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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Contents

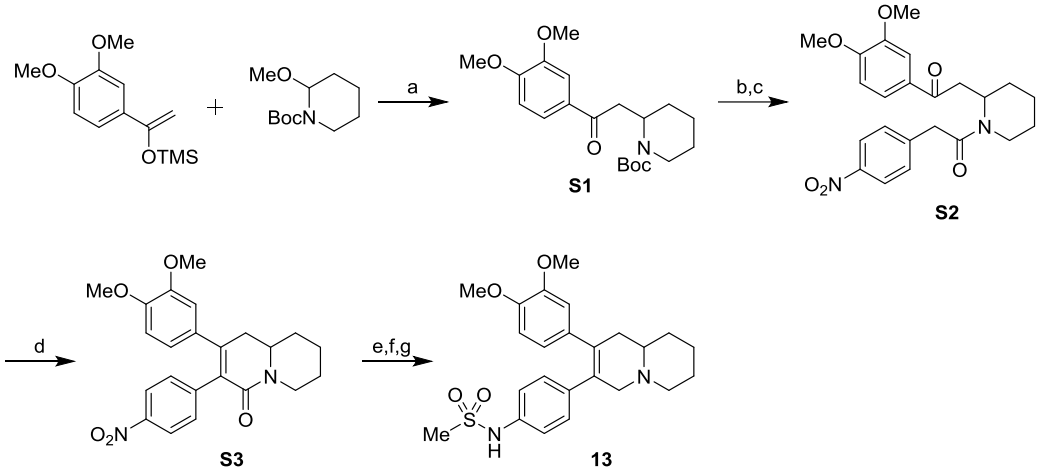
1. General Methods for Chemistry

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 $KMnO_4$ 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. ^{1}H NMR (400, 500, or 600 MHz) and ^{13}C NMR (75, 100, 125, or 150 MHz) spectra were recorded in δ units using residual $CHCl_3$ (δ 7.24 ppm) and $CDCl_3$ (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).

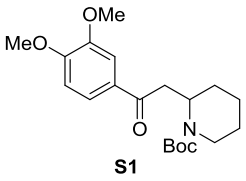
2. Synthesis of compounds (±)-5b, (±)-12b, and 13–15

2.1. Synthesis of compounds 13

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



[a]Reaction conditions: (a) $InCl_3$, CH_2Cl_2, 92%; (b) TFA, CH_2Cl_2; (c) 4-nitrophenylacetic acid, EDCI, DMAP, CH_2Cl_2, 83% (over two steps); (d) K_2CO_3, EtOH, reflux, 76%; (e) $SnCl_2$, EtOH, 75 °C; (f) Sodium bis(2-methoxyethoxy)aluminum hydride, 1,4-dioxane; (g) $MeSO_2Cl$, pyridine, CH_2Cl_2, 51% for **13** (over three steps).

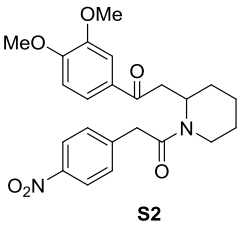


S1

*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_2Cl_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**.

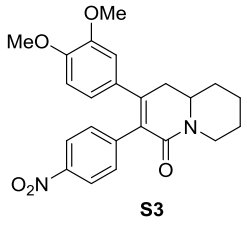
(1) Su, B.; Chen, F.; Wang, L.; Wang, Q. Design, Synthesis, Antiviral Activity, and Structure–Activity Relationships (SARs) of T wo Types of Structurally Novel Phenanthroindo/quinolizidine Analogues. *J. Agric. Food Chem.* **2014**, 62, 1233–1239.

(2) Brown, D. S.; Charreau, P.; Hansson, T.; Ley, S. V. Substitution reactions of 2-phenylsulphonyl-piperidines and -pyrrolidines with carbon nucleophiles: Synthesis of the pyrrolidine alkaloids norruspoline and ruspolinone. *Tetrahedron* **1991**, 47, 1311–132 8.



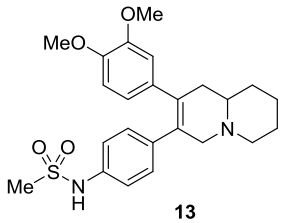
S2

*1-(3,4-Dimethoxyphenyl)-2-(1-(2-(4-nitrophenyl)acetyl)piperidin-2-yl)ethan-1-one (**S2**).* To a stirred solution of **S1** (11.3 g, 31.1 mmol) in 100 mL of CH_2Cl_2 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 CH_2Cl_2 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 H_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ 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**.



S3

*2-(3,4-Dimethoxyphenyl)-3-(4-nitrophenyl)-1,6,7,8,9,9a-hexahydro-4H-quinolizin-4-one (**S3**).* To a stirred solution of amide **S2** (6.31 g, 14.8 mmol) in 100 mL of EtOH was added K_2CO_3 (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 H_2O and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ 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**.



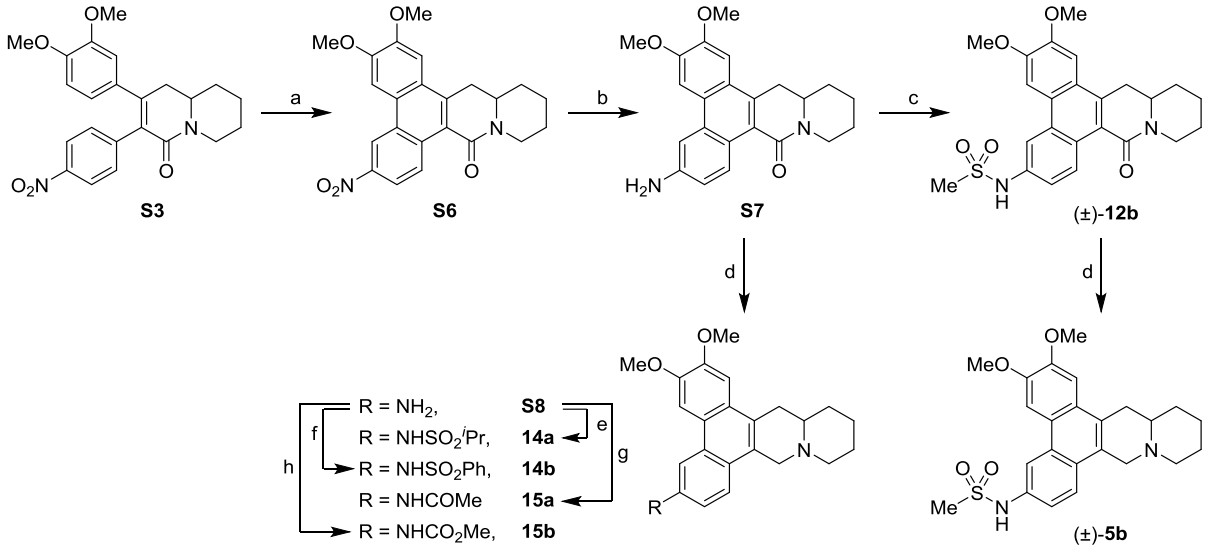
13

*N-(4-(8-(3,4-Dimethoxyphenyl)-1,3,4,6,9,9a-hexahydro-2H-quinolizin-7-yl)phenyl)methanesulfonamide (**13**).* To a stirred solution of **S3** (75 mg, 0.18 mmol) in 4 mL of EtOH was added $SnCl_2$ (171 mg, 0.902 mmol) at room temperature, and the reaction mixture was stirred for 3 h at 75 ℃. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ 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 ℃, and

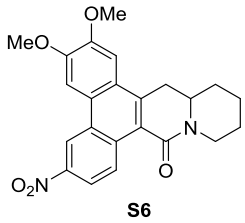
the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched by successive addition of H_2O, a 15% NaOH aq. soln., and H_2O. The suspension was then filtered over a Celite Pad, and the filtrate was concentrated in vacuo to afford crude quinolizidine **S5** as a brown solid. To a stirred solution of crude quinolizidine **S5** in 3 mL of CH_2Cl_2 was added pyridine (22 μL, 0.27 mmol) and methanesulfonyl chloride (21 μL, 0.27 mmol) at 0 ℃, and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH_2Cl_2/MeOH, 15:1) to give an sulfonamide **13** (41 mg, 51%) as a yellow waxy solid. ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 ($CHCl_3$) υ_{max} 3256, 2933, 2255, 1510, 1325, 1253, 1151, 1025, 910, 728 (cm^{-1}); HRMS (FAB): calcd. for $C_{24}H_{31}N_2O_4S$ $[M+H]^+$ 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]

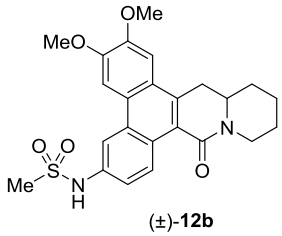


[a]Reaction conditions: (a) PIFA, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –10 °C, 95%; (b) $SnCl_2$, EtOH, 75 °C; (c) $MeSO_2Cl$, pyridine, CH_2Cl_2, 62% (d) $LiAlH_4$, THF, reflux, 77% for (±)-**5b**; (e) $^iPrSO_2Cl$, pyridine, CH_2Cl_2, 57% for **14a** (over three steps); (f) $PhSO_2Cl$, pyridine, CH_2Cl_2, 62% for **14b** (over three steps) (g) AcCl, CH_2Cl_2, 55% for **15a** (over three steps); (h) $MeCO_2Cl$, pyridine, CH_2Cl_2, 49% for **15b** (over three steps).



S6

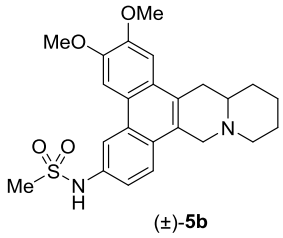
*2,3-Dimethoxy-6-nitro-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-9-one (**S6**).* To a stirred solution of **S3** (2.10 g, 5.14 mmol) in 40 mL of CH_2Cl_2 was added phenyliodine(III) bis(trifluoroacetate) (PIFA) (2.66 g, 6.17 mmol) and $BF_3{\cdot}OEt_2$ (950 µL, 7.70 mmol) 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_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH_2Cl_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**.



(±)-**12b**

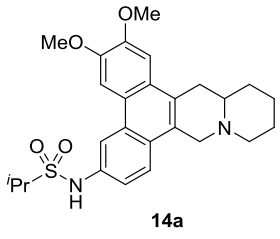
*N-(2,3-Dimethoxy-9-oxo-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-6-yl)methanesulfonamide ((±)-**12b**).* To a stirred solution of **S6** (95 mg, 0.23 mmol) in 8 mL of EtOH was added $SnCl_2$ (218 mg, 1.15 mmol) at room temperature, and the reaction mixture was stirred for 6 h at

75 ℃. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ 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 CH_2Cl_2 was added pyridine (28 μL, 0.35 mmol) and methanesulfonyl chloride (27 μL, 0.35 mmol) at 0 ℃, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH_2Cl_2/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**.



(±)-**5b**

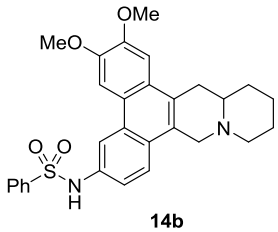
*N-(2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-6-yl)methanesulfonamide ((±)-**5b**).* To a stirred solution of (±)-**12b** (60 mg, 0.13 mmol) in 6 mL of THF was added $LiAlH_4$ (200 μL, 0.20 mmol, 1 M solution in THF) at 0 ℃, and the reaction mixture was refluxed for 2 h. The reaction mixture was quenched by successive addition of H_2O, a 15% NaOH aq. soln., and H_2O. 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 (CH_2Cl_2/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**.



14a

N-(2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[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 $SnCl_2$ (190 mg, 1.00 mmol) at room temperature, and the reaction mixture was stirred for 6 h at 75 ℃. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, 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 $LiAlH_4$ (400 μL, 0.40 mmol, 1 M solution in THF) at 0 ℃, and the reaction mixture was refluxed for 1 h. The reaction mixture was quenched by successive addition of H_2O, a 15% NaOH aq. soln., and H_2O. 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

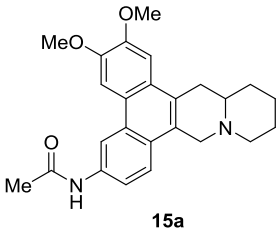
quinolizidine **S8** in 3 mL of CH_2Cl_2 was added pyridine (32 μL, 0.40 mmol) and 2-propanesulfonyl chloride (45 μL, 0.40 mmol) at 0 ℃, and the reaction mixture was stirred for 8 h at room temperature. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH_2Cl_2/MeOH, 15:1) to give a sulfonamide **14a** (53 mg, 57%) as a pale yellow solid. mp 255.1–257.3 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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 ($CHCl_3$) υ_{max} 2932, 2864, 2087, 1736, 1609, 1513, 1416, 1304, 1256, 1134, 1036, 967, 785, 688 (cm^{-1}); HRMS (FAB): calcd. for $C_{26}H_{33}N_2O_4S$ $[M+H]^+$ 469.2161, found 469.2157.



14b

N-(2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[f,h]pyrido[1,2-b]isoquinolin-6-yl)benzenesulfonamide (**14b**). To a stirred solution of **S6** (81 mg, 0.20 mmol) in 4 mL of EtOH was added $SnCl_2$ (190 mg, 1.00 mmol) at room temperature, and the reaction mixture was stirred for 6 h at 75 ℃. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, 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 $LiAlH_4$ (400 μL, 0.40 mmol, 1 M solution in THF) at 0 ℃, and the reaction mixture was refluxed for 1 h. The reaction mixture was quenched by successive addition of H_2O, a 15% NaOH aq. soln., and H_2O. 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_2Cl_2 was added pyridine (32 μL, 0.40 mmol) and benzenesulfonyl chloride (51 μL, 0.40 mmol) at 0 ℃, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH_2Cl_2/MeOH, 15:1) to give a sulfonamide **14b** (62 mg, 62%) as a white solid. mp 272.8–273.9 ℃; ^{1}H NMR

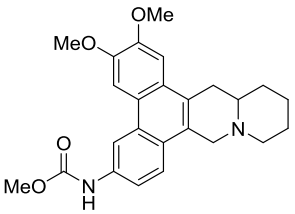
(500 MHz, $(CD_3)_2SO$) δ 8.20 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 2H), 7.72 (d, *J* = 9.1 Hz, 1H), 7.70 (s, 1H), 7.59–7.52 (m, 3H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.23 (s, 1H), 4.25 (d, *J* = 15.9 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 3.36 (d, *J* = 15.8 Hz, 1H), 3.11 (d, *J* = 10.7 Hz, 1H), 3.04 (d, *J* = 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); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) 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 ($CHCl_3$) υ_{max} 2930, 1738, 1611, 1513, 1256, 1154, 1090, 1041, 970, 869, 690 (cm^{-1}); HRMS (FAB): calcd. for $C_{29}H_{31}N_2O_4S$ $[M+H]^+$ 503.2005, found 503.2018.



15a

*N-(2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[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 ℃. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, 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 μL, 0.36 mmol, 1 M solution in THF) at 0 ℃, and the reaction mixture was refluxed for 1 h. The reaction mixture was quenched by successive addition of H_2O, a 15% NaOH aq. soln., and H_2O. 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_2Cl_2 was added acetyl chloride (26 μL, 0.36 mmol) at 0 ℃, 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_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH_2Cl_2/MeOH, 15:1) to give an amide **15a** (40 mg, 55%) as a pale yellow solid. mp 208.7–209.9 ℃; ^1H 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_3COOD) 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 ($CHCl_3$) υ_{max} 2983, 2234, 1733, 1301, 1031, 985, 911, 731 (cm^{-1}); HRMS (FAB): calcd. for $C_{25}H_{29}N_2O_3$ $[M+H]^+$ 405.2178, found 405.2183.



15b

*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 ℃. The reaction mixture was quenched with sat. $NaHCO_3$ solution, diluted with H_2O, 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 μL, 0.36 mmol, 1 M solution in THF) at 0 ℃, and the reaction mixture was refluxed for 1 h. The reaction mixture was quenched by successive addition of H_2O, a 15% NaOH aq. soln., and H_2O. 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_2Cl_2 was added pyridine (29 μL, 0.36 mmol) and methyl chloroformate (28 μL, 0.36 mmol) at 0 ℃, 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_2O, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was separated by silica gel column chromatography (CH_2Cl_2/MeOH, 15:1) to give a carbamate **15b** (37 mg, 49%) as a pale yellow solid. mp 215.2–216.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ($CHCl_3$) υ_{max} 2985, 2936, 1732, 1373, 1238, 1044, 910, 727 (cm^{-1}); HRMS (FAB): calcd. for $C_{25}H_{29}N_2O_4$ $[M+H]^+$ 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 × 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.

Compound	Retention Time, t_R (min)	Purity (%)
(*R*)-antofine (**1**)	9.363	98.6
(*R*)-cryptopleurine (**2**)	9.606	99.6
5a	6.708	97.7
5b	7.166	98.0
(±)-**5b**	7.205	97.8
(±)-**12b**	16.926	99.9
13	7.392	98.8
14a	7.426	96.0
14b	9.300	98.2
15a	9.340	96.1
15b	9.599	97.1

(*R*)-Antofine (1)

```
==========================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   9
Acq. Instrument : Agilent_HPLC                     Location : Vial 45
Injection Date  : 7/25/2013 4:30:17 AM                  Inj :   1
                                                 Inj Volume : 10.000 µl
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Additional Info : Peak(s) manually integrated
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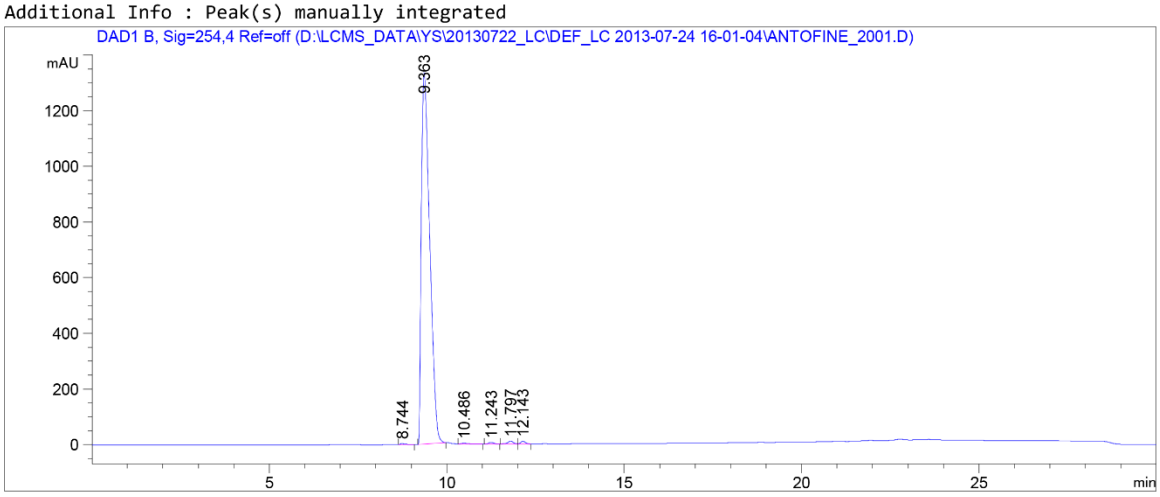


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                        Area Percent Report
==========================================================================

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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1   8.744 BB    0.1308   35.57224    3.96080   0.1613
   2   9.363 BB    0.2582 2.17394e4  1333.47498  98.5748
   3  10.486 BB    0.1548   32.25402    3.06459   0.1463
   4  11.243 BB    0.1527   58.20122    6.02334   0.2639
   5  11.797 BB    0.1620  104.48985    9.83407   0.4738
   6  12.143 BB    0.1434   83.78770    9.45482   0.3799

Totals :                  2.20537e4  1365.81260

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                        *** End of Report ***
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(*R*)-Cryptopleurine (2)

```
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Acq. Operator   : SYSTEM                       Seq. Line :   9
Acq. Instrument : Agilent_HPLC                  Location : Vial 66
Injection Date  : 7/26/2013 5:45:06 AM               Inj :   1
                                              Inj Volume : 10.000 µl
Acq. Method     : C:\CHEM32\1\DATA\DEF_LC 2013-07-25 17-15-24\DEFAULT.M
Last changed    : 7/25/2013 5:15:24 PM by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
Last changed    : 3/26/2015 5:10:56 PM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
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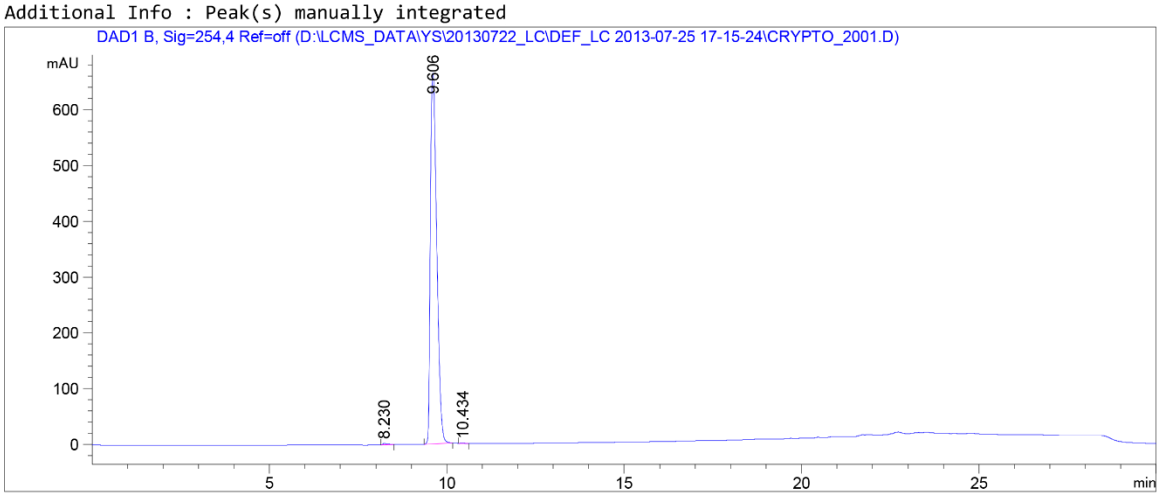


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1   8.230 BB    0.1140   23.16213    2.75635   0.2767
   2   9.606 BB    0.2004 8341.59766  664.58508  99.6360
   3  10.434 BB    0.1127    7.31297    1.03186   0.0873

Totals :                  8372.07275  668.37330


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                        *** End of Report ***
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(*R*)-*N*-(2,3-Dimethoxy-9,11,12,13,13a,14-hexahydrodibenzo[*f*,*h*]pyrrolo[1,2-*b*]isoquinolin-6-yl)methanesulfonamide (5a)

```
======================================================================
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Acq. Instrument : Agilent_HPLC                  Location : Vial 56
Injection Date  : 7/25/2013 6:18:48 PM               Inj :   3
                                               Inj Volume : 10.000 µl
Acq. Method     : C:\CHEM32\1\DATA\DEF_LC 2013-07-25 17-15-24\DEFAULT.M
Last changed    : 7/25/2013 5:15:24 PM by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
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Additional Info : Peak(s) manually integrated
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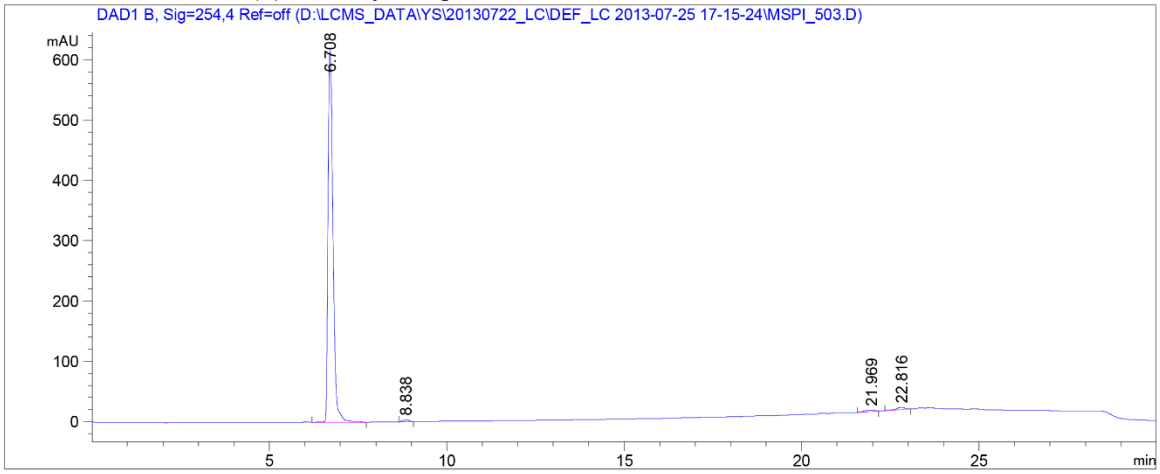


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                        Area Percent Report
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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   6.708 BB    0.1554 6090.07227  615.60669  97.7121
   2   8.838 BB    0.1605   38.06167    3.07385   0.6107
   3  21.969 BB    0.2841   44.42401    2.10574   0.7128
   4  22.816 BB    0.2447   60.10852    3.63843   0.9644

Totals :                  6232.66646  624.42471

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

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   8
Acq. Instrument : Agilent_HPLC                   Location : Vial 78
Injection Date  : 7/27/2013 5:26:43 AM                Inj :   2
                                                Inj Volume : 10.000 µl
Acq. Method     : C:\CHEM32\1\DATA\DEF_LC 2013-07-26 17-59-27\DEFAULT.M
Last changed    : 7/26/2013 5:59:27 PM by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
Last changed    : 3/26/2015 5:10:56 PM
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Additional Info : Peak(s) manually integrated
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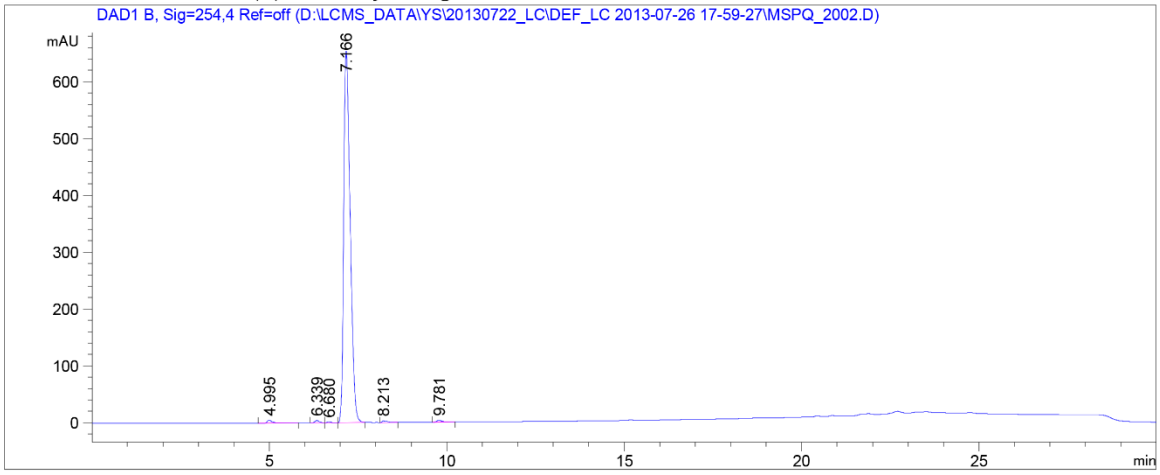


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1   4.995 BB    0.1561   56.41632    5.21959   0.6767
   2   6.339 BB    0.1231   33.45209    4.10218   0.4012
   3   6.680 BB    0.1095   12.73742    1.78007   0.1528
   4   7.166 BB    0.1877 8172.47949  654.23041  98.0200
   5   8.213 BB    0.1222   26.78800    2.94296   0.3213
   6   9.781 BB    0.1608   35.69016    3.33533   0.4281

Totals :                  8337.56348  671.61054

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                        *** End of Report ***
```

_N_-(2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9H-dibenzo[_f,h_]pyrido[1,2-_b_]isoquinolin-6-yl)methanesulfonamide ((±)-5b)

```
======================================================================
Acq. Operator   : SYSTEM                        Seq. Line :   7
Acq. Instrument : Agilent_HPLC                   Location : Vial 77
Injection Date  : 7/27/2013 4:24:19 AM                Inj :   3
                                               Inj Volume : 10.000 µl
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Last changed    : 7/26/2013 5:59:27 PM by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
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Additional Info : Peak(s) manually integrated
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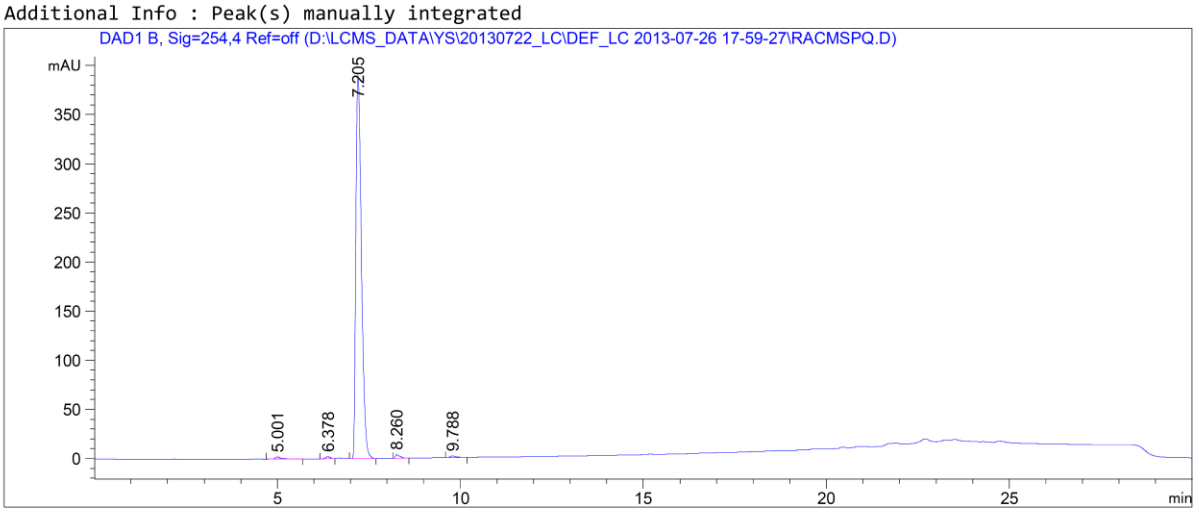


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1   5.001 BB    0.1621   26.86090    2.37301   0.6370
   2   6.378 BB    0.1218   17.20870    2.13966   0.4081
   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


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                        *** End of Report ***
```

_N_-(2,3-Dimethoxy-9-oxo-11,12,13,14,14a,15-hexahydro-9_H_-dibenzo[_f_,_h_]pyrido[1,2-_b_]isoquinolin-6-yl)methanesulfonamide ((±)-12b)

```
======================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Agilent_HPLC                     Location : Vial 31
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                                                  Inj Volume : 10.000 µl
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Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
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Additional Info : Peak(s) manually integrated
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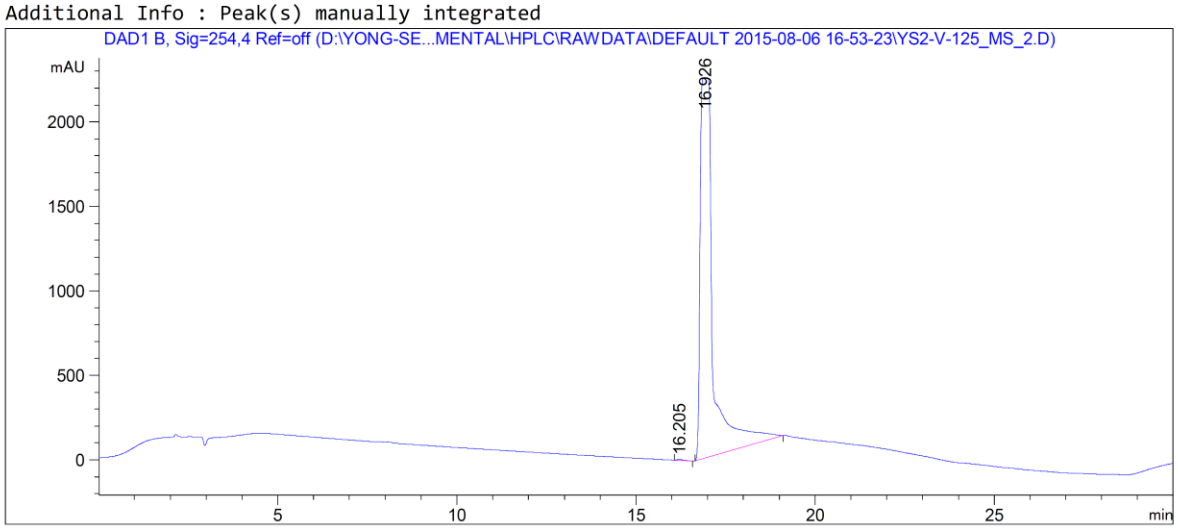


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                        Area Percent Report
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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


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

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1  16.205 BB    0.1519   74.54596    7.50295   0.1323
   2  16.926 BB    0.2977 5.62724e4  2250.84229  99.8677

Totals :                  5.63469e4  2258.34523


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                        *** End of Report ***
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_N_-(4-(8-(3,4-Dimethoxyphenyl)-6-oxo-1,3,4,6,9,9a-hexahydro-2_H_-quinolizin-7-yl)phenyl)methanesulfonamide (13)

```
======================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   6
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Injection Date  : 8/8/2015 12:46:51 PM                  Inj :   1
                                                  Inj Volume : 10.000 µl
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Last changed    : 8/8/2015 10:10:06 AM by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
Last changed    : 8/13/2015 10:44:50 AM
                  (modified after loading)
Additional Info : Peak(s) manually integrated
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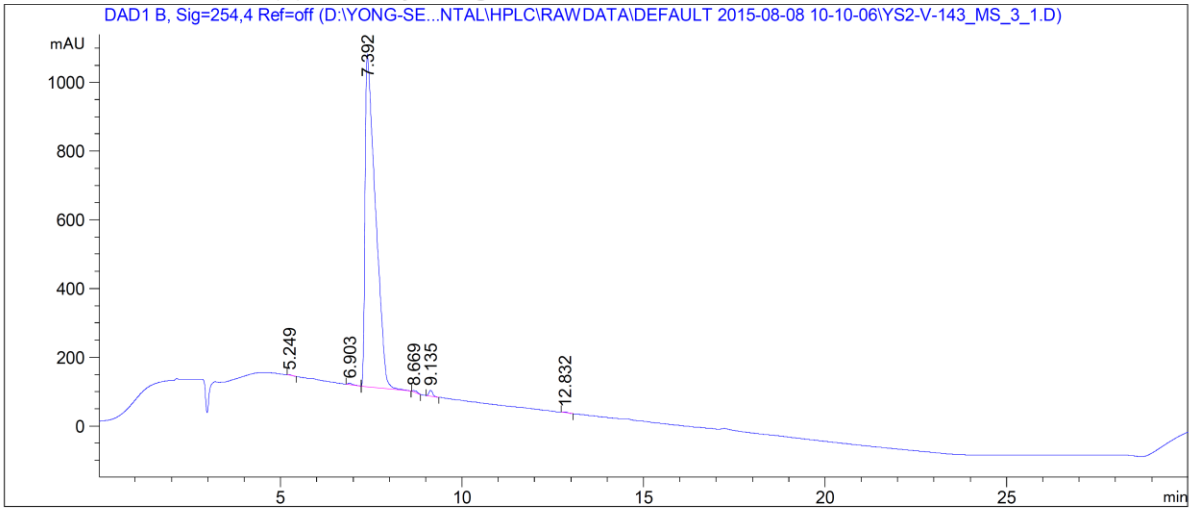


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======================================================================
                        Area Percent Report
======================================================================

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   5.249 BB    0.1108   11.41037    1.60812   0.0589
   2   6.903 BB    0.1324   36.80860    4.11376   0.1900
   3   7.392 BB    0.2809 1.91495e4   967.74664  98.8344
   4   8.669 BB    0.1266   37.98580    3.93621   0.1961
   5   9.135 BB    0.1060  118.81143   17.31701   0.6132
   6  12.832 BB    0.1373   20.81833    2.35164   0.1074

Totals :                  1.93754e4   997.07338


======================================================================
                        *** End of Report ***
```

_N_-(2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9_H_-dibenzo[_f,h_]pyrido[1,2-_b_]isoquinolin-6-yl)propane-2-sulfonamide (14a)

```
======================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Agilent_HPLC                     Location : Vial 62
Injection Date  : 8/12/2015 3:42:57 PM                  Inj :   1
                                                  Inj Volume : 10.000 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5.000 µl
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Last changed    : 8/12/2015 3:41:52 PM by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
Last changed    : 8/13/2015 11:14:12 AM
                  (modified after loading)
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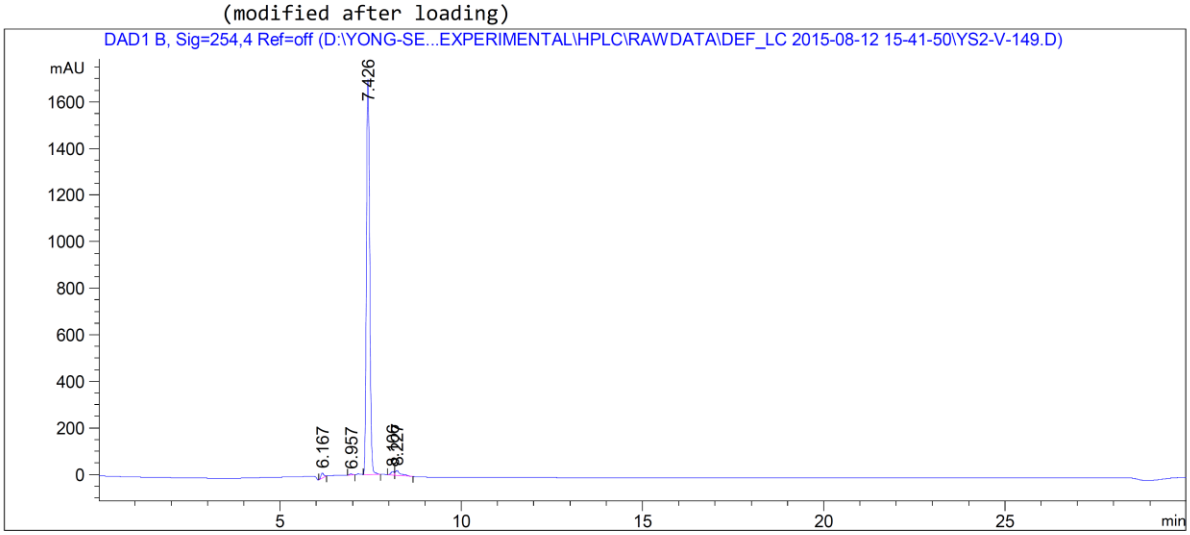


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======================================================================
                        Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      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   6.167 BB    0.0808  115.17827   21.40039   1.0240
   2   6.957 BB    0.0868   27.48657    5.10595   0.2444
   3   7.426 BB    0.1000 1.07931e4  1701.98499  95.9555
   4   8.106 BV    0.0927   98.29811   15.77552   0.8739
   5   8.227 VB    0.1381  213.96376   21.50491   1.9022

Totals :                  1.12480e4  1765.77176


======================================================================
                        *** End of Report ***
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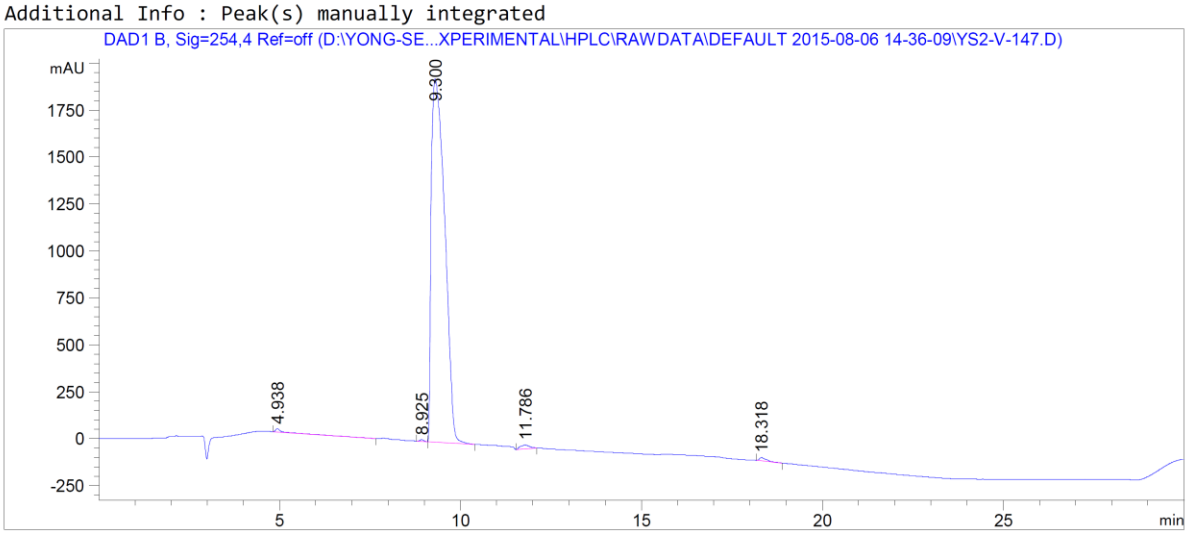
_N_-(2,3-dimethoxy-11,12,13,14,14a,15-hexahydro-9_H_-dibenzo[_f,h_]pyrido[1,2-_b_]isoquinolin-6-yl)benzenesulfonamide (14b)

```
======================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   1
Acq. Instrument : Agilent_HPLC                     Location : Vial 41
Injection Date  : 8/6/2015 2:37:07 PM                   Inj :   1
                                                  Inj Volume : 10.000 µl
Acq. Method     : D:\LC DATA\DEFAULT 2015-08-06 14-36-09\DEFAULT.M
Last changed    : 8/6/2015 2:36:09 PM by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
Last changed    : 8/13/2015 11:14:12 AM
                  (modified after loading)
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

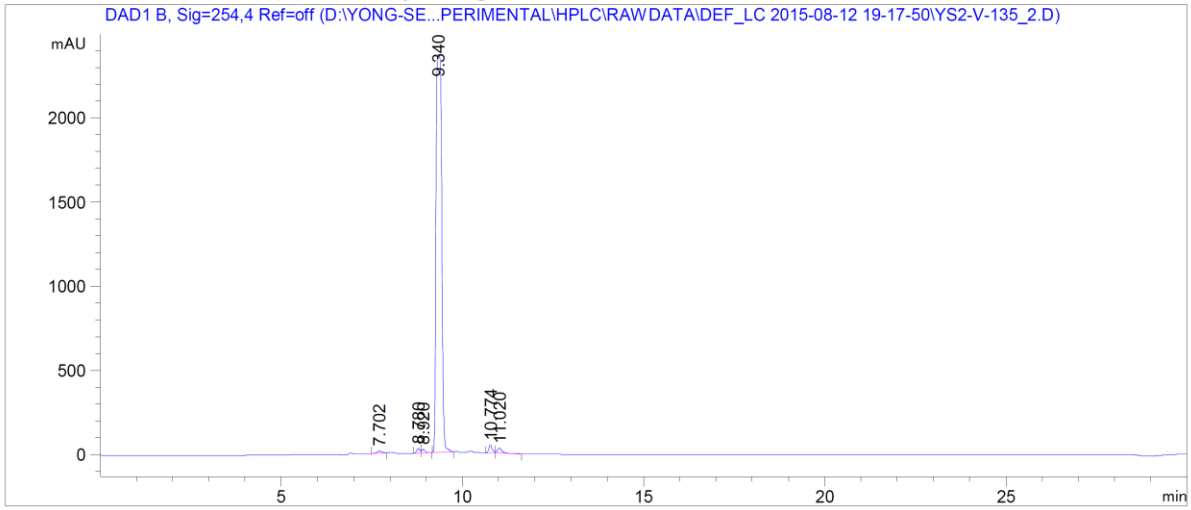
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.938 BB    0.1857  238.50041   17.64525   0.4696
   2   8.925 BV    0.1118   65.58762    8.92004   0.1291
   3   9.300 VB    0.4467 4.98822e4  1935.03870  98.2141
   4  11.786 BB    0.2580  370.95477   20.60879   0.7304
   5  18.318 BB    0.1839  232.00378   17.59076   0.4568

Totals :                  5.07893e4  1999.80353


======================================================================
                        *** End of Report ***
```

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

```
======================================================================
Acq. Operator   : SYSTEM                          Seq. Line :   2
Acq. Instrument : Agilent_HPLC                     Location : Vial 72
Injection Date  : 8/12/2015 7:50:07 PM                  Inj :   1
                                                  Inj Volume : 10.000 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5.000 µl
Acq. Method     : C:\CHEM32\1\DATA\DEF_LC 2015-08-12 19-17-50\DEFAULT.M
Last changed    : 8/12/2015 7:17:52 PM by SYSTEM
Analysis Method : C:\CHEM32\1\METHODS\DEF_LC.M
Last changed    : 8/13/2015 11:14:12 AM
                  (modified after loading)
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

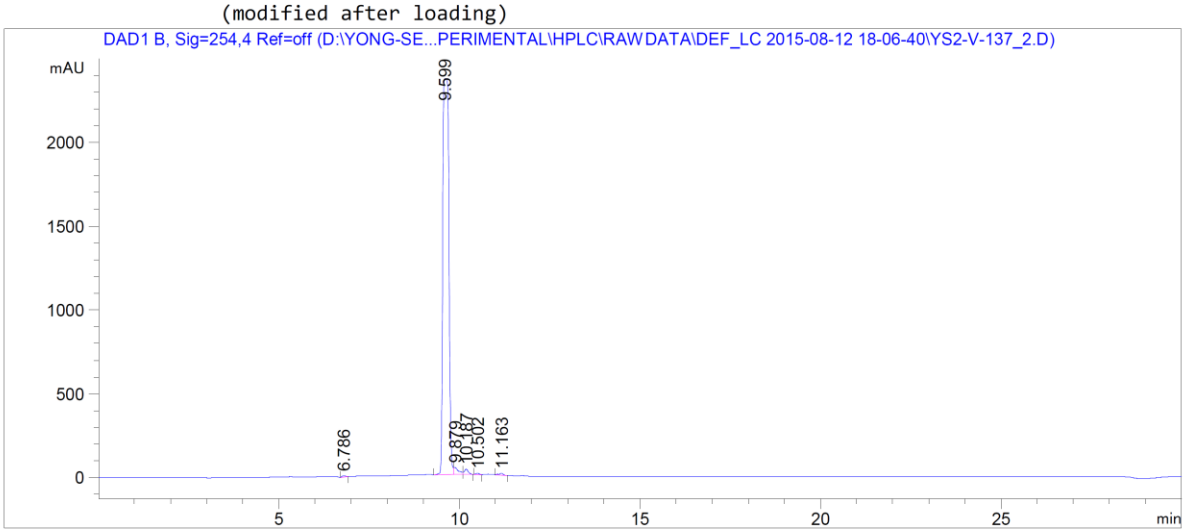
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.702 BB    0.1255  138.23685   15.28483   0.5233
   2   8.780 BV    0.0918  160.14354   26.75917   0.6062
   3   8.920 VB    0.1101  149.70096   20.27711   0.5667
   4   9.340 BB    0.1753 2.53767e4  2363.65649  96.0569
   5  10.774 BV    0.1011  312.07095   47.23480   1.1813
   6  11.020 VB    0.1418  281.54953   29.38539   1.0657

Totals :                  2.64184e4  2502.59779

======================================================================
```

Methyl (2,3-Dimethoxy-11,12,13,14,14a,15-hexahydro-9*H*-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)

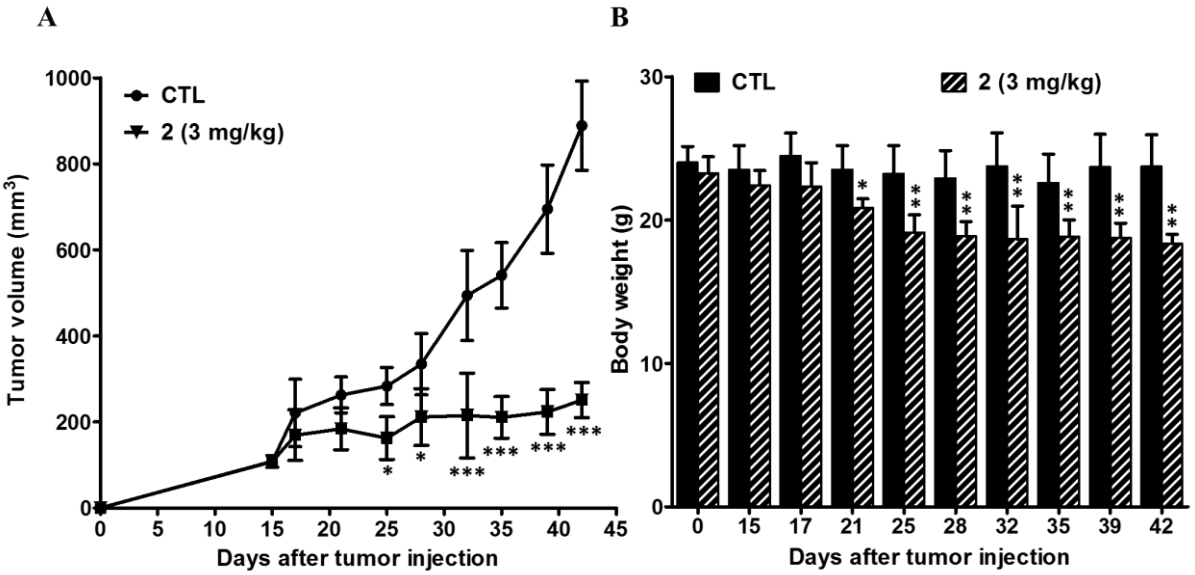


Figure S1. Antitumor activity of **2**. **A)** The antitumor activity of **2**. Caki-1 cells (1×10^7 cells/mouse) were subcutaneously injected into the flanks of nude mice. Treatment with the test compounds was initiated when tumor volumes reached ~100 mm^3. **2** (3 mg/kg body weight) was orally administered 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.