Supporting Information

Design, Synthesis, and Biological Activity of Sulfonamide Analogues of Antofine and Cryptopleurine as Potent and Orally Active Antitumor Agents

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1. General Methods for Chemistry

All chemicals were reagent grade and used as purchased. All reactions were performed under an inert atmosphere of dry nitrogen using distilled dry solvents. Reactions were monitored via TLC analysis using silica gel 60 F-254 thin-layer plates. Compounds were visualized on the TLC plates under UV light and by spraying with either KMnO₄ or anisaldehyde solutions. Flash column chromatography was conducted on silica gel 60 (230–400 mesh). Melting points were measured using a Buchi B-540 melting point apparatus without correction. ¹H NMR (400, 500, or 600 MHz) and ¹³C NMR (75, 100, 125, or 150 MHz) spectra were recorded in δ units using residual CHCl₃ (δ 7.24 ppm) and CDCl₃ (δ 77.0 ppm) as an internal standard. The IR spectra were measured on a Fourier Transform Infrared spectrometer. High-resolution mass spectra (HRMS) were recorded using FAB. All final target compounds were characterized and determined to be least >95% pure by analytical HPLC (Agilent 1200 Series, Agilent Technologies, Palo Alto, CA, USA) using the following method. Mobile phase A consisted of 0.1% formic acid in HPLC-grade water. HPLC analysis was performed using a reverse-phase Agilent Eclipse Plus C18 column (4.6 × 150 mm, 3.5 μm) at a flow rate of 0.7 mL/min (30–100% aqueous MeOH with 0.1% formic acid over 20 min and MeOH with 0.1% formic acid from 20 to 25 min).
2. Synthesis of compounds (±)-5b, (±)-12b, and 13‒15

2.1. Synthesis of compounds 13

**Scheme S1. Synthesis of compounds 13.a**

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MeO
\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {MeO};
  \node (b) at (1,0) {OMe};
  \node (c) at (2,0) {OTMS};
  \node (d) at (3,0) {MeO};
  \node (e) at (4,0) {OMe};
  \node (f) at (5,0) {\textbf{S1}};
  \draw[->] (a) -- (b);
  \draw[->] (b) -- (c);
  \draw[->] (c) -- (d);
  \draw[->] (d) -- (e);
  \draw[->] (e) -- (f);
\end{tikzpicture}
\end{center}
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\[ \text{MeO} \quad \text{OMe} \quad \text{OTMS} \quad \text{MeO} \quad \text{OMe} \quad \text{S1} \]

\[ \text{MeO} \quad \text{OMe} \quad \text{S3} \]

\[ \text{MeO} \quad \text{OMe} \quad \text{13} \]

\[ \text{MeO} \quad \text{OMe} \quad \text{Boc} \quad \text{S1} \]

\[ \text{MeO} \quad \text{OMe} \quad \text{Boc} \quad \text{S2} \]

\[ \text{MeO} \quad \text{OMe} \quad \text{Boc} \quad \text{S3} \]

\[ \text{MeO} \quad \text{OMe} \quad \text{Boc} \quad \text{13} \]

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*aReaction conditions: (a) InCl$_3$, CH$_2$Cl$_2$, 92%; (b) TFA, CH$_2$Cl$_2$; (c) 4-nitrophenylacetic acid, EDCI, DMAP, CH$_2$Cl$_2$, 83% (over two steps); (d) K$_2$CO$_3$, EtOH, reflux, 76%; (e) SnCl$_2$, EtOH, 75 °C; (f) Sodium bis(2-methoxyethoxy)aluminum hydride, 1,4-dioxane; (g) MeSO$_2$Cl, pyridine, CH$_2$Cl$_2$, 51% for 13 (over three steps).*

**tert-Butyl 2-(2-(3,4-dimethoxyphenyl)-2-oxoethyl)piperidine-1-carboxylate (S1).** To a stirred solution of tert-butyl 2-methoxypiperidine-1-carboxylate$^1$ (8.11 g, 37.7 mmol) in 30 mL of dry CH$_2$Cl$_2$ was added ((1-(3,4-dimethoxyphenyl)vinyl)oxy)trimethylsilane$^2$ (11.4 g, 45.2 mmol) and InCl$_3$ (418 mg, 1.89 mmol) and the reaction mixture was stirred for 1 h. The reaction mixture was filtered over a Celite pad, and the filtrate was concentrated in vacuo. The crude product was separated by silica gel column chromatography (hexane/EtOAc, 2:1) to give the desired ketone S1 (12.6 g, 92%) as a pale yellow solid. The spectral data of S1 were identical to those of 7b.

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To a stirred solution of S1 (11.3 g, 31.1 mmol) in 100 mL of CH₂Cl₂ was added TFA (25 mL) at room temperature, and the reaction mixture was stirred for 2 h. The reaction mixture was basified with 1 N NaOH and extracted with EtOAc. The solvent was concentrated in vacuo, and the crude amine was used for the next reaction without further purification. To a stirred solution of 4-nitrophenylacetic acid (6.76 g, 37.3 mmol) in 100 mL of CH₂Cl₂ was added EDCI (6.56 g, 34.2 mmol), DMAP (4.18 g, 34.2 mmol), and the obtained crude amine at room temperature, and the reaction mixture was stirred for 15 h. The reaction was quenched with 1 N HCl at room temperature, diluted with H₂O, and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (hexane/EtOAc, 1:3) to give an amide S2 (11.0 g, 83%) as a white waxy solid. The spectral data of S2 were identical to those of 8b.

To a stirred solution of amide S2 (6.31 g, 14.8 mmol) in 100 mL of EtOH was added K₂CO₃ (900 mg) at room temperature, and the reaction mixture was refluxed for 1.5 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The reaction mixture was diluted with H₂O and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (hexane/EtOAc, 1:1) to give an unsaturated amide S3 (4.59 g, 76%) as a yellow solid. The spectral data of S3 were identical to those of 9b.

To a stirred solution of S3 (75 mg, 0.18 mmol) in 4 mL of EtOH was added SnCl₂ (171 mg, 0.902 mmol) at room temperature, and the reaction mixture was stirred for 3 h at 75 °C. The reaction mixture was quenched with sat. NaHCO₃ solution, diluted with H₂O, and extracted with EtOAc. The organic layer was dried over MgSO₄ and concentrated in vacuo to afford crude aniline S4 as a yellow waxy solid. To a stirred solution of crude aniline S4 in 10 mL of 1,4-dioxane was carefully added Red-Al (170 μL, 0.54 mmol, > 60 wt. % in toluene) at 0 °C, and

2-(3,4-Dimethoxyphenyl)-3-(4-nitrophenyl)-1,6,7,8,9a-hexahydro-4H-quinoliniz-4-one (S3). To a stirred solution of amide S2 (6.31 g, 14.8 mmol) in 100 mL of EtOH was added K₂CO₃ (900 mg) at room temperature, and the reaction mixture was refluxed for 1.5 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The reaction mixture was diluted with H₂O and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (hexane/EtOAc, 1:1) to give an unsaturated amide S3 (4.59 g, 76%) as a yellow solid. The spectral data of S3 were identical to those of 9b.

N-(4-(8-(3,4-Dimethoxyphenyl)-1,3,4,6,9a-hexahydro-2H-quinoliniz-7-yl)phenyl)methanesulfonamide (13). To a stirred solution of S3 (75 mg, 0.18 mmol) in 4 mL of EtOH was added SnCl₂ (171 mg, 0.902 mmol) at room temperature, and the reaction mixture was stirred for 3 h at 75 °C. The reaction mixture was quenched with sat. NaHCO₃ solution, diluted with H₂O, and extracted with EtOAc. The organic layer was dried over MgSO₄ and concentrated in vacuo to afford crude aniline S4 as a yellow waxy solid. To a stirred solution of crude aniline S4 in 10 mL of 1,4-dioxane was carefully added Red-Al (170 μL, 0.54 mmol, > 60 wt. % in toluene) at 0 °C, and
the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched by successive addition of H₂O, a 15% NaOH aq. soln., and H₂O. The suspension was then filtered over a Celite Pad, and the filtrate was concentrated in vacuo to afford crude quinolizidine S5 as a brown solid. To a stirred solution of crude quinolizidine S5 in 3 mL of CH₂Cl₂ was added pyridine (22 μL, 0.27 mmol) and methanesulfonyl chloride (21 μL, 0.27 mmol) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with sat. NaHCO₃ solution, diluted with H₂O, and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH₂Cl₂/MeOH, 15:1) to give a sulfonamide 13 (41 mg, 51%) as a yellow waxy solid. ¹H NMR (500 MHz, CDCl₃) δ 6.99 (dd, J = 8.8 Hz, 11.7 Hz, 4H), 6.61 (q, J = 8.4 Hz, 2H), 6.40 (d, J = 1.2 Hz, 1H), 3.76 (s, 3H), 3.60 (d, J = 16.6 Hz, 1H), 3.51 (s, 3H), 3.09 (d, J = 11.2 Hz, 1H), 3.04 (d, J = 16.6 Hz, 1H), 2.90 (s, 3H), 2.50 (d, J = 16.8 Hz, 1H), 2.41 (d, J = 9.4 Hz, 1H), 2.35 (d, J = 13.2 Hz, 1H), 2.11 (dd, J = 11.0 Hz, 15.0 Hz, 1H), 1.83 (d, J = 8.5 Hz, 2H), 1.70 (brs, 2H), 1.38–1.31 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 147.9, 147.4, 138.0, 134.9, 133.9, 132.5, 130.7, 130.3 (2C), 120.6, 120.4 (2C), 112.8, 110.5, 59.7, 57.8, 55.7, 55.5, 55.4, 39.3, 39.2, 33.0, 25.6, 24.1; IR (CHCl₃) υmax 3256, 2933, 2255, 1510, 1325, 1253, 1151, 1025, 910, 728 (cm⁻¹); HRMS (FAB): calcd. for C₂₄H₃₁N₂O₄S [M+H]+ 443.2005, found 443.2006.
2.2. Synthesis of compounds (±)-5b, (±)-12b, 14, and 15

Scheme S2. Synthesis of compounds (±)-5b, (±)-12b, 14, and 15.\(^a\)

\(^a\)Reaction conditions: (a) PIFA, BF\(_3\)-OEt\(_2\), CH\(_2\)Cl\(_2\), –10 °C, 95%; (b) SnCl\(_2\), EtOH, 75 °C; (c) MeSO\(_2\)Cl, pyridine, CH\(_2\)Cl\(_2\), 62% (d) LiAlH\(_4\), THF, reflux, 77% for (±)-5b; (e) PrSO\(_2\)Cl, pyridine, CH\(_2\)Cl\(_2\), 57% for 14a (over three steps); (f) PhSO\(_2\)Cl, pyridine, CH\(_2\)Cl\(_2\), 62% for 14b (over three steps) (g) AcCl, CH\(_2\)Cl\(_2\), 55% for 15a (over three steps); (h) MeCO\(_2\)Cl, pyridine, CH\(_2\)Cl\(_2\), 49% for 15b (over three steps).

2,3-Dimethoxy-6-nitro-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-9-one (S6). To a stirred solution of S3 (2.10 g, 5.14 mmol) in 40 mL of CH\(_2\)Cl\(_2\) was added phenylidodine(III) bis(trifluoroacetate) (PIFA) (2.66 g, 6.17 mmol) and BF\(_3\)-OEt\(_2\) (950 μL, 7.70 mmol) at –10 °C, and the reaction mixture was stirred for 30 min at –10 °C. The reaction mixture was quenched with sat. NaHCO\(_3\) solution, diluted with H\(_2\)O, and extracted with CH\(_2\)Cl\(_2\). The organic layer was dried over MgSO\(_4\) and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH\(_2\)Cl\(_2\)/EtOAc, 10:1) to give an amide S6 (1.98 g, 95%) as a yellow solid. The spectral data of S6 were identical to those of 10b.

N-(2,3-Dimethoxy-9-oxo-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-6-yl)methanesulfonamide ((±)-12b). To a stirred solution of S6 (95 mg, 0.23 mmol) in 8 mL of EtOH was added SnCl\(_2\) (218 mg, 1.15 mmol) at room temperature, and the reaction mixture was stirred for 6 h at
75 °C. The reaction mixture was quenched with sat. NaHCO₃ solution, diluted with H₂O, and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated in vacuo to afford crude aniline S7 as a yellow solid. To a stirred solution of crude aniline S7 in 3 mL of CH₂Cl₂ was added pyridine (28 μL, 0.35 mmol) and methanesulfonyl chloride (27 μL, 0.35 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. NaHCO₃ solution, diluted with H₂O, and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH₂Cl₂/MeOH, 40:1) to give 14 (65 mg, 62%) as a pale yellow solid. The spectral data of (±)-12b were identical to those of 12b.

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N-(2,3\text{-Dimethoxy}-11,12,13,14,14a,15\text{-hexahydro}\text{-}9\text{H}-\text{dibenzof}[f,h]pyrido[1,2-b]isoquinolin-6-yl)methanesulfonylamine (\text{±\text{-}5b}).\] To a stirred solution of (±)-12b (60 mg, 0.13 mmol) in 6 mL of THF was added LiAlH₄ (200 μL, 0.20 mmol, 1 M solution in THF) at 0 °C, and the reaction mixture was refluxed for 2 h. The reaction mixture was quenched by successive addition of H₂O, a 15% NaOH aq. soln., and H₂O. The suspension was then filtered over a Celite Pad, and the filtrate was concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH₂Cl₂/MeOH, 15:1) to give the desired product 5b (44 mg, 77%) as a pale yellow solid. The spectral data of (±)-5b were identical to those of 5b.

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N-(2,3\text{-Dimethoxy}-11,12,13,14,14a,15\text{-hexahydro}\text{-}9\text{H}-\text{dibenzof}[f,h]pyrido[1,2-b]isoquinolin-6-yl)propane-2-sulfonamide (14a).\] To a stirred solution of S6 (81 mg, 0.20 mmol) in 4 mL of EtOH was added SnCl₂ (190 mg, 1.00 mmol) at room temperature, and the reaction mixture was stirred for 6 h at 75 °C. The reaction mixture was quenched with sat. NaHCO₃ solution, diluted with H₂O, and extracted with EtOAc. The organic layer was dried over MgSO₄ and concentrated in vacuo to afford crude aniline S7 as a yellow waxy solid. To a stirred solution of crude aniline S7 in 10 mL of THF was carefully added LiAlH₄ (400 μL, 0.40 mmol, 1 M solution in THF) at 0 °C, and the reaction mixture was refluxed for 1 h. The reaction mixture was quenched by successive addition of H₂O, a 15% NaOH aq. soln., and H₂O. The suspension was then filtered over a Celite Pad, and the filtrate was concentrated in vacuo to afford crude quinolizidine S8 as a brown solid. To a stirred solution of crude
quinolizidine S8 in 3 mL of CH₂Cl₂ was added pyridine (32 µL, 0.40 mmol) and 2-propanesulfonyl chloride (45 µL, 0.40 mmol) at 0 °C, and the reaction mixture was stirred for 8 h at room temperature. The reaction mixture was quenched with sat. NaHCO₃ solution, diluted with H₂O, and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH₂Cl₂/MeOH, 15:1) to give a sulfonamide 14a (53 mg, 57%) as a pale yellow solid. mp 255.1–257.3 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.12 (s, 1H), 7.67 (s, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.27–7.22 (m, 2H), 4.32 (d, J = 15.3 Hz, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.55 (d, J = 15.3 Hz, 1H), 3.36–3.25 (m, 2H), 3.10 (dd, J = 2.9 Hz, 16.4 Hz, 1H), 2.98–2.91 (m, 1H), 2.42–2.37 (m, 1H), 2.34–2.28 (m, 1H), 2.04 (d, J = 10.0 Hz, 1H), 1.90 (d, J = 12.7 Hz, 1H), 1.88–1.81 (m, 2H), 1.67–1.58 (m, 2H), 1.40 (dd, J = 4.1 Hz, 6.8 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 149.4, 148.5, 134.3, 129.2, 128.7, 127.2, 126.2, 125.9, 125.7, 123.4, 120.0, 115.2, 103.5 (2C), 57.8, 56.2, 55.9, 55.7, 55.6, 52.4, 34.3, 33.1, 25.5, 24.1, 16.7, 16.5; IR (CHCl₃) v max 2932, 2864, 2087, 1736, 1609, 1513, 1416, 1304, 1256, 1134, 1036, 967, 785, 688 (cm⁻¹); HRMS (FAB): calcd. for C₂₆H₃₈N₂O₄S [M+H]+ 469.2161, found 469.2157.

N-(2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzof[h]pyrido[1,2-b]isoquinolin-6-yl)benzenesulfonyl amide (14b). To a stirred solution of S6 (81 mg, 0.20 mmol) in 4 mL of EtOH was added SnCl₂ (190 mg, 1.00 mmol) at room temperature, and the reaction mixture was stirred for 6 h at 75 °C. The reaction mixture was quenched with sat. NaHCO₃ solution, diluted with H₂O, and extracted with EtOAc. The organic layer was dried over MgSO₄ and concentrated in vacuo to afford crude aniline S7 as a yellow waxy solid. To a stirred solution of crude aniline S7 in 10 mL of THF was carefully added LiAlH₄ (400 µL, 0.40 mmol, 1 M solution in THF) at 0 °C, and the reaction mixture was refluxed for 1 h. The reaction mixture was quenched by successive addition of H₂O, a 15% NaOH aq. soln., and H₂O. The suspension was then filtered over a Celite Pad, and the filtrate was concentrated in vacuo to afford crude quinolizidine S8 as a brown solid. To a stirred solution of crude quinolizidine S8 in 3 mL of CH₂Cl₂ was added pyridine (32 µL, 0.40 mmol) and benzenesulfonyl chloride (51 µL, 0.40 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. NaHCO₃ solution, diluted with H₂O, and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH₂Cl₂/MeOH, 15:1) to give a sulfonamide 14b (62 mg, 62%) as a white solid. mp 272.8–273.9 °C; ¹H NMR
(500 MHz, (CD$_3$)$_2$SO) δ 8.20 (s, 1H), 7.85 (d, $J = 7.7$ Hz, 2H), 7.72 (d, $J = 9.1$ Hz, 1H), 7.70 (s, 1H), 7.59–7.52 (m, 3H), 7.33 (d, $J = 8.8$ Hz, 1H), 7.23 (s, 1H), 4.25 (d, $J = 15.9$ Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.36 (d, $J = 15.8$ Hz, 1H), 3.11 (d, $J = 10.7$ Hz, 1H), 3.04 (d, $J = 15.4$ Hz, 1H), 2.67 (dd, $J = 10.7$ Hz, 16.2 Hz, 1H), 2.22–2.16 (m, 1H), 2.12 (t, $J = 11.1$ Hz, 1H), 1.91 (d, $J = 10.1$ Hz, 1H), 1.76 (d, $J = 9.9$ Hz, 1H), 1.68 (d, $J = 12.2$ Hz, 1H), 1.57 (q, $J = 11.1$ Hz, 1H), 1.38–1.29 (m, 2H); $^1$C NMR (125 MHz, (CD$_3$)$_2$SO) δ 149.4, 148.4, 139.7, 135.2, 132.9, 129.3 (2C), 128.5, 126.7 (2C), 126.0, 125.7, 125.2, 124.9, 123.8, 122.4, 119.0, 112.8, 104.2, 103.2, 57.0, 55.5 (2C), 55.3, 55.2, 33.9, 33.0, 25.4, 23.9; IR (CHCl$_3$) $\nu_{\text{max}}$ 2930, 1738, 1611, 1513, 1256, 1154, 1090, 1041, 970, 869, 690 (cm$^{-1}$); HRMS (FAB): calcd. for C$_{26}$H$_{31}$N$_2$O$_3$S [M+H]$^+$ 503.2005, found 503.208.

N-(2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzof[f,h]pyrido[1,2-b]isoquinolin-6-yl)acetamide (15a). To a stirred solution of S6 (74 mg, 0.18 mmol) in 4 mL of EtOH was added SnCl$_2$ (171 mg, 1.90 mmol) at room temperature, and the reaction mixture was stirred for 6 h at 75 $^\circ$C. The reaction mixture was quenched with sat. NaHCO$_3$ solution, diluted with H$_2$O, and extracted with EtOAc. The organic layer was dried over MgSO$_4$ and concentrated in vacuo to afford crude aniline S7 as a yellow waxy solid. To a stirred solution of crude aniline S7 in 10 mL of THF was carefully added LiAlH$_4$ (360 $\mu$L, 0.36 mmol, 1 M solution in THF) at 0 $^\circ$C, and the reaction mixture was refluxed for 1 h. The reaction mixture was quenched by successive addition of H$_2$O, a 15% NaOH aq. soln., and H$_2$O. The suspension was then filtered over a Celite Pad, and the filtrate was concentrated in vacuo to afford crude quinolizidine S8 as a brown solid. To a stirred solution of crude quinolizidine S8 in 3 mL of CH$_2$Cl$_2$ was added acetyl chloride (26 $\mu$L, 0.36 mmol) at 0 $^\circ$C, and the reaction mixture was stirred for 5 h at room temperature. The reaction mixture was quenched with sat. NaHCO$_3$ solution, diluted with H$_2$O, and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH$_2$Cl$_2$/MeOH, 15:1) to give an amide 15a (40 mg, 55%) as a pale yellow solid. mp 208.7–209.9 $^\circ$C; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.81 (s, 1H), 7.89 (s, 1H), 7.72 (d, $J = 8.7$ Hz, 1H), 7.56 (brs, 1H), 7.47 (d, $J = 9.2$ Hz, 1H), 7.22 (s, 1H), 4.45 (d, $J = 15.5$ Hz, 1H), 4.07 (s, 3H), 4.04 (s, 3H), 3.62 (d, $J = 15.5$ Hz, 1H), 3.31 (d, $J = 11.0$ Hz, 1H), 3.10 (d, $J = 13.3$ Hz, 1H), 2.92 (dd, $J = 10.6$ Hz, 16.0 Hz, 1H), 2.45 (t, $J = 10.1$ Hz, 1H), 2.31 (td, $J = 4.1$ Hz, 11.0 Hz, 1H), 2.25 (s, 3H), 2.04 (d, $J = 14.2$ Hz, 1H), 1.88 (d, $J = 12.8$ Hz, 1H), 1.81–1.75 (m, 2H), 1.61–1.41 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$+CD$_2$COOD) δ 170.3, 149.2, 148.9, 136.3, 128.9, 124.4, 124.0, 123.6, 123.4, 122.3, 118.7, 117.4, 111.9, 103.5, 103.4, 66.4, 65.2, 58.1,
55.8 (2C), 35.9, 30.9, 29.3, 27.0, 23.9; IR (CHCl$_3$) $\nu_{\text{max}}$ 2983, 2234, 1733, 1301, 1031, 985, 911, 731 (cm$^{-1}$); HRMS (FAB): calcd. for C$_{25}$H$_{29}$N$_2$O$_3$ [M+H]$^+$ 405.2178, found 405.2183.

Methyl (2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-6-yl)carbamate (15b). To a stirred solution of S6 (74 mg, 0.18 mmol) in 4 mL of EtOH was added SnCl$_2$ (171 mg, 1.90 mmol) at room temperature, and the reaction mixture was stirred for 6 h at 75 °C. The reaction mixture was quenched with sat. NaHCO$_3$ solution, diluted with H$_2$O, and extracted with EtOAc. The organic layer was dried over MgSO$_4$ and concentrated in vacuo to afford crude aniline S7 as a yellow waxy solid. To a stirred solution of crude aniline S7 in 10 mL of THF was carefully added LiAlH$_4$ (360 $\mu$L, 0.36 mmol, 1 M solution in THF) at 0 °C, and the reaction mixture was refluxed for 1 h. The reaction mixture was quenched by successive addition of H$_2$O, a 15% NaOH aq. soln., and H$_2$O. The suspension was then filtered over a Celite Pad, and the filtrate was concentrated in vacuo to afford crude quinolizidine S8 as a brown solid. To a stirred solution of crude quinolizidine S8 in 3 mL of CH$_2$Cl$_2$ was added pyridine (29 $\mu$L, 0.36 mmol) and methyl chloroformate (28 $\mu$L, 0.36 mmol) at 0 °C, and the reaction mixture was stirred for 4 h at room temperature. The reaction mixture was quenched with sat. NaHCO$_3$ solution, diluted with H$_2$O, and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH$_2$Cl$_2$/MeOH, 15:1) to give a carbamate 15b (37 mg, 49%) as a pale yellow solid. mp 215.2–216.5 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.52 (brs, 1H), 7.84 (s, 1H), 7.67 (d, $J = 8.8$ Hz, 1H), 7.41 (dd, $J = 1.7$ Hz, 8.8 Hz, 1H), 7.18 (s, 1H), 7.07 (brs, 1H), 4.37 (d, $J = 15.5$ Hz, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.81 (s, 3H), 3.55 (d, $J = 15.6$ Hz, 1H), 3.26 (d, $J = 11.0$ Hz, 1H), 3.04 (dd, $J = 3.2$ Hz, 16.4 Hz, 1H), 2.85 (dd, $J = 10.5$ Hz, 16.1 Hz, 1H), 2.38–2.30 (m, 1H), 2.30–2.23 (m, 1H), 2.01 (d, $J = 13.3$ Hz, 1H), 1.87 (d, $J = 15.2$ Hz, 1H), 1.80–1.71 (m, 2H), 1.59–1.37 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.3, 149.4, 148.4, 135.3, 129.4, 126.2, 125.5, 125.2 (2C), 123.6, 123.3, 117.8, 111.2, 103.9, 103.7, 57.5, 56.2, 55.94, 55.89, 55.8, 52.4, 34.6, 33.6, 25.8, 24.3; IR (CHCl$_3$) $\nu_{\text{max}}$ 2985, 2936, 1732, 1373, 1238, 1044, 910, 727 (cm$^{-1}$); HRMS (FAB): calcd. for C$_{25}$H$_{29}$N$_2$O$_3$ [M+H]$^+$ 421.2127, found 421.2133.
3. HPLC analysis

HPLC analysis used an Agilent 1200 Series HPLC (Agilent Technologies, Palo Alto, CA, USA). Mobile phase A consisted of 0.1% formic acid in HPLC grade water. The HPLC analysis was performed using a reversed-phase Agilent Eclipse Plus C18 column (4.6 x 150 mm, 3.5 μm) at a flow rate of 0.7 mL/min (30–100% aqueous MeOH with 0.1% formic acid over 20 min and MeOH with 0.1% formic acid from 20 to 25 min).

Table S1. Purity of all biologically evaluated compounds.

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<td>((R))-cryptopleurine (2)</td>
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<td>((\pm))-5b</td>
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(modified after loading)

Additional Info: Peak(s) manually integrated

Area Percent Report

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Dilution: 1.0000

Use Multiplier & Dilution Factor with ISTDs

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*** End of Report ***
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Additional Info : Peak(s) manually integrated

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,4 Ref=off

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(R)-N-(2,3-Dimethoxy-9,11,12,13a,14-hexahydrodibenzo[f,h]pyrrolo[1,2-b]isoquinolin-6-yl)methanesulfonamide (5a)
(R)-N-(2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-6-y1)methanesulfonamide (5b)

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Additional Info : Peak(s) manually integrated

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Use Multiplier & Dilution Factor with ISTDs

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Totals : 8337.56348 671.61854

*** End of Report ***
N-(2,3-Dimethoxy-11,12,13,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-6-yl)methanesulfonamide (±-5b)

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Additional Info : Peak(s) manually integrated

Area Percent Report

Sorted By : Signal
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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254.4 Ref=off

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3  7.205 BB  0.1635  4123.65967  389.67722  97.7976
4  8.260 BB  0.1094  31.10304  3.88670  0.7376
5  9.788 BB  0.1615  17.69142  1.64400  0.4196
Totals : 4216.52374  399.72059

*** End of Report ***
N-(2,3-Dimethoxy-9-oxo-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-6-yl)methanesulfonamide (±)-12b)
**N-(4-(8-(3,4-Dimethoxyphenyl)-6-oxo-1,3,4,6,9,9a-hexahydro-2H-quinolizin-7-yl)phenyl)methanesulfonamide (13)**

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**Additional Info**: Peak(s) manually integrated

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**Area Percent Report**

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**Use Multiplier & Dilution Factor with ISTDs**

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**Totals**: 1.93754e4 997.07338

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*** End of Report ***
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N-(2,3-dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,j]pyrido[1,2-b]isoquinolin-6-yl)benzenesulfonamide (14b)

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Additional Info : Peak(s) manually integrated

Area Percent Report

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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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Totals : 5.07893e4 1999.80353

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Additional Info : Peak(s) manually integrated

Area Percent Report

Sorted By : Signal
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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254.4 Ref=off

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<td>26.75917</td>
<td>0.6062</td>
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<tr>
<td>3</td>
<td>8.920 VB</td>
<td>0.1101</td>
<td>149.70096</td>
<td>20.27711</td>
<td>0.5667</td>
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<tr>
<td>4</td>
<td>9.340 BB</td>
<td>0.1753</td>
<td>2.53767e4</td>
<td>2363.65649</td>
<td>96.0569</td>
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<tr>
<td>5</td>
<td>10.774 BV</td>
<td>0.1011</td>
<td>312.07095</td>
<td>47.23480</td>
<td>1.813</td>
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<tr>
<td>6</td>
<td>11.020 VB</td>
<td>0.1418</td>
<td>281.54953</td>
<td>29.38539</td>
<td>1.0657</td>
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</tr>
</tbody>
</table>

Totals : 2.64184e4  2502.59779

==============================================================================

S20
Methyl (2,3-Dimethoxy-11,12,13,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-6-yl)carbamate (15b)

Acq. Operator : SYSTEM  Seq. Line : 1
Acq. Instrument : Agilent_HPLC  Location : Vial 52
Injection Date : 8/12/2015 6:07:44 PM  Inj : 1
Inj Volume : 10.000 µl
Different Inj Volume from Sequence !  Actual Inj Volume : 3.000 µl
Acq. Method : C:\CHEM32\1\DATA\DEF_LC 2015-08-12 18-06-40\DEFAULT.M
Last changed : 8/12/2015 6:06:42 PM by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
Last changed : 8/13/2015 11:14:12 AM
(modified after loading)

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 B, Sig=254,4 Ref=off

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %
-----|------|--------|----------|-----|
1 6.786 BB 0.0973 44.09681 7.01427 0.1565
2 9.599 BV 0.1591 2.73616e4 2362.70752 97.0841
3 9.879 VV 0.1277 397.97348 43.12104 1.4121
4 10.187 VB 0.1184 243.24095 30.71501 0.8631
5 10.502 BB 0.0973 46.50497 7.40675 0.1650
6 11.163 BB 0.1089 89.99634 12.08225 0.3193

Totals : 2.81834e4 2463.04684

*** End of Report ***
4. Antitumor activity of (R)-cryptopleurine (2)

Figure S1. Antitumor activity of 2. A) The antitumor activity of 2. Caki-1 cells (1 × 10^7 cells/mouse) were subcutaneously injected into the flanks of nude mice. Treatment with the test compounds was initiated when tumor volumes reached ~100 mm^3. 2 (3 mg/kg body weight) was orally administered five times per week in a volume of 200 µL. The control group was treated with an equal volume of vehicle. Tumor volumes were measured with a caliper every 2-3 days. B) The body weight change in the tumor xenograft model. Body weights were monitored every 2-3 days. *p < 0.05, **p < 0.01, ***p < 0.001 by t-test.