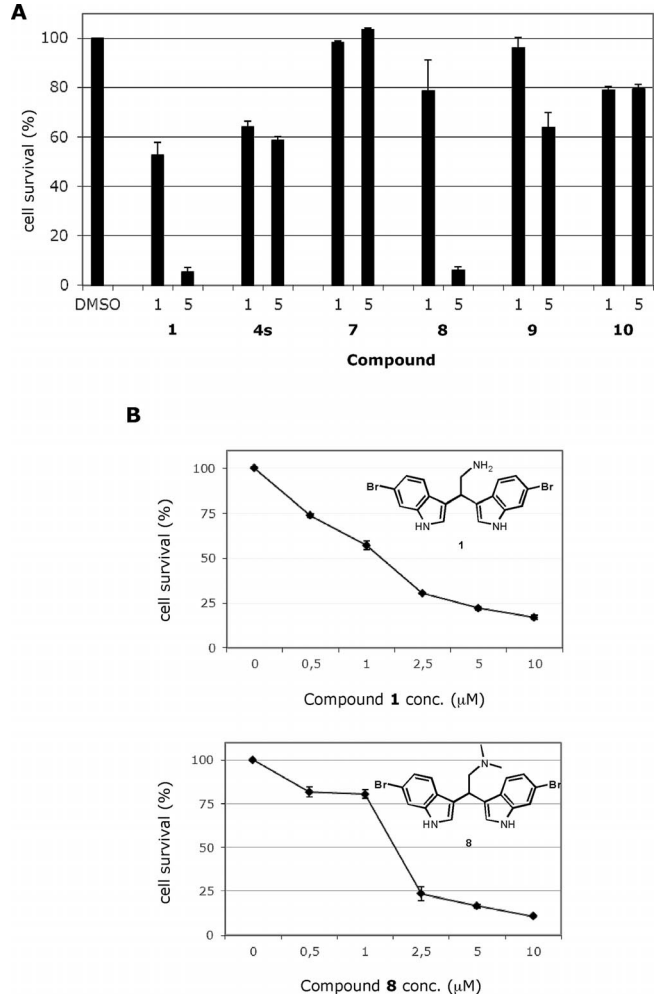


Figure 3. Reduction of cell survival induced by treatment with the indicated compounds. (A) Treatment was carried out at the indicated concentrations and repeated every 24 h, and analyzed by a trypan blue dye exclusion assay. The data are reported as mean ± standard deviation resulting from three independent experiments. (B) Dose–response experiments for compounds **1** (upper panel) and **8** (lower panel).

Conclusions

A simple and convenient method has been developed for the preparation of a variety of substituted bisindolyl-ethylamine derivatives through direct coupling of indoles with (acetylamino)acetaldehyde dimethyl acetal by employing a commercially available organocatalyst. The present protocol possesses several advantages over common reported methods, such as the use of an inexpensive catalyst, readily available starting materials, broad substrate scope, and excellent chemoselectivity. The choice of *N*-trifluoroacetyl protecting group, which is easily removed by mild and selective basic hydrolysis, allowed the free amines **6a**, **6l**, **6p** and natural product **1** to be obtained in very high yield. Several of the new bis-indolyl ethylamine derivatives were found to have an interesting biological activity in U937 tumor cells, and C-6 brominated marine natural product **1** was found to be the most active. The present study demonstrates, for the first time, the biological role of this marine alkaloid. The presence of bromine atoms and the ethylamine chain seem to have a fundamental synergic effect for the anticancer activity.

Experimental Section

Material and Methods: All reactions were run under an air atmosphere unless otherwise noted. Column chromatography purifications were performed in flash conditions using Merck 230–400 mesh silica gel. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel plates (silica gel 60 F_{254}), which were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM) or *p*-anisaldehyde. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 200 spectrometer, using $CDCl_3$, CD_3OD, [D_6]acetone, or [D_6]DMSO as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (*J* values) are given in Hertz [Hz]. ESI-MS spectra were recorded with a Waters Micromass ZQ instrument. IR spectra were obtained with a Nicolet Avatar 360 FTIR spectrometer; absorbance values are reported in cm^{-1}. Melting points were determined with a Buchi SMP-510 capillary melting point apparatus and are uncorrected. Elemental analyses were performed with a Carlo Erba analyzer and the results are within ±0.3 of the theoretical values (C, H, N). Indoles **2a**–**n** and **2p**–**w** are commercially available; indole **2o** and acetals **3a**–**b** were prepared as described previously.[15]

Diphenyl Phosphate Catalyzed Coupling of Indoles with (Acetylamino)acetaldehyde Dimethyl Acetal; General Procedure for the Synthesis of *N*-[2,2-Di(1*H*-indol-3-yl)ethyl]acetamide Derivatives 4a–w: Diphenyl phosphate (0.01 mmol) was added to a solution of the appropriate indole **2a**–**w** (0.2 mmol) and (acetylamino)acetaldehyde dimethyl acetal (**3a**; 0.1 mmol) in anhydrous acetonitrile (0.1 mL), and the resulting mixture was stirred at 80 °C for 5 h in a sealed tube, monitoring the progress of the reaction by TLC and HPLC-MS. After cooling to room temperature, saturated aqueous $NaHCO_3$ (15 mL) and dichloromethane (15 mL) were added and the two phases were separated. The aqueous solution was extracted with dichloromethane (3 × 15 mL). After drying over dry Na_2SO_4, the combined organic phases were concentrated in vacuo and the

resulting crude product was purified by column flash chromatography on silica gel.

***N*-[2,2-Di(1*H*-indol-3-yl)ethyl]acetamide (4a):** Yield: 31 mg (99%); white solid. The chemical-physical data are in agreement to those reported.[9c] ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 1.88 (s, 3 H, NHCOCH_3), 4.00 (dd, J_1 = 5.5, J_2 = 7.0 Hz, 2 H, CHCH_2NH), 4.71 (dd, J_1 = J_2 = 7.0 Hz, 1 H, CHCH$_2$NH), 5.66 (br. t, J = 5.5 Hz, 1 H, NHCOCH$_3$), 6.90 (d, J = 2.0 Hz, 2 H, Ar-H), 7.04 (ddd, J_1 = 1.0, J_2 = J_3 = 8.0 Hz, 2 H, Ar-H), 7.18 (ddd, J_1 = 1.0, J_2 = J_3 = 8.0 Hz, 2 H, Ar-H), 7.33 (dd, J_1 = 1.0, J_2 = 8.0 Hz, 2 H, Ar-H), 7.59 (dd, J_1 = 1.0, J_2 = 8.0 Hz, 2 H, Ar-H), 7.89 (br. d, J = 2.0 Hz, 2 H, NH) ppm.

***N*-[2,2-Bis(1-methyl-1*H*-indol-3-yl)ethyl]acetamide (4b):** Yield: 34 mg (98%); white solid. The chemical-physical data are in agreement to those reported.[9c] ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 1.80 (s, 3 H, NHCOCH_3), 3.64 (s, 6 H, NCH$_3$), 3.94 (dd, J_1 = 6.0, J_2 = 7.0 Hz, 2 H, CHCH_2NH), 4.64 (dd, J_1 = J_2 = 7.0 Hz, 1 H, CHCH$_2$NH), 5.66 (br. t, J = 6.0 Hz, 1 H, NHCOCH$_3$), 6.80 (s, 2 H, Ar-H), 6.99 (ddd, J_1 = 1.5, J_2 = 7.0, J_3 = 8.0 Hz, 2 H, Ar-H), 7.15 (ddd, J_1 = 1.0, J_2 = J_3 = 8.0 Hz, 2 H, Ar-H), 7.23 (d, J = 8.0 Hz, 2 H, Ar-H), 7.56 (d, J = 7.0 Hz, 2 H, Ar-H) ppm.

***N*-[2,2-Bis(2-methyl-1*H*-indol-3-yl)ethyl]acetamide (4c):** Yield: 30 mg (88%); white solid. The chemical-physical data are in agreement to those reported.[9c] ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 1.71 (s, 3 H, NHCOCH_3), 2.30 (s, 6 H, Ar-CH$_3$), 3.90 (dd, J_1 = 5.0, J_2 = 8.0 Hz, 2 H, CHCH_2NH), 4.57 (dd, J_1 = J_2 = 8.0 Hz, 1 H, CHCH$_2$NH), 6.76 (dd, J_1 = J_2 = 7.0 Hz, 2 H, Ar-H), 6.88 (dd, J_1 = J_2 = 7.0 Hz, 2 H, Ar-H), 7.16 (d, J = 7.0 Hz, 2 H, Ar-H), 7.33 (d, J = 7.0 Hz, 2 H, Ar-H), 7.74 (br. t, J = 5.0 Hz, 1 H, NHCOCH$_3$), 10.63 (br. s, 2 H, NH) ppm.

***N*-[2,2-Bis(2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (4f):** Eluent: ethyl acetate/cyclohexane (3:7), yield 44 mg (94%); white solid; m.p. 209–211 °C; TLC: R_f = 0.38 (ethyl acetate/cyclohexane, 1:1; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3355, 2934, 1650 cm^{-1}. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 1.55 (s, 3 H, NHCOCH_3), 4.02 (dd, J_1 = 5.0, J_2 = 8.0 Hz, 2 H, CHCH_2NH), 5.03 (dd, J_1 = J_2 = 8.0 Hz, 1 H, CHCH$_2$NH), 6.83 (dd, J_1 = J_2 = 8.0 Hz, 2 H, Ar-H), 7.02 (dd, J_1 = J_2 = 7.0 Hz, 2 H, Ar-H), 7.24 (m, 10 H, , 2 H, Ar-H), 7.57 (d, J = 8.0 Hz, 2 H, Ar-H), 7.66 (br. t, J = 5.0 Hz, 1 H, NHCOCH$_3$), 11.09 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]-DMSO, 25 °C): δ = 22.8, 34.9, 44.3, 111.6, 113.7, 119.0, 120.9, 121.2, 127.7, 128.1, 128.5, 129.2, 133.9, 135.9, 136.5, 169.7 ppm. MS (ESI): m/z = 468 [M – H]$^-$, 492 [M + Na]$^+$. $C_{32}H_{27}N_3O$ (469.58): calcd. C 81.85, H 5.80, N 8.95; found C 81.72, H 5.71, N 9.06.

***N*-[2,2-Bis(5-chloro-2-methyl-1*H*-indol-3-yl)ethyl]acetamide (4g):** Eluent: ethyl acetate, yield 37 mg (89%); brownish solid; m.p. 230–232 °C; TLC: R_f = 0.36 (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3412, 1642, 1371 cm^{-1}. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 1.75 (s, 3 H, NHCOCH_3), 2.31 (s, 6 H, Ar-CH$_3$), 3.87 (dd, J_1 = 5.0, J_2 = 7.5 Hz, 2 H, CHCH_2NH), 4.56 (dd, J_1 = J_2 = 7.5 Hz, 1 H, CHCH$_2$NH), 6.93 (dd, J_1 = 2.0, J_2 = 8.5 Hz, 2 H, Ar-H), 7.23 (d, J = 8.5 Hz, 2 H, Ar-H), 7.28 (d, J = 2.0 Hz, 2 H, Ar-H), 7.88 (br. t, J = 5.0 Hz, 1 H, NHCOCH$_3$), 11.00 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 12.7, 23.0, 34.1, 43.3, 111.5, 112.3, 117.7, 119.9, 123.1, 129.3, 134.0, 134.4, 169.8 ppm. MS (ESI): m/z (%) = 412 (100), 414 (65) [M – H]$^-$. $C_{22}H_{21}Cl_2N_3O$ (414.33): calcd. C 63.77, H 5.11, N 10.14; found C 63.51, H 5.13, N 10.02.

***N*-[2,2-Bis(4-bromo-1*H*-indol-3-yl)ethyl]acetamide (4h):** Eluent: ethyl acetate/cyclohexane (8:2), yield 36 mg (75%); yellowish solid; m.p. 199–200 °C; TLC: R_f = 0.50 (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3315, 1689 cm^{-1}. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 1.75 (s, 3 H, NHCOCH_3), 3.73 (dd, J_1 = 5.5, J_2 = 7.5 Hz, 2 H, CHCH_2NH), 5.84 (dd, J_1 = J_2 = 7.5 Hz, 1 H, CHCH$_2$NH), 6.93 (d, J = 2.5 Hz, 2 H, Ar-H), 6.94 (dd, J_1 = 7.5, J_2 = 8.0 Hz, 2 H, Ar-H), 7.11 (dd, J_1 = 1.0, J_2 = 7.5 Hz, 2 H, Ar-H), 7.36 (dd, J_1 = 1.0, J_2 = 8.0 Hz, 2 H, Ar-H), 7.97 (br. t, J = 5.5 Hz, 1 H, NHCOCH$_3$), 11.14 (br. d, J = 2.5 Hz, 2 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 23.1, 33.7, 44.9, 111.6, 113.5, 118.1, 122.3, 123.1, 124.7, 125.3, 138.7, 169.5 ppm. MS (ESI): m/z (%) = 472 (50), 474 (100), 476 (50). $C_{20}H_{17}Br_2N_3O$ (475.18): calcd. C 50.57, H 3.61, N 8.84; found C 50.71, H 3.55, N 8.69.

***N*-[2,2-Bis(4-methoxy-1*H*-indol-3-yl)ethyl]acetamide (4i):** Eluent: ethyl acetate/cyclohexane (8:2), yield 16 mg (42%); brownish solid; m.p. 134–136 °C; TLC: R_f = 0.46 (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3402, 2930, 1655, 1508 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 1.81 (s, 3 H, NHCOCH_3), 3.80 (s, 3 H, OCH$_3$), 3.82–3.96 (m, 2 H, CHCH_2NH), 5.51 (dd, J_1 = J_2 = 7.5 Hz, 1 H, CHCH$_2$NH), 6.47 (d, J = 7.5 Hz, 2 H, Ar-H), 6.51 (br. s, 1 H, NHCOCH$_3$), 6.69 (d, J = 2.0 Hz, 2 H, Ar-H), 6.92 (d, J = 8.0 Hz, 2 H, Ar-H), 7.06 (dd, J_1 = 7.5, J_2 = 8.0 Hz, 2 H, Ar-H), 8.26 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 20 °C): δ = 23.3, 34.2, 46.5, 55.2, 99.7, 104.8, 117.2, 119.0, 120.8, 122.4, 138.0, 154.4, 170.3 ppm. MS (ESI): m/z (%) = 378 [M + H]$^+$, 400 [M + Na]$^+$, 376 [M – H]$^-$, 436 [M + CH$_3$COO]$^-$. $C_{22}H_{23}N_3O_3$ (377.44): calcd. C 70.01, H 6.14, N 11.13; found C 69.83, H 6.09, N 11.20.

***N*-[2,2-Bis(5-fluoro-1*H*-indol-3-yl)ethyl]acetamide (4j):** Eluent: ethyl acetate/cyclohexane (8:2), yield 35 mg (98%); brownish oil; m.p. 140–142 °C; TLC: R_f = 0.41 (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3421, 3297, 1647, 1485 cm^{-1}. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 1.75 (s, 3 H, NHCOCH_3), 3.75 (dd, J_1 = 5.5, J_2 = 7.5 Hz, 2 H, CHCH_2NH), 4.51 (dd, J_1 = J_2 = 7.5 Hz, 1 H, CHCH$_2$NH), 6.86 (ddd, J_1 = 2.5, J_2 = J_3 = 9.0 Hz, 2 H, Ar-H), 7.18 (dd, J_1 = 2.5, J_2 = 10.5 Hz, 2 H, Ar-H), 7.31 (dd, J_1 = 5.0, J_2 = 9.0 Hz, 2 H, Ar-H), 7.31 (d, J = 2.0 Hz, 2 H, Ar-H), 7.94 (br. t, J = 5.5 Hz, 1 H, NHCOCH$_3$), 10.95 (br. d, J = 2.0 Hz, 2 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 23.1, 34.3, 43.8, 103.9 (d, J = 23 Hz, 1 C), 109.3 (d, J = 26 Hz, 1 C), 112.7 (d, J = 10 Hz, 1 C), 116.7 (d, J = 5.0 Hz, 1 C), 125.1, 127.3 (d, J = 10 Hz, 1 C), 133.6, 156.8 (d, J = 229 Hz, 1 C), 169.8 ppm. MS (ESI): m/z = 354 [M + H]$^+$, 376 [M + Na]$^+$, 352 [M – H]$^-$. $C_{20}H_{17}F_2N_3O$ (353.37): calcd. C 70.01, H 6.03, N 11.15; found C 69.83, H 6.09, N 11.20.

***N*-[2,2-Bis(5-chloro-1*H*-indol-3-yl)ethyl]acetamide (4k):** Eluent: ethyl acetate/cyclohexane (7:3), yield 19 mg (48%); brownish solid; m.p. 131–132 °C; TLC: R_f = 0.53 (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3422, 3296, 1649, 1460 cm^{-1}. ^{1}H NMR (200 MHz, CD_3OD, 20 °C): δ = 1.83 (s, 3 H, NHCOCH_3), 3.95 (dd, J_1 = 5.0, J_2 = 7.5 Hz, 2 H, CHCH_2NH), 4.73 (dd, J_1 = J_2 = 7.5 Hz, 1 H, CHCH$_2$NH), 7.05 (dd, J_1 = 2.0, J_2 = 8.5 Hz, 2 H, Ar-H), 7.27 (br. t, J = 5.0 Hz, 1 H, NHCOCH$_3$), 7.32 (d, J = 2.0 Hz, 2 H, Ar-H), 7.39 (d, J = 8.5 Hz, 2 H, Ar-H), 7.60 (d, J = 2.0 Hz, 2 H, Ar-H), 10.30 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, CD_3OD, 20 °C): δ = 22.1, 34.2, 43.8, 112.7, 116.5, 118.5, 121.2, 123.8, 124.3, 128.3, 135.5, 169.3 ppm. MS (ESI): m/z (%) = 384 (100), 386 (65) [M – H]$^-$. $C_{20}H_{17}Cl_2N_3O$ (386.28): calcd. C 62.19, H 4.44, N 10.88; found C 61.99, H 4.51, N 10.85.

***N*-[2,2-Bis(5-bromo-1*H*-indol-3-yl)ethyl]acetamide (4l):** Yield: 47 mg (98%); brownish solid. The chemical-physical data are in agreement to those reported.[9c] ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 1.84 (s, 3 H, NHCOCH_3), 3.89 (dd, J_1 = 5.5, J_2 = 7.0 Hz, 2 H,

CHCH_2NH), 4.51 (dd, $J_1 = J_2 = 7.0$ Hz, 1 H, CHCH$_2$NH), 5.55 (br. t, $J = 5.5$ Hz, 1 H, NHCOCH$_3$), 6.94 (d, $J = 2.0$ Hz, 2 H, Ar-H), 7.16–7.20 (m, 4 H, Ar-H), 7.57 (s, 2 H, Ar-H), 8.28 (br. s, $J = 2.0$ Hz, 2 H, NH) ppm.

***N*-[2,2-Bis(5-methoxy-1*H*-indol-3-yl)ethyl]acetamide (4m):** Yield: 37 mg (99%); white solid. The chemical-physical data are in agreement to those reported.[9c] ^{1}H NMR (200 MHz, [D$_6$]DMSO, 20 °C): $\delta = 1.76$ (s, 3 H, NHCOCH_3), 3.68 (s, 6 H, Ar-OCH$_3$), 3.75 (dd, $J_1 = 5.0$, $J_2 = 7.0$ Hz, 2 H, CHCH_2NH), 4.51 (dd, $J_1 = J_2 = 7.0$ Hz, 1 H, CHCH$_2$NH), 6.68 (dd, $J_1 = 2.5$, $J_2 = 8.5$ Hz, 2 H, Ar-H), 7.03 (d, $J = 2.5$ Hz, 2 H, Ar-H), 7.11 (d, $J = 2.0$ Hz, 2 H, Ar-H), 7.21 (d, $J = 8.5$ Hz, 2 H, Ar-H), 7.91 (br. t, $J = 5.0$ Hz, 1 H, NHCOCH$_3$), 10.64 (br. d, $J = 2.0$ Hz, 2 H, NH) ppm.

***N*-[2,2-Bis(5-hydroxy-1*H*-indol-3-yl)ethyl]acetamide (4n):** Eluent: ethyl acetate; Yield: 10 mg (29%); brownish solid; m.p. 153–155 °C; TLC: $R_f = 0.42$ (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3392, 2924, 1736, 1365 cm^{-1}. ^{1}H NMR (200 MHz, [D$_6$]acetone, 20 °C): $\delta = 1.82$ (s, 3 H, NHCOCH_3), 3.88 (dd, $J_1 = 5.0$, $J_2 = 7.5$ Hz, 2 H, CHCH_2NH), 4.55 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H, CHCH$_2$NH), 6.67 (dd, $J_1 = 2.5$, $J_2 = 8.5$ Hz, 2 H, Ar-H), 7.02 (d, $J = 2.5$ Hz, 2 H, Ar-H), 7.05 (d, $J = 2.0$ Hz, 2 H, Ar-H), 7.12 (br. t, $J = 5.0$ Hz, 1 H, NHCOCH$_3$), 7.19 (d, $J = 8.5$ Hz, 2 H, Ar-H), 7.67 (s, 2 H, Ar-OH), 9.75 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]acetone, 20 °C): $\delta = 22.1$, 34.5, 43.7, 103.4, 111.3, 111.5, 116.1, 122.9, 128.1, 131.8, 150.4, 169.1 ppm. MS (ESI): m/z = 372 [M + Na]$^+$, 348 [M – H]$^-$, 408 [M + CH$_3$COO]$^-$. $C_{20}H_{19}N_3O_3$ (349.39): calcd. C 68.75, H 5.48, N 12.03; found C 68.56, H 5.57, N 11.99.

***N*-{2,2-Bis[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl]ethyl}acetamide (4o):** Eluent: ethyl acetate, yield 38 mg (67%); white solid; m.p. 243–245 °C; TLC: $R_f = 0.50$ (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3425, 1630, 1356 cm^{-1}. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): $\delta = 1.33$ (s, 24 H, Bpin), 1.80 (s, 3 H, NHCOCH_3), 3.73 (dd, $J_1 = 5.5$, $J_2 = 7.5$ Hz, 2 H, CHCH_2NH), 4.80 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H, CHCH$_2$NH), 7.10 (d, $J = 2.0$ Hz, 2 H, Ar-H), 7.38 (d, $J = 8.0$ Hz, 2 H, Ar-H), 7.46 (d, $J = 8.0$ Hz, 2 H, Ar-H), 7.96 (s, 2 H, Ar-H), 8.02 (br. t, $J = 5.5$ Hz, 1 H, NHCOCH$_3$), 11.04 (br. d, $J = 2.0$ Hz, 2 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 20 °C): $\delta = 23.1$, 25.2, 29.5, 32.0, 83.5, 111.4, 117.6, 123.2, 123.2, 126.6, 127.0, 127.5, 138.9, 169.6 ppm. MS (ESI): m/z (%) = 567 (55), 568 (100), 569 (40) [M – H]$^-$. $C_{32}H_{41}B_2N_3O_5$ (569.31): calcd. C 67.51, H 7.26, N 7.38; found C 67.71, H 7.21, N 7.32.

Dimethyl 3,3′-(2-Acetamidoethane-1,1-diyl)bis(1*H*-indole-5-carboxylate) (4p): Eluent: ethyl acetate/dichloromethane (8:2), yield 23 mg (53%); white solid; m.p. 247–249 °C; TLC: $R_f = 0.26$ (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3359, 2923, 1688 cm^{-1}. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): $\delta = 1.75$ (s, 3 H, NHCOCH_3), 3.73 (dd, $J_1 = 5.5$, $J_2 = 7.0$ Hz, 2 H, CHCH_2NH), 3.79 (s, 6 H, Ar-COOCH$_3$), 4.74 (dd, $J_1 = J_2 = 7.0$ Hz, 1 H, CHCH$_2$NH), 7.30 (d, $J = 2.0$ Hz, 2 H, Ar-H), 7.41 (d, $J = 8.5$ Hz, 2 H, Ar-H), 7.68 (dd, $J_1 = 1.5$, $J_2 = 8.5$ Hz, 2 H, Ar-H), 8.01 (br. t, $J = 5.5$ Hz, 1 H, NHCOCH$_3$), 8.19 (d, $J = 1.5$ Hz, 2 H, Ar-H), 11.31 (br. d, $J = 2.0$ Hz, 2 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]-DMSO, 25 °C): $\delta = 22.9$, 33.7, 41.1, 53.6, 111.9, 118.2, 120.2, 121.8, 122.4, 124.8, 126.8, 139.5, 167.7, 169.8 ppm. MS (ESI): m/z = 434 [M + H]$^+$, 451 [M + NH$_4$]$^+$, 456 [M + Na]$^+$, 432 [M – H]$^-$. $C_{24}H_{23}N_3O_5$ (433.46): calcd. C 66.50, H 5.35, N 9.69; found C 66.71, H 5.31, N 9.62.

***N*-[2,2-Bis(5-nitro-1*H*-indol-3-yl)ethyl]acetamide (4q):** Yield: 18 mg (45%); yellow solid. The chemical-physical data are in agreement to those reported.[9c] ^{1}H NMR (200 MHz, [D$_6$]acetone, 20 °C): $\delta =$ 1.70 (s, 3 H, NHCOCH_3), 3.90 (dd, $J_1 = 5.0$, $J_2 = 7.5$ Hz, 2 H, CHCH_2NH), 4.87 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H, CHCH$_2$NH), 7.28 (br. t, $J = 5.0$ Hz, 1 H, NHCOCH$_3$), 7.44 (d, $J = 9.0$ Hz, 2 H, Ar-H), 7.47 (s, 2 H, Ar-H), 7.87 (dd, $J_1 = 2.0$, $J_2 = 9.0$ Hz, 2 H, Ar-H), 8.43 (d, $J = 2.0$ Hz, 2 H, Ar-H), 10.76 (br. s, 2 H, NH) ppm.

***N*-[2,2-Bis(6-chloro-1*H*-indol-3-yl)ethyl]acetamide (4r):** Eluent: ethyl acetate/cyclohexane (6:4), yield 25 mg (65%); brownish solid; m.p. 174–176 °C; TLC: $R_f = 0.60$ (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3403, 1644, 1554 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$, 20 °C): $\delta = 1.91$ (s, 3 H, NHCOCH_3), 3.97 (dd, $J_1 = 5.5$, $J_2 = 7.0$ Hz, 2 H, CHCH_2NH), 4.64 (dd, $J_1 = J_2 = 7.0$ Hz, 1 H, CHCH$_2$NH), 5.63 (br. t, $J = 5.5$ Hz, 1 H, NHCOCH$_3$), 6.97 (s, 2 H, Ar-H), 7.00 (dd, $J_1 = 2.0$, $J_2 = 7.5$ Hz, 2 H, Ar-H), 7.36 (d, $J = 2.0$ Hz, 2 H, Ar-H), 7.42 (d, $J = 7.5$ Hz, 2 H, Ar-H), 8.35 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$, 20 °C): $\delta = 23.4$, 34.1, 43.8, 111.2, 116.8, 120.2, 120.2, 122.6, 125.3, 128.1, 136.9, 170.4 ppm. MS (ESI): m/z (%) = 384 (100), 386 (65) [M – H]$^-$. $C_{20}H_{17}Cl_2N_3O$ (386.28): calcd. C 62.19, H 4.44, N 10.88; found C 62.01, H 4.39, N 10.82.

***N*-[2,2-Bis(6-bromo-1*H*-indol-3-yl)ethyl]acetamide (4s):** Yield: 43 mg (90%); white solid. The chemical-physical data are in agreement to those reported.[3a] ^{1}H NMR (200 MHz, CD$_3$OD, 20 °C): δ = 1.85 (s, 3 H, NHCOCH_3), 3.85–391 (m, 2 H, CHCH_2NH), 4.71 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H, CHCH$_2$NH), 7.03 (dd, $J_1 = 2.0$, $J_2 =$ 8.5 Hz, 2 H, Ar-H), 7.07 (d, $J = 0.5$ Hz, 2 H, Ar-H), 7.41 (d, $J =$ 8.5 Hz, 2 H, Ar-H), 7.49 (d, $J = 2.0$ Hz, 2 H, Ar-H), 8.06 (br. t, J = 5.5 Hz, 1 H, NHCOCH$_3$), 10.48 (br. s, 2 H, NH) ppm.

***N*-[2,2-Bis(6-methyl-1*H*-indol-3-yl)ethyl]acetamide (4t):** Eluent: ethyl acetate/cyclohexane (7:3), yield 30 mg (87%); brownish solid; m.p. 114–116 °C; TLC: $R_f = 0.65$ (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3404, 2923, 1648, 1454 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$, 20 °C): $\delta = 1.85$ (s, 3 H, NHCOCH_3), 2.44 (s, 6 H, Ar-CH$_3$), 3.98 (dd, $J_1 = 5.5$, $J_2 = 7.0$ Hz, 2 H, CHCH_2NH), 4.65 (dd, $J_1 = J_2 = 7.0$ Hz, 1 H, CHCH$_2$NH), 5.64 (br. t, $J = 5.5$ Hz, 1 H, NHCOCH$_3$), 6.84 (d, $J = 2.0$ Hz, 2 H, Ar-H), 6.89 (d, $J = 8.0$ Hz, 2 H, Ar-H), 7.12 (s, 2 H, Ar-H), 7.46 (d, $J = 8.0$ Hz, 2 H, Ar-H), 8.11 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$, 20 °C): δ = 21.7, 23.4, 34.2, 43.9, 111.2, 116.6, 119.1, 121.1, 121.5, 124.7, 131.8, 137.1, 170.4 ppm. MS (ESI): m/z = 346 [M + H]$^+$, 368 [M + Na]$^+$, 344, [M – H]$^-$, 404, [M + CH$_3$COO]$^-$. $C_{22}H_{23}N_3O$ (345.44): calcd. C 76.49, H 6.71, N 12.16; found C 76.61, H 6.73, N 12.12.

***N*-[2,2-Bis(7-bromo-1*H*-indol-3-yl)ethyl]acetamide (4u):** Eluent: ethyl acetate/cyclohexane (1:1), yield 32 mg (68%); white solid; m.p. 207–211 °C; TLC: $R_f = 0.70$ (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3420, 1630, 1433 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$, 20 °C): $\delta = 1.91$ (s, 3 H, NHCOCH_3), 4.03 (dd, $J_1 = 5.5$, $J_2 =$ 7.0 Hz, 2 H, CHCH_2NH), 4.70 (dd, $J_1 = J_2 = 7.0$ Hz, 1 H, CHCH$_2$NH), 5.58 (br. t, $J = 5.5$ Hz, 1 H, NHCOCH$_3$), 6.95 (dd, $J_1 = J_2 = 8.0$ Hz, 2 H, Ar-H), 7.12 (d, $J = 2.0$ Hz, 2 H, Ar-H), 7.35 (d, $J = 8.0$ Hz, 2 H, Ar-H), 7.52 (d, $J = 8.0$ Hz, 2 H, Ar-H), 8.27 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$, 20 °C): $\delta = 23.4$, 34.7, 43.7, 104.9, 117.9, 118.7, 120.8, 122.6, 124.6, 127.9, 135.3, 170.3 ppm. MS (ESI): m/z (%) = 472 (50), 474 (100), 476 (50) [M – H]$^-$. $C_{20}H_{17}Br_2N_3O$ (475.18): calcd. C 50.55, H 3.61, N 8.84; found C 50.41, H 3.56, N 8.77.

***N*-[2,2-Bis(7-methyl-1*H*-indol-3-yl)ethyl]acetamide (4v):** Eluent: ethyl acetate/dichloromethane (1:1), yield 34 mg (98%); brownish solid; m.p. 228–230 °C; TLC; $R_f = 0.30$ (ethyl acetate; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3404, 2923, 1648, 1454 cm^{-1}. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): $\delta = 1.75$ (s, 3 H, NHCOCH_3), 2.42 (s, 6 H, Ar-CH$_3$), 3.77 (dd, $J_1 = 5.5$, $J_2 = 7.5$ Hz, 2 H, CHCH_2NH), 4.60 (dd, $J_1 = J_2 = 7.5$ Hz, 1 H, CHCH$_2$NH), 6.75–6.84 (m, 4 H,

Ar-H), 7.13 (d, J = 2.0 Hz, 2 H, Ar-H), 7.30–7.36 (m, 2 H, Ar-H), 7.91 (br. t, J = 5.5 Hz, 1 H, N*H*COCH$_3$), 10.76 (br. d, J = 2.0 Hz, 2 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 17.2, 23.2, 34.5, 44.2, 117.1, 117.3, 118.7, 120.8, 121.7, 122.5, 126.9, 136.4, 169.7 ppm. MS (ESI): m/z = 346 [M + H]$^+$, 368 [M + Na]$^+$, 344 [M – H]$^-$. $C_{22}H_{23}N_3O$ (345.44): calcd. C 76.49, H 6.71, N 12.16; found C 76.64, H 6.66, N 12.05.

General Procedure for the Synthesis of 2,2-Di(1*H*-indol-3-yl)ethanamine Derivatives 6a, 6l, 6p and 1: Diphenyl phosphate (0.02 mmol) was added to a solution of the appropriate indole derivative **2** (0.4 mmol) and (trifluoroacetylamino)acetaldehyde dimethyl acetal (**3b**; 0.2 mmol) in anhydrous acetonitrile (0.2 mL), and the resulting mixture was stirred at 80 °C for 12–48 h in a sealed tube, monitoring the progress of the reaction by TLC and HPLC-MS. After cooling to room temperature, saturated aqueous $NaHCO_3$ (30 mL) and dichloromethane (30 mL) were added and the two phases were separated. The aqueous solution was extracted with dichloromethane (3 × 20 mL). After drying over dry Na_2SO_4, the combined organic phases were concentrated in vacuo and the resulting crude product **5** was characterized and utilized without further purification.

***N*-[2,2-Di(1*H*-indol-3-yl)ethyl]-2,2,2-trifluoroacetamide (5a):** TLC: R_f = 0.35 (cyclohexane/ethyl acetate, 7:3; UV, CAM). ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 4.13 (dd, J_1 = 5.5, J_2 = 7.0 Hz, 2 H, CHC*H*$_2$NH), 4.80 (dd, J_1 = J_2 = 7.0 Hz, 1 H, C*H*CH$_2$NH), 6.49 (br. t, J = 5.5 Hz, 1 H, N*H*COCH$_3$), 6.98 (d, J = 2.0 Hz, 2 H, Ar-H), 7.09 (dd, J_1 = J_2 = 8.0 Hz, 2 H, Ar-H), 7.23 (dd, J_1 = J_2 = 8.0 Hz, 2 H, Ar-H), 7.38 (d, J = 8.0 Hz, 2 H, Ar-H), 7.60 (d, J = 8.0 Hz, 2 H, Ar-H), 8.08 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 20 °C): δ = 34.0, 43.8, 111.4, 115.7, 115.8 (q, J = 286.0 Hz, 1 C), 119.3, 119.7, 122.2, 122.4, 126.5, 136.7, 157.2 (q, J = 37.0 Hz, 1 C) ppm. MS (ESI): m/z = 372 [M + H]$^+$, 389 [M + NH$_4$]$^+$, 394 [M + Na]$^+$, 370 [M – H]$^-$.

***N*-[2,2-Bis(5-bromo-1*H*-indol-3-yl)ethyl]-2,2,2-trifluoroacetamide (5l):** TLC: R_f = 0.47 (cyclohexane/ethyl acetate, 1:1; UV, CAM). ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 4.06 (dd, J_1 = 5.5, J_2 = 7.0 Hz, 2 H, CHC*H*$_2$NH), 4.66 (dd, J_1 = J_2 = 7.0 Hz, 1 H, C*H*CH$_2$NH), 6.54 (br. t, J = 5.5 Hz, 1 H, N*H*COCH$_3$), 7.03 (d, J = 2.5 Hz, 2 H, Ar-H), 7.21–7.32 (m, 4 H, Ar-H), 7.65 (d, J = 1.0 Hz, 2 H, Ar-H), 8.31 (br. s, 2 H, N*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 20 °C): δ = 33.9, 43.5, 113.0, 113.0, 114.9, 115.8 (q, J = 286.0 Hz, 1 C), 121.7, 123.3, 125.4, 128.1, 135.3, 157.4 (q, J = 37.0 Hz, 1 C) ppm. MS (ESI): m/z (%) = 526 (50), 528 (100), 530 (50) [M – H]$^-$.

Dimethyl 3,3′-[2-(2,2,2-Trifluoroacetamido)ethane-1,1-diyl]bis(1*H*-indole-5-carboxylate) (5p): TLC: R_f = 0.25 (cyclohexane/ethyl acetate, 6:4; UV, CAM). ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 3.80 (s, 6 H, NHCOC*H*$_3$), 3.90 (dd, J_1 = 5.0, J_2 = 7.5 Hz, 2 H, CHC*H*$_2$NH), 4.90 (dd, J_1 = J_2 = 7.5 Hz, 1 H, C*H*CH$_2$NH), 7.36 (d, J = 2.0 Hz, 2 H, Ar-H), 7.42 (d, J = 8.5 Hz, 2 H, Ar-H), 7.69 (dd, J_1 = 1.5, J_2 = 8.5 Hz, 2 H, Ar-H), 8.21 (d, J = 1.5 Hz, 2 H, Ar-H), 9.61 (br. t, J = 5.0 Hz, 1 H, N*H*COCH$_3$), 11.36 (br. d, J = 2.0 Hz, 2 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 33.0, 44.8, 52.1, 112.0, 116.3 (q, J = 286.0 Hz, 1 C), 117.3, 120.4, 121.6, 122.5, 124.9, 126.7, 139.5, 156.7 (q, J = 36.0 Hz, 1 C), 167.7 ppm. MS (ESI): m/z = 488 [M + H]$^+$, 505 [M + NH$_4$]$^+$, 510 [M + Na]$^+$, 486 [M – H]$^-$.

***N*-[2,2-Bis(6-bromo-1*H*-indol-3-yl)ethyl]-2,2,2-trifluoroacetamide (5s):** TLC: R_f = 0.28 (cyclohexane/ethyl acetate, 7:3; UV, CAM). ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 4.08 (dd, J_1 = 5.5, J_2 = 7.0 Hz, 2 H, CHC*H*$_2$NH), 4.71 (dd, J_1 = J_2 = 7.0 Hz, 1 H, C*H*CH$_2$NH), 6.43 (br. t, J = 5.5 Hz, 1 H, N*H*COCH$_3$), 7.01 (d, J = 2.5 Hz, 2 H, Ar-H), 7.16 (dd, J_1 = 1.5, J_2 = 8.5 Hz, 2 H, Ar-H), 7.36 (d, J = 8.5 Hz, 2 H, Ar-H), 7.54 (d, J = 1.5 Hz, 2 H, Ar-H), 8.18 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 20 °C): δ = 33.9, 43.6, 114.4, 115.7, 115.7 (q, J = 286.0 Hz, 1 C), 116.2, 120.5, 122.5, 123.1, 125.3, 137.4, 157.3 (q, J = 37.0 Hz, 1 C) ppm. MS (ESI): m/z (%) = 526 (50), 528 (100), 530 (50) [M – H]$^-$.

A mixture of crude trifluoroacetamide derivative **5** and potassium carbonate (1 mmol) in MeOH (1.87 mL) and H_2O (0.13 mL) was stirred and heated at reflux for 1–2 h. The MeOH was removed under reduced pressure and water was added (30 mL). The aqueous solution was extracted with dichloromethane (3 × 30 mL) and the resulting solution was dried with Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography on neutral alumina.

2,2-Di(1*H*-indol-3-yl)ethanamine (6a): Yield: 30 mg (55%); white solid. The chemical-physical data are in agreement to those reported.[21] ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 3.88 (d, J = 7.0 Hz, 2 H, CHC*H*$_2$NH$_2$), 4.69 (dd, J_1 = J_2 = 7.0 Hz, 1 H, C*H*CH$_2$NH), 6.85 (dd, J_1 = J_2 = 8.0 Hz, 2 H, Ar-H), 6.98 (dd, J_1 = J_2 = 8.0 Hz, 2 H, Ar-H), 7.14 (d, J = 2.0 Hz, 2 H, Ar-H), 7.28 (d, J = 8.0 Hz, 2 H, Ar-H), 7.47 (d, J = 8.0 Hz, 2 H, Ar-H), 10.71 (br. s, 2 H, N*H*) ppm.

2,2-Bis(5-bromo-1*H*-indol-3-yl)ethanamine (6l): Eluent: dichloromethane/methanol/ammonia, 98:1:1, yield 76 mg (88%); white solid; m.p. 136–138 °C; TLC: R_f = 0.19 (silica gel; dichloromethane/methanol/TEA, 90:9:1; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3411, 3012, 2962 cm^{-1}. ^{1}H NMR (200 MHz, CD_3OD, 20 °C): δ = 3.32 (d, J = 7.5 Hz, 2 H, CHC*H*$_2$NH$_2$), 4.43 (dd, J_1 = J_2 = 7.5 Hz, 1 H, C*H*CH$_2$NH$_2$), 7.15 (dd, J_1 = 2.0, J_2 = 8.5 Hz, 2 H, Ar-H), 7.16 (s, 2 H, Ar-H), 7.27 (d, J = 8.5 Hz, 2 H, Ar-H), 7.61 (d, J = 1.5 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (50 MHz, CD_3OD, 20 °C): δ = 37.1, 45.5, 111.4, 112.6, 115.8, 121.1, 123.4, 123.7, 128.6, 135.7 ppm. MS (ESI): m/z (%) = 430 (50), 432 (100), 434 (50) [M – H]$^-$. $C_{18}H_{15}Br_2N_3$ (433.14): calcd. C 49.91, H 3.49, N 9.70; found C 49.89, H 3.48, N 9.75.

Dimethyl 3,3′-(2-Aminoethane-1,1-diyl)bis(1*H*-indole-5-carboxylate) (6p): Eluent: dichloromethane/methanol/ammonia (98:1:1), yield 53 mg (68%); white solid; m.p. 154–156 °C; TLC: R_f = 0.23 (silica gel; dichloromethane/methanol/TEA, 90:9:1; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3413, 1642, 1433 cm^{-1}. ^{1}H NMR (200 MHz, CD_3OD, 20 °C): δ = 3.44 (d, J = 7.5 Hz, 2 H, CHC*H*$_2$NH$_2$), 3.84 (s, 6 H, COOC*H*$_3$), 4.67 (dd, J_1 = J_2 = 7.5 Hz, 1 H, C*H*CH$_2$NH$_2$), 7.26 (s, 2 H, Ar-H), 7.38 (dd, J_1 = 0.5, J_2 = 8.5 Hz, 2 H, Ar-H), 7.78 (dd, J_1 = 1.5, J_2 = 8.5 Hz, 2 H, Ar-H), 8.32 (dd, J_1 = 0.5, J_2 = 1.5 Hz, 2 H, NH) ppm. ^{13}C NMR (50 MHz, CD_3OD, 20 °C): δ = 36.9, 45.6, 50.8, 110.8, 117.5, 120.1, 121.7, 122.3, 123.8, 126.4, 139.8, 168.7 ppm. MS (ESI): m/z = 392 [M + H]$^+$, 414 [M + Na]$^+$, 390 [M – H]$^-$. $C_{22}H_{21}N_3O_4$ (391.43): calcd. C 67.51, H 5.41, N 10.74; found C 67.44, H 5.36, N 10.68.

2,2-Bis(6-bromo-1*H*-indol-3-yl)ethanamine (1): Yield: 71 mg (82%); white solid. The chemical-physical data are in agreement to those reported.[3a] ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 3.20 (d, J = 7.0 Hz, 2 H, CHC*H*$_2$NH$_2$), 3.34 (br. s, 2 H, CHCH$_2$N*H*$_2$), 4.33 (dd, J_1 = J_2 = 7.0 Hz, 1 H, C*H*CH$_2$NH), 6.98 (dd, J_1 = 1.5, J_2 = 8.5 Hz, 2 H, Ar-H), 7.25 (d, J = 1.5 Hz, 2 H, Ar-H), 7.38 (d, J = 8.5 Hz, 2 H, Ar-H), 7.48 (d, J = 1.5 Hz, 2 H, Ar-H), 10.99 (br. s, 2 H, NH) ppm.

2,2-Bis(6-bromo-1*H*-indol-3-yl)-*N*,*N*-dimethylethanamine (8): To a stirred solution of 2,2-bis(6-bromo-1*H*-indol-3-yl)ethanamine (**1**; 44 mg, 0.10 mmol) in methanol (2 mL) was added glacial acetic acid (26 μL, 0.46 mmol) followed by sodium cyanoborohydride (14 mg, 0.23 mmol) under Argon at 0 °C. A solution of formalde-

hyde (38%, 21 μL, 0.28 mmol) in methanol (1.4 mL) was then added. The resulting mixture was stirred at room temperature for 1 h. Aqueous Na_2CO_3 (2 N, 15 mL) was added to adjust the pH to 8–9 and the methanol was removed under reduce pressure. The residue was partitioned between $CHCl_3$ and water and the organic layer was washed with water (15 mL) and brine (15 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by column flash chromatography (silica gel; dichloromethane/methanol/ammonia, 99:1:0.1) to afford **8** (42 mg, 90%) as a white solid. TLC: R_f = 0.49 (dichloromethane/methanol/ammonia, 95:5:0.1; UV, CAM). FTIR (neat): $\tilde{\nu}_{max}$ = 3023, 1433 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 2.42 [s, 6 H, $CHCH_2N(CH_3)_2$], 3.09 [d, J = 7.5 Hz, 2 H, $CHCH_2N(CH_3)_2$], 4.68 [dd, J_1 = J_2 = 7.5 Hz, 1 H, $CHCH_2N(CH_3)_2$], 6.83 (d, J = 2.0 Hz, 2 H, Ar-H), 7.12 (dd, J_1 = 1.5, J_2 = 8.5 Hz, 2 H, Ar-H), 7.19 (d, J = 1.5 Hz, 2 H, Ar-H), 7.38 (d, J = 8.5 Hz, 2 H, Ar-H), 8.56 (br. s, 2 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 20 °C): δ = 32.3, 45.6, 64.6, 114.1, 115.3, 117.7, 120.3, 122.3, 122.9, 125.5, 137.5 ppm. MS (ESI): m/z = 458 (50), 460 (100), 462 (50) $[M - H]^-$. $C_{20}H_{19}Br_2N_3$ (461.20): calcd. C 52.09, H 4.15, N 9.11; found C 52.00, H 4.11, N 9.01.

Bis(6-bromo-1*H*-indol-3-yl)methane (9): H_2SO_4 (96%, 2.6 μL) was added to a solution of 6-bromoindole (195 mg, 0.92 mmol) and aqueous 37% formaldehyde (37 μL, 0.49 mmol) in CH_3OH (1 mL). The mixture was stirred at room temperature in the dark for 2 h, and concentrated in the dark to give a crude solid that was purified by flash chromatography (neutral aluminum oxide; cyclohexane/ethyl acetate, 7:3).[18] Yield: 92 mg (49%); white solid. The chemical-physical data are in agreement with those reported.[22] ^1H NMR (200 MHz, [D$_6$]acetone, 20 °C): δ = 4.20 (s, 2 H, CH_2), 7.09 (dd, J_1 = 2.0, J_2 = 8.5 Hz, 2 H, Ar-H), 7.17 (d, J = 2.0 Hz, 2 H, Ar-H), 7.49 (d, J = 8.5 Hz, 2 H, Ar-H), 7.57 (d, J = 1.5 Hz, 2 H, Ar-H), 10.17 (br. s, 2 H, NH) ppm.

Biological Tests

Cell Cultures, Treatments and Cell Survival Studies: Immortalized promonocytic leukaemia (U937), obtained from American Type Culture Collection (ATCC, Rochville, MD, USA), were grown in RPMI 1640 (Cambrex, Walkersville, MD, USA) supplemented with 10% foetal bovine serum, 1% penicillin-streptomycin and 1% glutamine, in a humidified atmosphere at 37 °C as described previously.[20]

Compounds **1**, **4s**, **7**, **8**, **9**, **10** were dissolved at concentrations ranging from 10 to 25 mM in DMSO as stock solutions, stored at –80 °C and subsequently diluted before use. Treatments were carried out at the reported concentrations and repeated every 24 h. Cellular viability was evaluated by a Trypan blue dye exclusion assay 48 h after treatment start, with a TC-10 automated cell counter (Bio-Rad).

Cell Cycle and Hypodiploidy Analysis: Cell cycle and hypodiploid cells were analyzed by using the propidium iodide staining procedure as previously reported.[21] Cells were fixed in ice-cold 70% ethanol and stained by using a propidium iodide staining solution (50 mg mL^{-1}). Cytofluorimetric acquisitions were carried out with a BD FACScalibur flow cytometer (BD Biosciences, San Jose, CA, USA) and sample analysis was carried out with FlowJo 8.6.3 software (Tree Star, Inc., Ashland, OR, USA). Cell cycle percentage values were calculated by using a Dean–Jett–Fox model and the significance of changes was evaluated by a Student t-test ($P < 0.05$).

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for all new compounds. Cell cycle alterations and hypodiploidy studies of compounds **1** and **7**–**10** are reported.

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