

Supporting Information

New C5-Alkylated Indolobenzazepinones Acting as Inhibitors of Tubulin Polymerization: Cytotoxic and Antitumor Activities

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General procedures for preparation of compounds **4a**, **4b**, **4c**, **4d**, **4e**, **4g**, **4h**, **4i**, **4j**, **4k**, their precursors and their characterization. Cytometric flow studies of **4f** on K562 cells. Elemental analysis data.

General procedure for preparation of α -substituted benzylamine derivatives 5g-5i.

Formic acid (4 mL, 106 mmol) was added to a solution of the appropriate ketone (20.3 mmol) in formamide (22 mL). The reaction mixture was stirred at 180-190°C for 6 h, formic acid (3 mL, 80 mmol) being added every hour during this period. After cooling, water (50 mL) was added and the resulting mixture was extracted with AcOEt (4×50 mL). The combined organic extracts were washed with brine (1×50 mL), dried (MgSO₄), filtered and evaporated *in vacuo* to give a pale yellow oil. This oil was diluted with EtOH (100 mL) and water (150 mL). A 35% aqueous solution of HCl (50 mL) was added and the resulting mixture was refluxed for 8 h. EtOH and excess HCl were removed *in vacuo* and a 33% aqueous solution of NH₃ was added dropwise at 0 °C until a pH = 10 was attained. The resulting aqueous mixture was extracted with Et₂O (4×100 mL). The combined organic extracts were washed with water (1×50 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. Unless otherwise stated, the resulting oil was purified by flash silica gel column chromatography using the solvent mixture indicated to give the following α -substituted benzylamines :

(R,S)-1-Phenylbutylamine (5g). Prepared as described above starting from butyrophenone and purified by chromatography using CH₂Cl₂/AcOEt 9/1 then CH₂Cl₂/MeOH/Et₃N 90/9/1: 85%; pale oil. ¹H NMR (250 MHz, CDCl₃) δ 7.32 (m, 5H), 3.89 (t, *J* = 6.8 Hz, 1H), 1.64 (br s, 4H), 1.38 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 146.6, 128.4, 126.9, 126.3, 56.0, 41.7, 19.7, 14.0; FTIR (v/cm⁻¹) 3262, 3188.

(R,S)-1-Phenylpentylamine (5h). Prepared as described above starting from valerophenone and used without further purification: 98%; pale oil. ¹H NMR (250 MHz, CDCl₃) δ 7.32 (m, 5H), 3.88 (t, *J* = 6.8 Hz, 1H), 1.66 (q, *J* = 6.8 Hz, 2H), 1.53 (br s, 2H), 1.33 (m, 4H), 0.88 (t, *J* = 5.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 146.8, 128.4, 126.7, 126.3, 56.9, 39.4, 28.8, 22.7, 14.0; FTIR (v/cm⁻¹) 3366, 3292.

(R,S)-1-Phenyl-2-methylpropylamine (5i). Prepared as described above starting from isobutyrophenone and purified by chromatography using CH₂Cl₂/AcOEt 9/1 then CH₂Cl₂/MeOH/Et₃N 90/9/1: 94%; pale oil. ¹H NMR (250 MHz, CDCl₃) δ 7.23 (m, 5H), 3.54 (d, *J* = 6.8 Hz, 1H), 1.77 (sept, *J* = 6.8 Hz, 1H), 1.40 (br s, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.70 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 145.5, 128.1, 127.0, 126.8, 62.5, 35.4, 19.8, 18.9; FTIR (v/cm⁻¹) 3374, 3267.

General procedure for preparation of *N*-Boc derivatives 6a-6e and 6g-6i. A solution of di-*tert*-butyl dicarbonate (4.58 g, 21 mmol) in dry DCM (11 mL) was added under argon at 0 °C to a solution of benzylamines **5a-5e** and **5g-5i** (15 mmol) and triethylamine (2.09 mL, 15 mmol) in dry DCM (33 mL). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue was dissolved with DCM (60 mL) and water (40 mL). The aqueous layer was extracted with DCM (3×50 mL). The combined organic extracts were washed with water (25 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. The resulting white solid was purified by flash silica gel column chromatography (heptane/AcOEt 9/1) to give carbamates **6a-6e** and **6g-6i**.

***N*-(*tert*-Butyloxycarbonyl)benzylamine (6a).** Prepared from **5a** as described above: 98%; white solid; mp 57 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 7.29 (m, 5H), 4.99 (br s, 1H), 4.27 (d, *J* = 5.2 Hz, 2H), 1.43 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 155.8, 138.8, 128.5, 127.3, 127.2, 79.3, 44.5, 28.3; FTIR (ν/cm⁻¹) 3341, 3307, 1678.

(*R,S*)-*N*-(*tert*-Butyloxycarbonyl)-α-methylbenzylamine (6b). Prepared from **5b** as described above: 94%; white solid; mp 78 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 7.32 (m, 5H), 4.77 (m, 2H), 1.43 (s, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 154.7, 145.1, 128.5, 127.5, 125.8, 79.3, 50.2, 28.3, 22.6; FTIR (ν/cm⁻¹) 3388, 1683, 1511. Anal. (C₁₃H₁₉NO₂) C, H, N.

(*R*)-*N*-(*tert*-Butyloxycarbonyl)-α-methylbenzylamine (6c). Prepared from **5c** as described above: 99%; white solid; mp 78 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 7.32 (m, 5H), 4.77 (m, 2H), 1.43 (s, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 154.7, 145.1, 128.5, 127.1, 125.8, 79.3, 50.2, 28.3, 22.6; FTIR (ν/cm⁻¹) 3388, 1683, 1511. [α]_D = + 24.6 (CHCl₃, c = 5.90). Anal. (C₁₃H₁₉NO₂) C, H, N.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)-α-methylbenzylamine (6d). Prepared from **5d** as described above: 94%; white solid; mp 78 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 7.32 (m, 5H), 4.77 (m, 2H), 1.43 (s, 12H); ¹³C NMR (75 MHz, CDCl₃) δ 154.5, 145.2, 128.5, 127.1, 125.8, 79.3, 50.2, 28.3, 22.6; FTIR (ν/cm⁻¹) 3388, 1683, 1511. [α]_D = - 44.6 (CHCl₃, c = 6.06). Anal. (C₁₃H₁₉NO₂) C, H, N.

(*R*)-*N*-(*tert*-Butyloxycarbonyl)-α-ethylbenzylamine (6e). Prepared from **5e** as described above: 74%; white solid; mp 68 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 7.33 (m, 5H), 4.92 (m, 1H), 4.65 (m, 1H), 1.83 (m, 2H), 1.47 (s, 9H), 0.95 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.3, 142.9, 128.4, 127.0, 126.3, 79.3, 56.3, 29.8, 28.3, 10.6; FTIR (ν/cm⁻¹) 3384, 1682, 1517. [α]_D = + 50.9 (CHCl₃, c = 3.96). Anal. (C₁₄H₂₁NO₂) C, H, N.

(*R,S*)-*N*-(*tert*-Butyloxycarbonyl)- α -*n*-propylbenzylamine (6g). Prepared from **5g** as described above: 73%; white solid; mp 106 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 7.33 (m, 5H), 4.88 (m, 1H), 4.67 (m, 1H), 1.71 (m, 2H), 1.41 (s, 9H), 1.28 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.3, 143.2, 128.4, 127.0, 126.3, 79.3, 54.7, 39.1, 27.9, 19.4, 13.8; FTIR (ν /cm⁻¹) 3334, 1673. Anal. (C₁₅H₂₃NO₂) C, H, N.

(*R,S*)-*N*-(*tert*-Butyloxycarbonyl)- α -*n*-butylbenzylamine (6h). Prepared from **5h** as described above: 84%; white solid; mp 63 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 7.30 (m, 5H), 4.81 (m, 1H), 4.59 (m, 1H), 1.72 (m, 2H), 1.41 (s, 9H), 1.35 (m, 4H), 0.87 (br t, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.3, 143.2, 128.5, 127.0, 126.3, 79.3, 54.9, 36.7, 28.4, 28.3, 22.4, 13.9; FTIR (ν /cm⁻¹) 3340, 1701, 1686. Anal. (C₁₆H₂₅NO₂) C, H, N.

(*R,S*)-*N*-(*tert*-Butyloxycarbonyl)- α -*i*-propylbenzylamine (6i). Prepared from **5i** as described above: 73%; white solid; mp 61 °C (Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 7.40 (m, 5H), 4.96 (m, 1H), 4.51 (m, 1H), 2.18 (m, 1H), 1.49 (s, 9H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.5, 142.1, 128.3, 126.9, 126.8, 79.3, 60.4, 33.8, 28.4, 19.7, 18.5; FTIR (ν /cm⁻¹) 3366, 1683. Anal. (C₁₅H₂₃NO₂) C, H, N.

General procedure for preparation of *o*-boronic acids 7a-7e and 7g-7i. *tert*-Butyllithium (4.94 mL, 8.4 mmol, 1.7 M in pentane) was added under argon at -78 °C to a solution of **6a-6e** and **6g-6i** (3 mmol) in dry THF (15 mL). The reaction mixture was allowed to warm to -20 °C for 2.5 h. Trimethylborate (2 mL, 15 mmol) was added at -20 °C and the reaction was allowed to warm to rt for 2 h. A 5% aqueous solution of HCl was added at 0 °C with vigorous stirring until a pH = 5 – 6 was attained (\approx 3 mL). The aqueous layer was extracted with DCM (3 \times 25 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO₄), filtered and evaporated *in vacuo* to give a mixture of boronic acids **7a-7e** and **7g-7i** and starting material (ratio calculated by integration of ¹³C NMR aromatic CH signals). The crude boronic acids were used in the following steps without further purification.

General procedure for preparation of ethyl 1-(benzenesulfonyl)-1*H*-3-iodoindole-2-carboxylates 9b, 9c. Sulfuric acid (2 mL) was added to a solution of indole-2-carboxylic acid **8b, 8c** (20 mmol) in absolute ethanol (60 mL). The reaction mixture was refluxed overnight. After cooling to rt, the solvent was removed under vacuum, the residue was dissolved in DCM (50 mL) and the resulting solution was washed with a 1 M aqueous solution of NaHCO₃ (3 \times 20 mL) and water (2 \times 20 mL), dried (MgSO₄), filtered and evaporated *in vacuo*

to give the corresponding ethyl ester as a solid. The ethyl ester (19.0 mmol) was dissolved in DMF (11 mL) and potassium hydroxide (4.05 g, 72.4 mmol) was added portion-wise. The reaction mixture was stirred at rt for 15 min and a solution of iodine (4.84 g, 19.0 mmol) in DMF (11 mL) was added. The reaction mixture was stirred at rt for a further 45 min and then poured into a mixture of a 25% aqueous solution of NaHSO₃ (8 mL), 33% aqueous solution of NH₄OH (16 mL) and water (320 mL). The resulting precipitate was filtered and dried *in vacuo* to give a yellow solid which was dissolved in hot EtOH (60 mL) and crystallized at 0°C to give the iodoindole as needles. A solution of the iodoindole (14.8 mmol) in THF (70 mL) was added at 0°C under argon to a suspension of sodium hydride (22.3 mmol, 60% in oil) in dry THF (70 mL). The reaction mixture was stirred for 45 min and benzenesulfonyl chloride (6.0 mL, 29.8 mmol) was added. The reaction mixture was warmed to rt and left overnight. The solvent was removed *in vacuo* and the residue was dissolved with DCM (100 mL) and water (20 mL). The aqueous layer was extracted with DCM (3×20 mL). The combined organic extracts were washed with water (40 mL) and a 1 M aqueous solution of NaHCO₃ (2×20 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. The resulting brown oil was dissolved in hot hexane/Et₂O 1/1 and crystallized at 0 °C to give compounds **9b**, **9c**.

Ethyl 1-(benzenesulfonyl)-5-methoxy-1*H*-3-iodoindole-2-carboxylate (9b). Prepared from **8b** as described above: 69%; white solid; mp 109 °C (hexane/Et₂O). ¹H NMR (250 MHz, CDCl₃) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.89 (d, *J* = 9.3 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.02 (dd, *J* = 2.5 and 9.2 Hz, 1H), 6.80 (d, *J* = 2.5 Hz, 1H), 4.53 (q, *J* = 7.1 Hz, 2H), 8.85 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 161.7, 157.6, 137.1, 134.1, 134.0, 132.7, 130.0, 129.1, 127.3, 117.1, 116.0, 104.7, 74.1, 62.8, 55.7, 14.1; FTIR (ν/cm⁻¹) 1725, 1190, 735. Anal. (C₁₇H₁₄INO₅S•0.1 C₂H₅OC₂H₅) C, H, N.

Ethyl 1-(benzenesulfonyl)-5-fluoro-1*H*-3-iodoindole-2-carboxylate (9c). Prepared from **8c** as described above: 69%; white solid; mp 111 °C (hexane/Et₂O). ¹H NMR (300 MHz, CDCl₃) δ) 7.92-7.96 (m, 3H), 7.56 (tt, *J* = 7.4 and 2.1 Hz, 1H), 7.42-7.48 (m, 2H), 7.13 (td, *J* = 8.8 Hz, *J* = 2.6 Hz, 1H), 7.06 (dd, *J* = 8.8 Hz and 2.6 Hz, 1H), 4.52 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 161.7, 160.0, 137.3, 134.6, 129.1, 127.6, 116.5, 115.9, 109.1, 72.4, 63.2, 14.3; FTIR (ν/cm⁻¹) 1727, 1152. Anal. (C₁₇H₁₃FINO₄S) C, H, N.

General procedure for preparation of Suzuki cross-coupling products 10a-10e and 10g-10k. Under argon, a 1.5 M aqueous solution of Na₂CO₃ (0.75 mL, 1.1 mmol) was added to a

solution of iodindoles **9a-9c** (0.57 mmol), *o*-boronic acids **7a-7e** and **7g-7i** (0.74 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.04 mmol) in toluene/EtOH 1/1 (10 mL). The reaction mixture was stirred at reflux for 20 h. After cooling, ice was added and the mixture was extracted with AcOEt (3×20 mL). The combined organic extracts were washed with water (10 mL), dried (MgSO₄), filtered and evaporated *in vacuo*. The resulting oil was purified by flash silica gel column chromatography (heptane/AcOEt 95/5 to 75/25) to give compounds **10a-10e** and **10g-10k** as a mixture of atropoisomers

Ethyl 1-(benzenesulfonyl)-3-[2-(*tert*-butyloxycarbonylamino)methyl]phenyl]-1*H*-indole-2-carboxylate (10a). Prepared from **5a** and **9a** as described above: 54%; white foam. ¹H NMR (250 MHz, CDCl₃) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.62 (m, 6H), 7.46 (m, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 5.23 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.92 (dd, *J* = 3.4 and 14.6 Hz, 2H), 1.58 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 161.8, 155.7, 138.6, 137.2, 136.2, 134.1, 130.2, 130.1, 129.8, 129.1, 129.0, 128.9, 127.7, 127.3, 127.2, 127.1, 124.7, 121.2, 115.3, 79.1, 62.2, 42.2, 28.3, 13.6; FTIR (ν/cm⁻¹) 3425, 1716, 1189; HRMS (ESI+) calcd for [C₂₉H₃₀N₂O₆SNa]⁺: 557.1722, found: 557.1714.

(*R,S*)-Ethyl 1-(benzenesulfonyl)-3-{2-[1-(*tert*-butyloxycarbonylamino)ethyl]phenyl}-1*H*-indole-2-carboxylate (10b). Prepared from **5b** and **9a** as described above: 64%; white foam. ¹H NMR (250 MHz, CDCl₃) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.45 (m, 7H), 7.26 (m, 2H), 7.09 (m, 1H), 4.81 (m, 1H), 4.56 (q, *J* = 6.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.37 (s, 9H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 162.0, 154.4, 143.2, 137.7, 136.1, 134.0, 131.0, 129.7, 129.4, 129.3, 129.2, 129.1, 129.0, 127.4, 126.9, 125.7, 124.5, 124.6, 121.3, 114.9, 79.4, 61.9, 48.3, 28.2, 22.4, 13.6; FTIR (ν/cm⁻¹) 3414, 1718, 1188 cm⁻¹; MS (IE): 548 [M⁺]; HRMS (ESI+) calcd for [C₃₀H₃₂N₂O₆NaS]⁺: 571.1879, found: 571.1859. Anal. (C₃₀H₃₂N₂O₆S•0.11 CHCl₃) C, H, N.

(*R*)-Ethyl 1-(benzenesulfonyl)-3-{2-[1-(*tert*-butyloxycarbonylamino)ethyl]phenyl}-1*H*-indole-2-carboxylate (10c). Prepared from **5c** and **9a** as described above: 60%; white foam. ¹H NMR (250 MHz, CDCl₃) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.45 (m, 7H), 7.26 (m, 2H), 7.09 (m, 1H), 4.81 (m, 1H), 4.56 (qu, *J* = 6.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.37 (s, 9H), 1.16 (d, *J* = 6.7 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 162.0, 154.4, 143.2, 137.7, 136.1, 134.0, 131.0, 129.7, 129.4, 129.3, 129.2, 129.1, 129.0, 127.4, 126.9, 125.7, 124.5, 124.6, 121.3, 114.9, 79.1, 61.9, 48.3, 28.2, 22.4, 13.6; FTIR (ν/cm⁻¹) 3414, 1718, 1188 cm⁻¹; MS (IE): 548 [M⁺]; HRMS (ESI+) calcd for [C₃₀H₃₂N₂O₆NaS]⁺: 571.1879, found: 571.1859. [α]_D = - 5.7 (CHCl₃, c = 1.00).

(S)- Ethyl 1-(benzenesulfonyl)-3-{2-[1-(*tert*-butyloxycarbonylamino)ethyl]phenyl}-1*H*-indole-2-carboxylate (10d). Prepared from **5d** and **9a** as described above: 52%; white foam. ^1H NMR (250 MHz, CDCl_3) δ 8.04 (d, $J = 8.1$ Hz, 2H), 7.95 (d, $J = 8.9$ Hz, 1H), 7.45 (m, 7H), 7.26 (m, 2H), 7.09 (m, 1H), 4.81 (m, 1H), 4.56 (qu, $J = 6.7$ Hz, 1H), 4.23 (q, $J = 7.1$ Hz, 2H), 1.37 (s, 9H), 1.16 (d, $J = 6.7$ Hz, 3H), 1.03 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.0, 154.4, 143.2, 137.7, 136.1, 134.0, 131.0, 129.7, 129.4, 129.3, 129.2, 129.1, 129.0, 127.4, 126.9, 125.7, 124.5, 124.6, 121.3, 114.9, 79.1, 61.9, 48.3, 28.2, 22.4, 13.6; FTIR (v/cm^{-1}) 3414, 1718, 1188; MS (IE): 548 [M^+]; HRMS (ESI+) calcd for $[\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_6\text{NaS}]^+$: 571.1879, found: 571.1859. $[\alpha]_{\text{D}} = +5.4$ (CHCl_3 , $c = 0.52$).

(R)-Ethyl 1-(benzenesulfonyl)-3-{2-[1-(*tert*-butyloxycarbonylamino)propyl]phenyl}-1*H*-indole-2-carboxylate (10e). Prepared from **5e** and **9a** as described above: 62%; white foam. ^1H NMR (250 MHz, CDCl_3) δ 8.10 (m, 3H), 7.74 (d, $J = 7.4$ Hz, 1H), 7.63 - 7.10 (m, 8H), 4.85 (m, 1H), 4.39 (m, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 2.25 (m, 1H), 1.93 (m, 1H), 1.57 (s, 9H), 1.09 (t, $J = 7.1$ Hz, 3H), 0.51 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.1, 152.8, 141.9, 137.7, 135.8, 133.9, 131.4, 130.5, 129.6, 129.5, 129.0, 127.7, 127.4, 127.3, 126.8, 125.3, 124.5, 124.3, 122.2, 114.8, 79.4, 61.9, 53.8, 30.2, 28.2, 13.7, 10.2; FTIR (v/cm^{-1}) 3347, 1724, 1681, 1173; HRMS (ESI+) calcd for $[\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_6\text{SNa}]^+$: 585.2035, found: 585.2040.

(R,S)-Ethyl 1-(benzenesulfonyl)-3-{2-[1-(*tert*-butyloxycarbonylamino)butyl]phenyl}-1*H*-indole-2-carboxylate (10g). Prepared from **5g** and **9a** as described above: 81%; white foam. FTIR (v/cm^{-1}) 3408, 1684, 1172; HRMS (ESI+) calcd for $[\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_6\text{SNa}]^+$: 599.2192, found: 599.2203.

(R,S)-Ethyl 1-(benzenesulfonyl)-3-{2-[1-(*tert*-butyloxycarbonylamino)pentyl]phenyl}-1*H*-indole-2-carboxylate (10h). Prepared from **5h** and **9a** as described above: 54%; white foam. ^1H NMR (250 MHz, CDCl_3) δ 8.15 (m, 3H), 7.63 - 7.10 (m, 10H), 4.87 (m, 1H), 4.46 (m, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 1.39 - 1.23 (m, 6H), 1.34 (s, 9H), 1.05 (t, $J = 7.1$ Hz, 3H), 0.95 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 162.1, 154.4, 142.3, 137.9, 135.8, 133.8, 131.1, 130.9, 130.0, 129.2, 129.0, 128.9, 127.4, 127.3, 126.9, 126.8, 126.7, 125.2, 124.3, 114.6, 78.4, 61.8, 52.4, 35.1, 28.2, 27.8, 22.1, 13.8, 13.6; FTIR (v/cm^{-1}) 3355, 1724, 1694, 1189; HRMS (ESI+) calcd for $[\text{C}_{33}\text{H}_{38}\text{N}_2\text{O}_6\text{SNa}]^+$: 613.2348, found: 613.2347.

(R,S)-Ethyl 1-(benzenesulfonyl)-3-{2-[1-(*tert*-butyloxycarbonylamino)(2-methyl)propyl]phenyl}-1*H*-indole-2-carboxylate (10i). Prepared from **5i** and **9a** as described above: 42%; white foam. FTIR (v/cm^{-1}) 3315, 1725, 1682, 1173; HRMS (ESI+) calcd for $[\text{C}_{32}\text{H}_{36}\text{N}_2\text{O}_6\text{SNa}]^+$: 599.2192, found: 599.2177.

(S)-Ethyl 1-(benzenesulfonyl)-3-{2-[1-(*tert*-butyloxycarbonylamino)ethyl]phenyl}-5-methoxy-1*H*-indole-2-carboxylate (10j). Prepared from **5f** and **9b** as described above: 51%; white foam. ¹H NMR (250 MHz, CDCl₃) δ 7.99 (m, 3H), 7.58 - 7.04 (m, 9H), 4.84 (m, 1H), 4.52 (q, *J* = 6.5 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.37 (s, 9H), 1.08 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 162.1, 157.4, 154.5, 143.9, 137.4, 131.1, 130.9, 130.7, 130.3, 129.2, 129.1, 129.9, 127.3, 126.9, 126.8, 123.7, 122.2, 117.5, 115.9, 103.6, 79.1, 62.0, 55.5, 48.4, 28.3, 22.7, 13.7; FTIR (ν/cm⁻¹) 3410, 1718, 1177; HRMS (ESI+) calcd for [C₃₁H₃₄N₂O₇SNa]⁺: 601.1984, found: 601.1979.

(R,S)-Ethyl 1-(benzenesulfonyl)-3-{2-[1-(*tert*-butyloxycarbonylamino)propyl]phenyl}-5-fluoro-1*H*-indole-2-carboxylate (10k). Prepared from **5f** and **9c** as described above: 51%; white foam. ¹H NMR (300 MHz, CDCl₃) δ 7.97-8.05 (m, 3H), 7.59 - 7.07 (m, 9H), 4.81 (m, 1H), 4.32 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.26 (m, 1H), 1.98 (m, 1H), 1.33 (s, 9H), 1.09 (t, *J* = 7.4 Hz, 3 H), 0.60 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (75.5 MHz, CDCl₃) δ 161.9, 158.8, 157.3, 142.5, 137.7, 134.3, 132.2, 131.3, 130.9, 129.4, 129.3, 127.6, 127.5, 127.2, 126.9, 125.6, 116.2, 115.2, 108.2, 79.4, 62.3, 53.7, 29.3, 28.4, 13.9, 10.5; FTIR (ν/cm⁻¹) 3412, 1720, 1186; HRMS (ESI+) calcd for [C₃₁H₃₃FN₂O₆SNa]⁺: 603.1941, found: 603.1945.

General procedure for preparation of lactams 4a-4e and 4g-4k. Trifluoroacetic acid (0.18 mL, 2.3 mmol) was added at 0 °C to a solution of *N*-Boc protected derivatives **10a-10e** and **10g-10k** (0.33 mmol) in dry DCM (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 DCM and made basic with a 1 M aqueous solution of NaOH. The aqueous layer was extracted with DCM (3×10 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO₄), filtered and evaporated *in vacuo* to give the corresponding amine. This crude product (0.16 mmol) was dissolved in absolute ethanol (2 mL) and a solution of sodium (29 mg, 1.3 mmol) in absolute ethanol (2 mL) was added. The reaction mixture was stirred at reflux for 10 h. Silica was added and the solvent was evaporated *in vacuo*. The resulting residue was purified by flash silica gel column chromatography (heptane/AcOEt 90/10 to 30/70) to give lactams **4a-4e** and **4g-4k**.

5,8-Dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one (4a). Prepared from **10a** as described above: 70%; white solid; mp 221 °C (heptane/AcOEt); ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.03 (s, 1H), 8.40 (br t, *J* = 5.3 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.40 (m, 3H), 7.37 (m, 2H), 7.24 (t, *J* = 7.9 Hz, 1H), 4.11 (d, *J* = 5.3 Hz, 2H); ¹³C NMR (300

MHz, DMSO- d_6) δ 163.5, 136.9, 136.5, 133.3, 129.9, 128.1, 128.0, 127.2, 126.3, 124.4, 124.2, 120.8, 120.6, 116.0, 112.7, 42.6; FTIR (ν/cm^{-1}) 3171, 1653; HRMS (ESI+) calcd for $[\text{C}_{16}\text{H}_{13}\text{N}_2\text{O}]^+$: 249.1028, found: 249.1038.

(R,S)-5-Methyl-5,8-dihydroindolo[2,3-d][2]benzazepin-7(6H)-one (4b). Prepared from **10b** as described above: 68%; white solid; mp 215 °C (heptane/AcOEt); ^1H NMR (250 MHz, CDCl_3) δ 10.30 (br s, 1H), 8.06 (m, 2H), 7.53 - 7.12 (m, 6H), 6.46 (br s, 1H), 4.41 (m, 1H), 1.79 (m, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 162.6, 140.0, 136.5, 133.0, 130.2, 127.4, 126.4, 124.3, 124.2, 123.6, 120.8, 120.5, 115.8, 112.7, 47.4, 17.05; FTIR (ν/cm^{-1}) 3193, 1634; MS (ESI+) : 301 $[\text{M}+\text{K}^+]$; HRMS (ESI+) calcd for $[\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}]^+$: 263.1184, found: 263.1175.

(R)-5-Methyl-5,8-dihydroindolo[2,3-d][2]benzazepin-7(6H)-one (4c). Prepared from **10c** as described above: 49%; white amorphous solid; ^1H NMR (250 MHz, CDCl_3) δ 10.30 (s br, 1H), 8.06 (m, 2H), 7.53 - 7.12 (m, 6H), 6.46 (br s, 1H), 4.41 (m, 1H), 1.79 (m, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 162.6, 140.0, 136.5, 133.0, 130.2, 127.4, 126.4, 124.3, 124.2, 123.6, 120.8, 120.5, 115.8, 112.7, 47.4, 17.1; FTIR (ν/cm^{-1}) 3193, 1634; MS (ESI+) : 301 $[\text{M}+\text{K}^+]$; HRMS (ESI+) calcd for $[\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}]^+$: 263.1184, found: 263.1175. $[\alpha]_{\text{D}} = +122.1$ (CHCl_3 , $c = 0.13$). Anal. ($\text{C}_{17}\text{H}_{14}\text{N}_2\text{O} \cdot 0.4 \text{CH}_3\text{CO}_2\text{C}_2\text{H}_5$) C, H, N.

(S)-5-Methyl-5,8-dihydroindolo[2,3-d][2]benzazepin-7(6H)-one (4d). Prepared from **10d** as described above: 67%; white amorphous solid; ^1H NMR (250 MHz, CDCl_3) δ 10.30 (br s, 1H), 8.06 (m, 2H), 7.53 - 7.12 (m, 6H), 6.46 (br s, 1H), 4.41 (m, 1H), 1.79 (m, 3H); ^{13}C NMR (75 MHz, DMSO- d_6) δ 162.6, 140.0, 136.5, 133.0, 130.2, 127.4, 126.4, 124.3, 124.2, 123.6, 120.8, 120.5, 115.8, 112.7, 47.4, 17.4; FTIR (ν/cm^{-1}) 3193, 1634; MS (ESI+) : 301 $[\text{M}+\text{K}^+]$; HRMS (ESI+) calcd for $[\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}]^+$: 263.1184, found: 263.1175. $[\alpha]_{\text{D}} = -190.7$ (CHCl_3 , $c = 0.10$).

(R)-5-Ethyl-5,8-dihydroindolo[2,3-d][2]benzazepin-7(6H)-one (4e). Prepared from **10e** as described above: 80%; white solid; mp 156 °C (heptane/AcOEt); ^1H NMR (250 MHz, CDCl_3) δ 11.61 (br s, 1H), 8.07 (m, 2H), 7.56 (m, 4H), 7.33 (m, 4H), 4.12 (m, 1H), 2.20 (m, 2H), 1.15 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.9, 139.9, 138.4, 137.1, 133.9, 128.7, 128.5, 127.7, 126.9, 125.1, 121.5, 123.8, 120.9, 119.0, 112.8, 54.7, 30.3, 11.6; FTIR (ν/cm^{-1}) 3179, 1635; HRMS (ESI+) calcd for $[\text{C}_{18}\text{H}_{16}\text{N}_2\text{ONa}]^+$: 299.1160, found: 299.1175. $[\alpha]_{\text{D}} = +58$ (CHCl_3 , $c = 0.10$).

(R,S)-5-Propyl-5,8-dihydroindolo[2,3-d][2]benzazepin-7(6H)-one (4g). Prepared from **10g** as described above: 44%; amorphous solid; ^1H NMR (250 MHz, CDCl_3) δ 9.72 (br s, 1H),

8.11 (d, $J = 8.0$ Hz, 1H), 8.05 (d, $J = 7.3$ Hz, 1H), 7.57 - 7.26 (m, 6H), 6.05 (br s, 1H), 4.23 (m, 1H), 2.13 (m, 2H), 1.67 (m, 2H), 1.02 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.5, 138.5, 137.0, 133.8, 133.9, 128.8, 128.5, 127.7, 126.9, 125.2, 123.9, 121.6, 121.0, 118.9, 112.7, 52.7, 33.2, 19.3, 14.1; FTIR (v/cm^{-1}) 3172, 1626; HRMS (ESI+) calcd for $[\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}]^+$: 291.1497, found: 291.1481.

(*R,S*)-5-Butyl-5,8-dihydroindolo[2,3-d][2]benzazepin-7(6*H*)-one (4h). Prepared from **10h** as described above: 57%; amorphous solid; ^1H NMR (250 MHz, CDCl_3) δ 10.75 (br s, 1H), 8.09 (d, $J = 8.0$ Hz, 1H), 8.05 (d, $J = 7.4$ Hz, 1H), 7.58 (d, $J = 8.2$ Hz, 1H), 7.48 - 7.23 (m, 5H), 6.69 (br s, 1H), 4.20 (m, 1H), 2.25 (m, 2H), 1.42 (m, 4H), 0.90 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.4, 138.5, 136.9, 133.7, 133.9, 128.5, 128.4, 127.7, 126.9, 125.1, 123.8, 121.6, 121.0, 118.9, 112.7, 52.9, 30.9, 29.7, 28.9, 13.9; FTIR (v/cm^{-1}) 3252, 1633; HRMS (ESI+) calcd for $[\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}]^+$: 305.1654, found: 315.1613. Anal. ($\text{C}_{20}\text{H}_{20}\text{N}_2\text{O} \cdot 0.4 \text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$) C, H, N.

(*R,S*)-5-iso-Propyl-5,8-dihydroindolo[2,3-d][2]benzazepin-7(6*H*)-one (4i). Prepared from **10i** as described above: 58%; amorphous solid; ^1H NMR (250 MHz, CDCl_3) δ 9.91 (br s, 1H), 8.13 (d, $J = 8.0$ Hz, 1H), 8.06 (d, $J = 7.7$ Hz, 1H), 7.56 - 7.31 (m, 6H), 3.77 (m, 1H), 2.12 (m, 1H), 1.15 (m, 3H), 0.87 (m, 3H); FTIR (v/cm^{-1}) 3195, 1635; HRMS (ESI+) calcd for $[\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}]^+$: 291.1497, found: 291.1506.

(*S*)-11-Methoxy-5-methyl-5,8-dihydroindolo[2,3-d][2]benzazepin-7(6*H*)-one (4j). Prepared from **10j** as described above: 63%; amorphous solid; ^1H NMR (250 MHz, CDCl_3) δ 11.16 (br s, 1H), 8.02 (d, $J = 7.6$ Hz, 1H), 7.47 (m, 5H), 7.02 (m, 1H), 4.42 (m, 1H), 3.83 (s, 3H), 1.82 (m, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 164.6, 155.1, 139.0, 133.7, 132.5, 129.2, 127.8, 126.8, 125.4, 123.7, 118.5, 116.2, 113.7, 102.3, 55.9, 48.5, 17.4; FTIR (v/cm^{-1}) 3189, 1634; HRMS (ESI+) calcd for $[\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_2]^+$: 293.1266, found: 293.1285; $[\alpha]_{\text{D}} = -192$ (CHCl_3 , $c = 0.16$). Anal. ($\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2 \cdot 0.45 \text{CH}_3\text{OH}$) C, H, N.

(*R,S*)-5-Ethyl-11-fluoro-5,8-dihydroindolo[2,3-d][2]benzazepin-7(6*H*)-one (4k). Prepared from **10k** as described above: 72%; white solid; mp 135 °C (Et_2O); ^1H NMR (500 MHz, CDCl_3) δ 10.63 (br s, 1H, 1H), 7.90 (d, $J = 7.3$ Hz, 1H), 7.68 (d, $J = 9.1$ Hz, 1H), 7.36-7.46 (m, 1H, 4H), 7.08 (td, $J = 8.9$ Hz and 2.1 Hz, 1H), 6.55 (br s, 1H), 4.07 (br s, 1H), 2.07-2.33 (m, 2H), 1.02-1.21 (m, 3H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 164.3, 158.8, 138.4, 133.6, 133.1, 128.3, 128.2, 128.1, 128.0, 127.4, 125.5, 114.5, 113.8, 106.5, 55.2, 24.9, 11.8; FTIR (v/cm^{-1}) 3178, 1626, 1501, 1300, 1146; HRMS (ESI+) calcd for $[\text{C}_{18}\text{H}_{15}\text{FN}_2\text{ONa}]^+$: 317.1066, found: 317.1077. Anal. ($\text{C}_{18}\text{H}_{15}\text{FN}_2\text{O} \cdot 0.3 \text{CH}_3\text{CO}_2\text{C}_2\text{H}_5 \cdot 0.3 \text{CH}_2\text{Cl}_2$) C, H, N.

Cytometric flow studies. The effect of 4f on the cell cycle of K562 cells as a function of treatment time and concentration.

The effect of compound **4f** on the cell cycle of K562 cells was investigated by flow cytometry at various concentrations and at different times (Table, A-C) (see Experimental Section for procedures). After 6h treatment (A), a net progression in the number of cells arrested at the G2/M growth stage was observed with increasing concentration of **4f** (4.9% at 0.05 μM to 32% in G2/M stage at 0.5 μM). After 16h (B) and 24h (C) of treatment with 0.5 μM of **4f**, 51.5% and 44.7%, respectively, of cells were arrested at the G2/M stage.

Table. Effect of Compound **4f** on Cell Cycle Distribution in K562 Cancer Cells as a Function of Concentration and Treatment Time.^a

A : 6h treatment with 4f

Concentration (μM)	G0/G1 %	S %	G2/M %
Control	1.4	97.1	1.2
0.05	0.3	94.3	4.9
0.1	0.2	91.1	8.1
0.5	0.2	67.8	32

B : 16h treatment with 4f

Concentration (μM)	G0/G1 %	S %	G2/M %
Control	2.1	96.4	0.9
0.05	1	97.6	1.1
0.1	2.4	52.8	43.4
0.5	0.6	47.3	51.5

C : 24h treatment with 4f

Concentration (μM)	G0/G1 %	S %	G2/M %
Control	11.3	83.4	3.9
0.05	14.6	49.1	24.9
0.1	7.6	69.5	20.3
0.5	1.2	53.4	44.7

^aData are representative of three independent experiments.

Elemental analysis data:

Comp	Formula	Calcd C (found)	Calcd H (found)	Calcd N (found)
4c	$C_{17}H_{14}N_2O \cdot 0.4 CH_3CO_2CH_2CH_3$	75.08 (75.31)	5.83 (6.13)	9.41 (9.05)
4f	$C_{18}H_{16}N_2O \cdot 0.2 CH_3CO_2CH_2CH_3 \cdot 0.2 C_7H_{16}$	77.27 (77.59)	6.68 (6.53)	8.92 (9.03)
4h	$C_{20}H_{20}N_2O \cdot 0.4 CH_3CO_2CH_2CH_3$	76.39 (76.35)	6.89 (6.86)	8.25 (8.33)
4k	$C_{18}H_{15}FN_2O \cdot 0.3 CH_3CO_2CH_2CH_3 \cdot 0.3 CH_2Cl_2$	67.86 (67.83)	5.35 (5.51)	7.99 (7.82)
4j	$C_{18}H_{16}N_2O_2 \cdot 0.45 CH_3OH$	72.24 (72.61)	5.85 (5.92)	9.13 (8.75)
6b	$C_{13}H_{19}NO_2$	70.56 (70.35)	8.65 (8.72)	6.33 (6.31)
6c	$C_{13}H_{19}NO_2$	70.56 (70.31)	8.65 (8.71)	6.33 (6.34)
6d	$C_{13}H_{19}NO_2$	70.56 (70.55)	8.65 (8.47)	6.33 (6.38)
6e	$C_{14}H_{21}NO_2$	71.46 (71.75)	8.99 (8.96)	5.95 (6.01)
6f	$C_{14}H_{21}NO_2$	71.46 (71.79)	8.99 (9.01)	5.95 (6.01)
6g	$C_{15}H_{23}NO_2$	72.25 (72.47)	9.30 (9.31)	5.62 (5.52)
6h	$C_{16}H_{25}NO_2$	72.96 (73.23)	9.57 (9.53)	5.32 (5.31)
6i	$C_{15}H_{23}NO_2$	72.25 (72.24)	9.30 (9.34)	5.62 (5.61)
9a	$C_{17}H_{14}INO_4S$	44.85 (45.14)	3.10 (3.17)	3.08 (3.05)
9b	$C_{17}H_{14}INO_5S \cdot 0.1 CH_3CH_2OCH_2CH_3$	43.66 (43.96)	3.16 (3.12)	2.93 (2.95)
9c	$C_{17}H_{13}FINO_4S$	43.14 (43.34)	2.77 (2.77)	2.96 (3.01)
10b	$C_{30}H_{32}N_2O_6S \cdot 0.11 CHCl_3$	64.38 (64.03)	5.76 (6.17)	4.99 (4.85)
10f	$C_{31}H_{34}N_2O_6S \cdot 0.85 CH_3CH_2OH \cdot 0.85 H_2O$	63.66 (63.95)	6.66 (7.05)	4.54 (4.81)
13	$C_{19}H_{18}N_2O \cdot 0.4 CH_3CO_2CH_2CH_3 \cdot 0.4 H_2O$	74.34 (74.41)	6.66 (6.37)	8.42 (8.56)