SUPPORTING INFORMATION

Rigid Analogues of Antimitotic Indolobenzazepinones : New Insights into Tubulin Binding via Molecular Modeling

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General Remarks

Instrumental

- Melting points (**M.p.**) were measured in capillary tubes in a Büchi B-540 apparatus and are uncorrected.
- Infrared spectra (**I.R.**) were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer.
- Proton (^{1}**H**) and carbon (^{13}**C**) NMR spectra were recorded on Bruker spectrometers: Avance 300 MHz (QNP - C13, P31, F19 - probe or Dual C13 probe) and Avance 500 MHz (BB0 - ATM probe or BBI - ATM probe). Carbon NMR (^{13}C) spectra were recorded at 125 or 75 MHz, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence. NMR experiments were carried out in deuterochloroform ($CDCl_3$), deuterated methanol (CD_3OD) and deuterated dimethylsulfoxide (DMSO-d_6). Chemical shifts (δ) are reported in parts per million (ppm) with reference to $CDCl_3$ (^{1}H: 7.26; ^{13}C: 77.00), CD_3OD (^{1}H: 3.31; ^{13}C: 49.00) and DMSO-d_6 (^{1}H: 2.50; ^{13}C: 39.50). The following abbreviations are used for the proton spectra multiplicities: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad. Coupling constants (J) are reported in Hertz (Hz). Values in italics refer to the minor diastereomer/atropoisomer, where applicable.
- Mass spectra (**MS**) were obtained either with an LCT (Micromass) instrument using electrospray ionization (ES), or from a Time of Flight analyzer (ESI-MS) for the high resolution mass spectra (HRMS).
-Elemental analyses (**Anal.**) were performed by the analytical service of the ICSN (Gif-sur-Yvette, France) on a Perkin Elmer CHN 2400 analyzer with detection by catharometry.

Chromatography

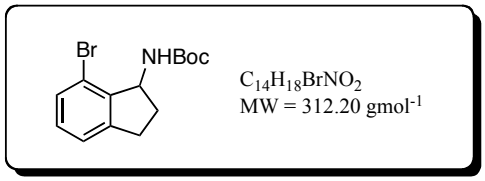
- Thin-layer chromatography was performed on silica gel 60 F254 on aluminum plates (Merck) and visualized under a UVP Mineralight UVLS-28 lamp (254 nm) and with ninhydrin and phosphomolybdic acid in ethanol.
- Flash chromatography was conducted on Merck silica gel 60 (40-63 μm) at medium pressure (300 mbar) or on CombiFlash (Serlabo Technologies).

Solvents and reagents

All reagents were obtained from commercial suppliers unless otherwise stated. When necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under argon. Organic extracts were dried over magnesium sulfate ($MgSO_4$).

Experimental procedures

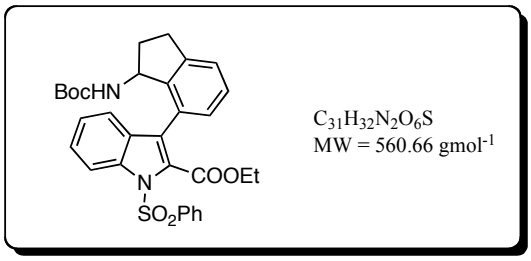
N-Boc-7-Bromo-1-aminoindane 8



8

A mixture of 7-bromoindan-1-one (0.33 g, 1.58 mmol), Ti(O*i*Pr)$_4$ (4.7 mL, 15.8 mmol) and a 2M solution of NH_3 in EtOH (7.8 mL, 15.8 mmol) was stirred for 16h at room temperature. $NaBH_4$ (0.60 g, 15.8 mmol) was added portionwise and the mixture was stirred for 16h at room temperature. The solution was diluted with water and AcOEt and filtered. The aqueous layer was extracted with AcOEt (4×20 mL) and the organic layers were washed with water (3×20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. This crude product was dissolved in THF (10 mL). Di-*tert*-butyldicarbonate (0.75 g, 3.44 mmol) and triethylamine (0.33 mL, 2.4 mmol) were then added at 0°C. The resulting mixture was stirred for 20 min, warmed to room temperature, and then stirred 18 h. The solution was diluted with 10 mL of a 1 M aqueous solution of $NaHCO_3$ and extracted with ether (2×10 mL). The combined extracts were washed with brine (10 mL), filtered and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography on silica gel (heptane/AcOEt 9/1) affording the desired product **8** as a white solid in 57% yield. **M.p.** 85-88°C ; **R$_f$** 0.14 (heptane/ethyl acetate 9/1) ; **I.R.** (neat, cm^{-1}) ν 3318, 1681, 1520, 1162, 764 ; **^{1}H NMR (300 MHz, CDCl$_3$)** δ 7.38-7.33 (m, 1H), 7.18-7.06 (m, 2H), 5.19 (brs, 1H), 4.68 (brs, 1H), 3.19-3.02 (m, 1H), 2.95-2.80 (m, 1H), 2.52-2.34 (m, 1H), 2.14-2.00 (m, 1H), 1.46 (s, 9H) ; **^{13}C NMR (75 MHz, CDCl$_3$)** δ 155.2 (CO), 146.6 (C), 142.0 (C), 130.5 (CH), 130.0 (CH), 123.8 (CH), 120.3 (C), 79.4 (C), 57.0 (CH), 33.2 (CH_2), 31.0 (CH_2), 28.5 ($3CH_3$); **MS** *m/z* 334.0 [$(M+Na)^+$], 336.0 [$(M+Na)^+$] ; **HRMS** *m/z* [$(M+Na)^+$] calcd for $C_{14}H_{18}NO_2Na^{79}Br$ 334.0419 found 334.0426, [$(M+Na)^+$] calcd for $C_{14}H_{18}NO_2Na^{81}Br$ 336.0398 found 336.0399 ; **Anal.** Calcd (%) for $C_{14}H_{18}BrNO_2$: C, 53.86; H, 5.81; N, 4.49; found C, 53.86; H, 5.69; N, 4.37.

Ethyl 3-(3-(*tert*-butoxycarbonylamino)-2,3-dihydro-1*H*-inden-4-yl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate 11



11

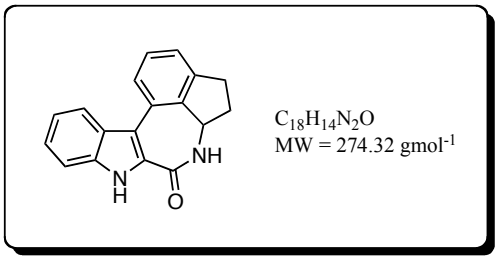
To a solution of **8** (0.322 g, 1.03 mmol) in dry degassed dioxane (2 mL) at 25°C under argon were successively added dropwise Et_3N (0.57 mL, 4.12 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol), *S*-Phos (85 mg, 0.21 mmol) and pinacolborane (0.49 mL, 3.09 mmol). The solution was heated to 80°C for 5h. After cooling, the resulting brown mixture was filtered through celite and washed with CH_2Cl_2. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL) and water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To this crude product in dry degassed dioxane (4 mL) was added CsF (0.313 g, 2.06 mmol) previously fused under vacuum. Ethyl 3-iodoindole-2-carboxylate (**10)** (0.24, 0.51 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol) and dppf (43 mg, 0.08 mmol) were placed in a second round-bottom flask under argon in dry dioxane (8 mL). This second reaction mixture was stirred at room temperature for 30 min, and then added to the solution containing the boronic ester by cannula. The solution was heated to 80°C for 6h. After cooling, the resulting brown mixture was filtered through celite and washed with CH_2Cl_2. The solvent was removed *in vacuo* and the residue was taken up in CH_2Cl_2 (10 mL) and water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography on silica gel (heptane/AcOEt 8/2) affording the desired product **11**, as a mixture of atropoisomeres, as a white foam in 48% yield. ; **I.R.** (neat, cm^{-1}) ν 3412, 3203, 2974, 1710, 1370, 1170. ; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8;14-7.98 (m, 3H), 7.63-7.47 (m, 3H), 7.44-7.36 (m, 1H), 7.34-7.26 (m, 2H), 7.26-6.97 (m, 3H), 5.19-5.02 (m, 1H), 4.93 (q, *J* = 6.0 Hz, 1H), 4.31-4.13 (m, 2H), 3.17-2.83 (m, 2H), 2.54-2.32 (m, 1H), 2.04-1.90 (m, 1H), 1.24 (brs, 9H), 1.11-

1.01 (2t, *J* = 7.2 Hz, 3H).; **MS** *m/z* 583 [(M+Na)$^+$]. ; **HRMS** *m/z* [(M+Na)$^+$] calcd for $C_{31}H_{32}N_2O_6NaS$ 583.1879 found 583.1885.

General Procedure for Preparation of Lactams 5 and 6.

Trifluoroacetic acid (2.3 mmol, 7 eq) was added at 0 °C to a solution of *N*-Boc protected derivatives (0.33 mmol, 1 eq) in dry CH_2Cl_2 (2.4 mL). The reaction mixture was stirred at rt overnight. Solvent and excess TFA were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 and made basic with a 1 M aqueous solution of NaOH. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the corresponding amine. This crude product was dissolved in absolute ethanol (2 mL) and a solution of sodium (2.6 mmol, 8 eq) in absolute ethanol (2 mL) was added. The reaction mixture was stirred at reflux for 10 h. The mixture was diluted in CH_2Cl_2 and a solution of HCl 10% was added until pH =1. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with water (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash silica gel column chromatography (CH_2Cl_2/MeOH, 10/0 to 90/10) to give the desired lactams.

Compound 5

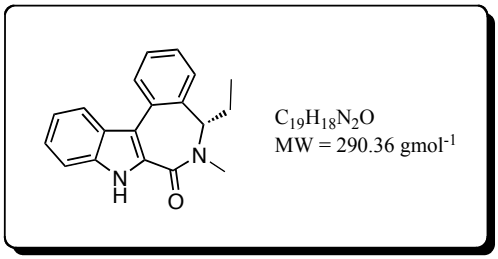


5

Obtained according to the general procedure for preparation of lactams starting from compound **11** (0.115 g, 0.21 mmol). The resulting residue was purified by flash silica gel column chromatography (CH_2Cl_2/MeOH 10/0 to 9/1) to give the desired lactam as a white solid in 60% yield. ; **M.p.** 281-284°C. ; **R_f** 0.15 (CH_2Cl_2/MeOH 97/3). ; **I.R.** (neat, cm^{-1}) ν 3239, 3169, 1618, 1600, 1526, 1332, 738. ; **^{1}H NMR (500 MHz, DMSO)** δ 11.94 (s, 1H), 8.17 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.6Hz, 1H), 7.53

(d, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 4.76 (dd, *J* = 8.5 Hz, *J'* = 5 Hz, 1H), 3.19-3.11 (m, 1H), 3.02-2.94 (m, 1H), 2.61-2.54 (m, 1H), 2.29-2.21 (m, 1H).; **^{13}C NMR (125 MHz, DMSO)** δ 163.2 (CO), 142.5 (C), 141.7 (C), 136.4 (C), 130.6 (C), 130.0 (C), 128.7 (CH), 124.3 (CH), 123.6 (CH), 122.6 (CH), 120.9 (CH), 120.6 (CH), 115.7 (C), 112.7 (CH), 112.6 (C), 55.6 (CH), 30.7 (CH_2), 29.0 (CH_2). ; **MS** *m/z* 273 [$(M-H)^-$]. ;**HRMS** *m/z* [$(M-H)^-$] calcd for $C_{18}H_{13}N_2O$ 273.1028 found 273.1033. Anal. Calc for $C_{18}H_{14}N_2O.0.5H_2O$: C, 76.32 ; H, 5.30 ; N, 9.89. Found : C, 76.18 ; H, 5.15 ; N, 9.91.

(*S*)-5-Ethyl-6-methyl-5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one 15



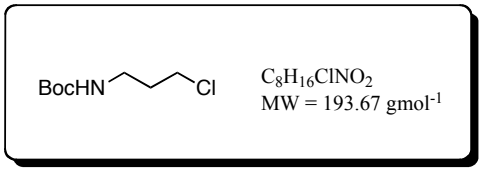
15

Di-*tert*-butylcarbonate (15.7 mg, 0.072 mmol) was added to a solution of compound **4** (20 mg, 0.072 mmol) and triethylamine (10 μL, 0.072 mmol) in dry CH_2Cl_2 (160 μL) under Ar. The reaction mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (5 mL) and water (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting white solid was dissolved in dry THF (0.5 mL) at 0°C. NaH (2.1 mg, 0.078 mmol) was added portionwise and then MeI (48 μL, 0.052 mmol) was added. The mixture was allowed to come to room temperature for 12 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (0.5 mL). TFA (19 μL, 0.25 mmol) was added and the solution was stirred at room temperature overnight. Water was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting white solid was purified by flash chromatography on silica gel (heptane/EtOAc, 50/50) to give compound **15** as a mixture of rotamers (7/3) in 53% yield. ; **I.R.** (neat, cm^{-1}) ν $\bar{3}$212, 1597. *;* **^{1}H NMR (500 MHz, $CDCl_3$)** δ 9.62 (brs, 1H), 8.02-8.10 (m, 2H), 7. 21-7.54 (m, 6H,), 4.21 (t, *J* = 8.1 Hz), 3.37 (s, 3H), 1.63-1.83 (m, 2H), 0.76 (t, 3H, *J* = 7.5

Hz). ; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 162.2, 137.5 136.4, 132.0, 129.9, 129.8, 128.8, 128.6, 127.0, 125.0, 121.9, 121.2, 117.8, 117.1, 112.6, 70.8, 38.6, 24.4, 12.1. ; **$[\alpha]_D$** = - 65.1 ($CHCl_3$, c = 0.31). Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.62 ; H, 6.20 ; N, 9.65. Found : C, 78.99 ; H, 6.36 ; N, 9.51.

***N*-Boc-3-Chloropropylamine 16**

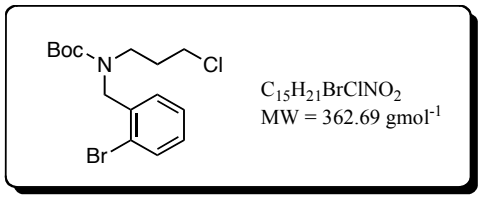
Wu S., Lee S., Beak P., *J. Am. Chem. Soc*, **1996**, *118*, 715-721.



16

To a solution of di-*tert*-butyldicarbonate (3.12 g, 14.3 mmol) and triethylamine (2.38 mL, 18.5 mmol) in THF (20 mL) was added 3-chloropropylamine hydrochloride (2.00 g, 15.4 mmol) at 0°C. The resulting mixture was stirred for 20 min, warmed to room temperature, and then stirred 18 h. The mixture was diluted with 20 mL of a 1 M aqueous solution of $NaHCO_3$ and extracted with ether (2×10 mL). The extracts were washed with brine (10 mL), filtered and concentrated *in vacuo*. The resulting white oil was purified by flash chromatography on silica gel (CH_2Cl_2/ MeOH/NH_3 98/1.5/0.17) affording the desired product 16 as a clear oil in 80% yield. *;* **^{1}H NMR (300 MHz, $CDCl_3$)** δ 4.65 (m, 1H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.28 (m, 2H), 1.97 (m, 2H), 1.45 (s, 9H).

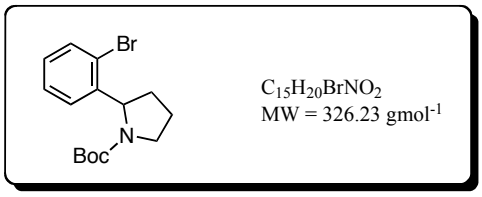
***N*-Boc-(2-bromobenzyl)-(3-chloropropyl)amine 17**



17

A solution of *N*-Boc-3-chloropropylamine (1.6 g, 8.3 mmol) in THF (15 mL) was added at 0°C under argon to a suspension of sodium hydride (0.66 g, 16.6 mmol, 60% in oil) in dry THF (15 mL). The reaction mixture was stirred for 5 minutes at 0°C and 2-bromobenzylbromide (3.11 g, 12.4 mmol) was added slowly. The reaction mixture was heated to reflux for 4h. Water (10 mL) was added and the aqueous layer was extracted with ether (3×10 mL). The combined organic extracts were washed with water (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting clear oil was purified by flash chromatography on silica gel (heptane/AcOEt 9/1) affording the desired product **17** as a clear oil in 84% yield. ; **R_f** 0.62 (heptane/AcOEt 7/3). ; **I.R.** (neat, cm^{-1}) ν 2973, 1692, 1526, 1155, 748.; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.25-7.10 (m, 2H), 4.63-4.45 (m, 2H), 3.59-3.50 (m, 2H), 3.38 (m, 2H), 2.02 (m, 2H), 1.51-1.41 (m, 9H).; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 155.6 (CO), 137.2-137.0 (C), 132.8 (CH), 128.6 (2CH), 127.6 (CH), 123.0 (C), 80.2 (C), 51.3/50.1 (CH_2), 45.0-44.6 (CH_2), 42.4 (CH_2), 31.4 (CH_2), 28.3 ($3CH_3$).; **MS** *m/z* 384.0 [$(M+Na)^+$], 386.0 [$(M+Na)^+$]. ; **HRMS** *m/z* [$(M+Na)^+$] calcd for $C_{15}H_{21}NO_2NaCl^{79}Br$ 384.0342 found 384.0355, [$(M+Na)^+$] calcd for $C_{15}H_{21}NO_2NaCl^{81}Br$ 386.0321 found 386.0328.

N-**Boc-2-(*o*-bromophenyl)pyrrolidine 18**



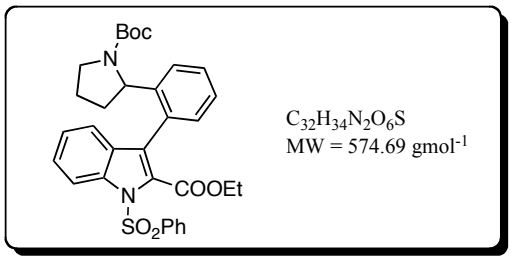
18

A solution of compound **17** (1.09 g, 3.0 mmol) in dry THF (6 mL) was slowly transferred to a solution of freshly prepared LDA (diisopropylamine (0.85 mL, 6.0 mmol), *n*-BuLi (3.75 mL, 1.6 M in hexane, 6 mmol)) and THF (15 mL) at -78°C. The resulting reaction mixture was stirred at -78°C for 5h. Water (10 mL) and ether (20mL) were then added to quench the reaction. The aqueous layer was extracted with ether (3×20 mL) and the combined organic extracts were washed with water (10mL) and brine (10mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (heptane/AcOEt 9/1) affording the desired product **18** as a clear oil in 78% yield. ; **R_f** 0.31

(heptane/AcOEt 8/2). ; **I.R.** (neat, cm^{-1}) ν 2976, 1685, 1158, 762.; **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.52 (dd, *J* = 7.9 Hz, *J* = 1.1 Hz, 1H), 7.29-7.22 (m, 1H), 7.18-7.04 (m, 2H), 5.26-5.07 (m, 1H), 3.74-3.46 (m, 2H), 2.24-2.27 (m, 1H), 1.92-1.76 (m, 3H), 1.46 (brs, 3H); 1.18 (brs, 6H).; **^{13}C NMR (75 MHz, $CDCl_3$)** δ 154.3 (CO), 143.8 (C), 132.6 (CH), 128.0 (CH), 127.2 (CH), 126.4 (CH), 121.9 (C), 79.2 (C), 60.9 (CH), 47.6 (CH_2), 33.9 (CH_2), 28.3 ($3CH_3$), 23.0 (CH_2).; **MS** *m/z* 348.0 [$(M+Na)^+$], 350.0 [$(M+Na)^+$]. ; **HRMS** *m/z* [$(M+Na)^+$] calcd for $C_{15}H_{20}NO_2Na^{79}Br$ 348.0575 found 348.0565, [$(M+Na)^+$] calcd for $C_{15}H_{20}NO_2Na^{81}Br$ 350.0555 found 350.0542. ; **Anal.** Calcd (%) for $C_{15}H_{20}BrNO_2$: C, 55.23; H, 6.18; N, 4.29; found C, 55.59; H, 6.04; N, 4.15.

Ethyl 1-(Benzenesulfonyl)-3-{2-[1-*tert*-butylcarbonyl-amino)pyrrolidin]phenyl}-1*H*-indole-2-carboxylate 20

Baudoin O., Cesario M., Guénard D., Guéritte F., *J. Org. Chem.*, **2002**, 67, 1199-1207

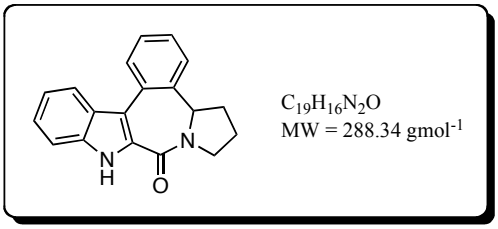


20

To a solution of compound **18** (0.402 g, 1.23 mmol) in dry degassed dioxane (2.4 mL) at 25°C under argon were successively added dropwise Et_3N (0.70 mL, 5.05 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol), *S*-Phos (100 mg, 0.24 mmol) and pinacolborane (0.54 mL, 3.87 mmol). The solution was heated to 80°C for 4h. After cooling, the resulting brown mixture was filtered through celite and washed with CH_2Cl_2. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL) and water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. To this crude product in dry degassed dioxane (5 mL) was added CsF (0.372 g, 2.46 mmol) previously fused under vacuum. Ethyl 3-iodoindole-2-carboxylate (**10**, 0.28, 0.61 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol) and dppf (51 mg, 0.09 mmol) were placed in a second round-bottom flask under argon in dry dioxane (10 mL). This second reaction mixture

was stirred at room temperature for 30 min and then added to the boronic ester solution by cannula. The solution was heated to 80°C for 6h. After cooling, the resulting brown mixture was filtered through celite and washed with CH_2Cl_2. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL) and water (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude was purified by flash chromatography on silica gel (heptane/AcOEt 8/2), affording the desired product **20** as a white solid in 28% yield.. ; **M.p.** 63-65°C. ; **I.R.** (neat, cm^{-1}) n 2974, 1727, 1690, 1390, 1372, 1185, 750. ; **^{1}H NMR (300 MHz, $CDCl_3$)** d 8.18-7.98 (m, 3H), 7.62-7.32 (m, 6H), 7.26-7.04 (m, 4H), 4.82-4.73 (m, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.69-3.32 (m, 2H), 1.82-1.56 (m, 4H), 1.47-1.36 (m, 9H), 1.09 (t, *J* = 7.0 Hz, 3H).; **^{13}C NMR (75 MHz, $CDCl_3$)** d Carbon peaks were difficult to sort. ; **MS** *m/z* 597 $[(M+Na)^+]$. ; **HRMS** *m/z* $[(M+Na)^+]$ calcd for $C_{32}H_{34}N_2O_6Na$ 597.2036 found 597.2028.

Compound 6



$C_{19}H_{16}N_2O$
MW = 288.34 $gmol^{-1}$

6

Obtained according to the general procedure for preparation of lactams starting from compound **20** (86 mg, 0.15 mmol).

The resulting residue was purified by flash silica gel column chromatography (CH_2Cl_2/MeOH 10/0 to 9/1) to give the desired lactam **6** as a white solid in 42% yield.. ; **M.p.** 298-299°C. ; **R_f** 0.45 (CH_2Cl_2/MeOH 96/4). ; **I.R.** (neat, cm^{-1}) n 3199, 1607, 1519, 1420, 743, 718. ; **^{1}H NMR (500 MHz, DMSO)** d 12.06 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 7.6Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 4.53 (d, *J* = 7.3 Hz, 1H), 3.70-3.61 (m, 1H), 3.57-3.51 (m, 1H), 2.80-2.73 (m, 1H), 2.36-2.25 (m, 1H), 2.13-2.06 (m, 2H).; **^{13}C NMR (125 MHz, $CDCl_3$)** d 160.2 (CO), 137.2 (C), 136.4 (C), 133.3 (C), 130.9 (C), 127.8 (CH), 127.7 (CH), 126.6 (CH), 124.4 (C), 124.4 (CH), 123.6 (CH), 120.8 (CH), 120.6 (CH), 115.7 (C),

112.7 (CH), 57.5 (CH), 46.5 (CH_2), 27.7 (CH_2), 23.8 (CH_2). ; **MS** *m/z* 311 [$(M+Na)^+$]. ; **HRMS** *m/z* [$(M+Na)^+$]calcd for $C_{19}H_{16}N_2ONa$ 311.1160 found 311.114. Anal. Calcd for $C_{19}H_{16}N_2O.0.2CDCl_3$: C, 73.81 ; H, 5.16 ; N, 8.97. Found : C, 73.73 ; H, 5.42 ; N, 8.84.

Cell Culture and Proliferation Assay

Cancer cell lines were obtained from the American Type Culture Collection (Rockville, MD, USA) and were cultured according to the supplier's instructions. Briefly, human KB epidermal carcinoma cells and MCF7 and MCF7R (resistant) breast carcinoma cells were grown in Dulbecco minimal essential medium (DMEM) containing 4.5 g/L glucose supplemented with 10% fetal calf serum (FCS) and 1% glutamine, 100 UI penicillin, 100µg/ml streptomycin and 1.5 µg/ml fungizone. Human HCT116 and HCT15 (resistant) colorectal carcinoma cells and human HL60 and HL60R (resistant) promyelocytic leukemia cells were grown in RPMI 1640 containing 10% fetal calf serum (FCS) and 1% glutamine. All cell lines were maintained at 37°C in a humidified atmosphere containing 5% CO_2. Cell viability was assessed using Promega CellTiter-Blue TM reagent according to the manufacturer's instructions. Briefly, cells were seeded in 96-well plates (5 x 10^3 cells/well) containing 50 ml growth medium. After 24h of culture, the cells were supplemented with 50 ml of the studied compound dissolved in DMSO (less than 0.1% in each preparation). After 72h of incubation, 20 ml of resazurin was added for 2h before recording fluorescence (λ_{ex} = 560nm, λ_{em} = 590nm) using a Victor microtiter plate fluorimeter (Perkin-Elmer, USA). The IC_{50} corresponds to the concentration of the studied compound that caused a decrease of 50% in fluorescence of drug-treated cells compared with untreated cells.