Supporting Information

Discovery and Optimization of Indolyl-Containing 4-Hydroxy-2-Pyridone Type II DNA Topoisomerase Inhibitors Active against Multi-Drug Resistant Gram-Negative Bacteria

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**Supplemental Graph 1:** Energy profile for rotation about the C-C bond in the 5-indolyl-4-hydroxy-2-pyridones shown in Figure 2 vs. dihedral bond angle (of the highlighted bonds) is plotted. Density functional minimization optimization on eighty distinct rotational steps from 0 to 360° was performed using B3LYP/6-31G* and PM3 level of theory.
1-(2-(((tert-Butyldimethylsilyloxy)methyl)-1-methyl-6-vinyl-1H-indol-5-yl)but-2-en-1-ol (22a). Compound 22a was prepared from 21 and 1-propenylmagnesium chloride according to the procedure used to prepare 22c (99%, pale yellow oil). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.00 - 0.12 (m, 6 H), 0.85 - 0.94 (m, 9 H), 1.70 - 1.78 (m, 3 H), 3.78 - 3.80 (m, 3 H), 4.82 (s, 2 H), 5.24 - 5.33 (m, 1 H), 5.52 - 5.69 (m, 2 H), 5.71 - 5.90 (m, 2 H), 6.29 - 6.38 (m, 1 H), 7.24 - 7.33 (m, 1 H), 7.42 (s, 1 H), 7.64 - 7.70 (m, 1 H).

1-(2-(((tert-Butyldimethylsilyloxy)methyl)-1-methyl-6-vinyl-1H-indol-5-yl)but-3-en-1-ol (22b). Compound 22b was prepared from 21 and allylmagnesium chloride according to the procedure used to prepare 22c (95%). $^1$H NMR (500 MHz, acetone-d$_6$) $\delta$ 0.09 (s, 3 H), 0.10 (s, 3 H), 0.91 (s, 9 H), 2.40 - 2.55 (m, 2 H), 3.83 (s, 3 H), 4.01 (d, $J=4.1$ Hz, 1 H), 4.90 (s, 2 H), 4.94 - 5.11 (m, 3 H), 5.21 (dd, $J=10.9$, 1.7 Hz, 1 H), 5.68 (dd, $J=17.3$, 1.6 Hz, 1 H), 5.82 - 5.98 (m, 1 H), 6.37 (s, 1 H), 7.27 (dd, $J=17.3$, 11.0 Hz, 1 H), 7.50 (s, 1 H), 7.66 (s, 1 H).

1-(2-(((tert-Butyldimethylsilyloxy)methyl)-1-methyl-6-vinyl-1H-indol-5-yl)hex-5-en-1-ol (22d). Compound 22d was prepared from 21 and 4-pentenylmagnesium bromide according to the procedure used to prepare 22c (90%). LC−MS $m / z$ = 400.1 [M+H]$^+$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.91 (s, 9 H), 1.41 - 1.51 (m, 1 H), 1.55 - 1.73 (m, 1 H), 1.78 - 1.88 (m, 2 H), 2.07 - 2.13 (m, 2 H), 3.80 (s, 3 H), 4.83 (s, 2 H), 4.94 (ddt, $J=10.3$, 2.1, 1.2, 1.2 Hz, 1 H), 5.01 (dq, $J=17.0$, 1.8 Hz, 1 H), 5.09 (t, $J=6.5$ Hz, 1 H), 5.29 (dd, $J=10.7$, 1.6 Hz, 1 H), 5.65 (dd, $J=17.2$, 1.7 Hz, 1 H), 5.81 (ddt, $J=17.0$, 10.2, 6.7, 6.7 Hz, 1 H), 6.35 (s, 1 H), 7.24 (dd, $J=17.7$, 11.0 Hz, 1 H), 7.40 (s, 1 H), 7.66 (s, 1 H).

2-(((tert-Butyldimethylsilyloxy)methyl)-1-methyl-1,5-dihydrocyclopenta[f]indol-5-ol (23a). Compound 23a was prepared from 22a according to the procedure used to prepare 23c (82%). LC−MS $m / z$ = 330.2 [M+H]$^+$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.06 (s, 6 H), 0.90 (s, 9 H), 3.79 (s, 3 H), 4.82 (s, 2 H), 5.24 (br. s, 1 H), 6.33 - 6.40 (m, 2 H), 6.79 - 6.84 (m, 1 H), 7.14 (s, 1 H), 7.68 (d, $J=0.95$ Hz, 1 H).

2-(((tert-Butyldimethylsilyloxy)methyl)-1-methyl-5,6,7,8-tetrahydro-1H-cycloocta[f]indol-5-ol (23d). To a solution of 22d (6.25 g, 15.64 mmol) in CH$_2$Cl$_2$ (65 mL) at room temperature was added imidazole (1.90 g, 27.91 mmol) followed TBSCl (3.60 g, 23.88 mmol). The reaction mixture was stirred overnight under an inert atmosphere. Additional imidazole (0.70 g, 10.30 mmol) and TBSCl (1.30 g, 8.63 mmol) were added and the mixture was stirred for an additional 6 h. The reaction mixture was washed with water (60 mL) followed by brine (60 mL) and dried over Na$_2$SO$_4$. The solvent was concentrated and the residue was purified by silica gel chromatography using 0-10% EtOAc in hexanes (containing 2% NEt$_3$). The intermediate (6.127 g, 11.92 mmol, 76%) was dissolved in toluene (240 mL, 0.05M) under an argon atmosphere and Grubbs second generation catalyst (300 mg, 0.35 mmol, 0.03 equiv) was added. The mixture was heated at 50 °C for 2 h until starting material was consumed. Upon cooling to room temperature and removing the solvent in vacuo, the residue was purified by silica gel chromatography (EtOAc/hexanes, 0-10% gradient) to provide a ~2:1 mixture (5.058 g) of cyclization products favoring the desired 8-member ring compound. To a solution of the mixture obtained above in THF (30 mL) was added TBAF (1M THF, 32.0 mL, 32.0 mmol). The reaction mixture was stirred for 96 h at room temperature. Upon consumption of the starting material, solvent was concentrated and the residue was partitioned between H$_2$O and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (80 mL X 3). The combined organic layers were washed with brine (80 mL) and dried over Na$_2$SO$_4$. Upon removal
of the solvent, two products were separated by column chromatography (EtOAc/hexanes, 10-60% gradient) yielding the 8-membered ring diol intermediate (0.6234 g, 20% over 2 steps) and the 7-member ring diol (0.3949 g, 14% over 2 steps) as colorless solids. To a suspension of the 8-membered ring diol intermediate (0.6234 g, 2.42 mmol) in CH$_2$Cl$_2$ (15 mL) was added imidazole (0.20 g, 2.94 mmol). The reaction was cooled to 0 °C before a solution of TBSCl (0.40 g, 2.65 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise. The mixture was stirred at 0 °C and was slowly warmed to room temperature over 1.5 h. The reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL) and washed with H$_2$O (40 mL) and the organic phase was dried over Na$_2$SO$_4$. Upon removal of the solvent, silica gel chromatography (EtOAc/hexanes, 0-80% gradient) afforded

23d (0.6987 g, 77%). LC−MS $m / z = 372.3$ [M+H$^+$].

2-(((tert-Butyldimethylsilyloxy)methyl)-1-methyl-6,7-dihydrocyclopenta[f]indol-5(1H)-one (24a). Compound 24a was prepared from 23a according to the procedure used to prepare 24c as a yellow solid in 82% yield. LC−MS $m / z = 330.1$ [M+H$^+$]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.08 (s, 6 H), 0.90 (s, 9 H), 2.72 - 2.78 (m, 2 H), 3.22 - 3.28 (m, 2 H), 3.81 (s, 3 H), 4.83 (s, 2 H), 6.49 (d, $J=0.63$ Hz, 1 H), 7.29 (s, 1 H), 8.02 (s, 1 H).

2-((tert-Butyldimethylsilyl)oxy)methyl)-1-methyl-7,8-dihydro-1H-benzo[f]indol-5(6H)-one (24b). Compound 24b was prepared from 23b according to the procedure used to prepare 23c. To the crude metathesis product, PtO$_2$ (200 mg, 0.88 mmol, 0.07 equiv) was added and the mixture was hydrogenated at 1 atm of H$_2$ until the olefin intermediate was completely consumed. The catalyst was then filtered, the toluene was concentrated and the residue was purified by column chromatography (EtOAc/hexanes, 0-15% gradient). To a solution of this intermediate (4.04 g, 11.69 mmol) in CH$_2$Cl$_2$ (120 mL) was added activated MnO$_2$ in three portions (11.4 g, 11.4 g, and 5.7 g, 118, 118, and 59 mmol) with 20 min intervals. Upon complete consumption of the starting material, the MnO$_2$ was filtered and washed with CH$_2$Cl$_2$. The filtrate was concentrated and the residue was purified by column chromatography (EtOAc/hexanes, 0-15% gradient) to afford an off-white solid (2.58 g, 64%). LC−MS $m / z = 344.5$ [M+H$^+$]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.07 (s, 6 H), 0.90 (s, 9 H), 2.16 (quintet, $J=6.3$ Hz, 2 H), 2.68 (t, $J=6.3$ Hz, 2 H), 3.10 (t, $J=6.3$ Hz, 2 H), 3.78 (s, 3 H), 4.82 (s, 2 H), 6.45 (s, 1 H), 7.09 (s, 1 H), 8.37 (s, 1 H).

2-(((tert-Butyldimethylsilyloxy)methyl)-1-methyl-7,8,9,10-tetrahydro-1H-cycloocta[f]indol-5(6H)-one (24d). Compound 24d was prepared from 23d according to the procedure used to prepare 24c (53%). LC−MS $m / z = 372.3$ [M+H$^+$]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.45 - 1.52 (m, 2 H), 1.87 (m, 4 H), 3.07 (t, $J=7.1$ Hz, 2 H), 3.27 (t, $J=6.8$ Hz, 2 H), 3.78 (s, 3 H), 4.82 (s, 2 H), 6.43 (s, 1 H), 7.06 (s, 1 H), 7.42 (s, 1 H), 8.22 (s, 1 H).

Methyl 2-((tert-butyldimethylsilyloxy)methyl)-5-(2,4-dimethoxybenzyl)-8-hydroxy-1-methyl-6-oxo-1,5,6,9-tetrahydropyrido[3',2':4,5]cyclopenta[1,2-f]indole-7-carboxylate (25a). Compound 25a was prepared from 24a according to the procedure used to prepare 25c (33%, yellow foam). LC−MS $m / z = 605.3$ [M+H$^+$].

Methyl 9-((tert-butyldimethylsilyloxy)methyl)-1-(2,4-dimethoxybenzyl)-4-hydroxy-8-methyl-2-oxo-2,5,6,8-tetrahydro-1H-indolo[6,5-h]quinoline-3-carboxylate (25b). Compound 25b was prepared from 24b according to the procedure used to prepare 25c (63%, yellow foam). LC−MS $m / z = 619.6$ [M+H$^+$]; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.06 (s, 6 H), 0.90 (s, 9 H), 2.58 - 2.72 (m, 2 H), 2.89 (t, $J=6.6$ Hz, 2 H), 3.62 (s, 3 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 

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3.97 (s, 3 H), 4.77 (s, 2 H), 5.37 (s, 2 H), 6.42 (d, \(J=2.4\) Hz, 1 H), 7.14 (d, \(J=8.4\) Hz, 1 H), 7.18 (s, 1 H), 7.63 (s, 1 H), 13.60 (s, 1 H).

**Methyl 11-(((tert-butyldimethylsilyl)oxy)methyl)-1-(2,4-dimethoxybenzyl)-4-hydroxy-10-methyl-2-oxo-2,5,6,7,8,10-hexahydro-1H-pyrido[3′,2′:7,8]cycloocta[1,2-f]indole-3-carboxylate (25d).** Compound 25d was prepared from 24d according to the procedure used to prepare 25c (51%, yellow foam). LC−MS \(m / z = 647.5\) [M+H]+; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 0.10\) (s, 3 H), 0.11 (s, 3 H), 0.91 (s, 9 H), 1.33 - 1.51 (m, 3 H), 1.80 - 1.90 (m, 1 H), 2.02 (t, \(J=7.7\) Hz, 1 H), 2.13 (t, \(J=12.0\) Hz, 1 H), 2.55 (dd, \(J=13.6, 7.3\) Hz, 1 H), 2.82 (dd, \(J=13.2, 7.6\) Hz, 1 H), 3.10 (s, 3 H), 3.76 (s, 3 H), 3.77 (s, 3 H), 4.03 (s, 3 H), 4.80 (d, \(J=13.2\) Hz, 1 H), 4.82 (d, \(J=13.2\) Hz, 1 H), 4.96 - 5.26 (m, 2 H), 6.12 (d, \(J=2.5\) Hz, 1 H), 6.24 (s, 1 H), 6.32 (dd, \(J=8.5, 2.2\) Hz, 1 H), 6.81 (d, \(J=8.5\) Hz, 1 H), 7.04 (s, 1 H), 7.11 (s, 1 H), 13.73 (s, 1 H).

**5-(2,4-Dimethoxybenzyl)-8-hydroxy-2-(hydroxymethyl)-1-methyl-6-oxo-1,5,6,9-tetrahydropyrido[3′,2′:4,5]cyclopenta[1,2-f]indole-7-carboxylic acid (26a).** Compound 26a was prepared from 25a according to the procedure used to prepare 26c (91%, yellow foam). LC−MS \(m / z = 477.0\) [M+H]+.

**1-(2,4-Dimethoxybenzyl)-4-hydroxy-9-(hydroxymethyl)-8-methyl-2-oxo-2,5,6,8-tetrahydro-1H-indolo[6,5-h]quinoline-3-carboxylic acid (26b).** Compound 26b was prepared from 25b according to the procedure used to prepare 26c (88%, yellow solid). LC−MS \(m / z = 491.0\) [M+H]+; \(^1\)H NMR (500 MHz, DMSO-d\(_6\)) \(\delta 2.54 - 2.64\) (m, 2 H), 3.60 (s, 3 H), 3.74 (s, 3 H), 4.60 (s, 2 H), 5.37 (s, 2 H), 6.22 (s, 1 H), 6.48 (dd, \(J=8.4, 2.4\) Hz, 1 H), 6.55 (d, \(J=2.4\) Hz, 1 H), 7.02 (d, \(J=8.4\) Hz, 1 H), 7.49 (s, 1 H), 7.69 (s, 1 H), 13.60 (br. s, 1 H), 15.99 (br. s, 1 H).

**1-(2,4-Dimethoxybenzyl)-4-hydroxy-11-(hydroxymethyl)-10-methyl-2-oxo-2,5,6,7,8,10-hexahydro-1H-pyrido[3′,2′:7,8]cycloocta[1,2-f]indole-3-carboxylic acid (26d).** Compound 26d was prepared from 25d according to the procedure used to prepare 26c (84%, yellow solid). LC−MS \(m / z = 519.2\) [M+H]+; \(^1\)H NMR (500 MHz, DMSO-d\(_6\)) \(\delta 1.26 - 1.46\) (m, 3 H), 1.84 (t, \(J=7.1\) Hz, 1 H), 1.94 - 2.02 (m, 1 H), 2.08 (t, \(J=12.0\) Hz, 1 H), 2.57 (dd, \(J=13.7, 7.4\) Hz, 1 H), 2.77 (dd, \(J=12.9, 7.6\) Hz, 1 H), 3.28 (s, 3 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 4.62 (s, 2 H), 4.97 (d, \(J=15.8\) Hz, 1 H), 5.11 (br. d, \(J=15.8\) Hz, 1 H), 5.24 (br. s, 1 H), 6.28 (s, 1 H), 6.32 (d, \(J=2.5\) Hz, 1 H), 6.35 (dd, \(J=8.4, 2.5\) Hz, 1 H), 6.55 (d, \(J=8.4\) Hz, 1 H), 7.30 (s, 1 H), 7.34 (s, 1 H), 13.90 (s, 1 H), 16.27 (s, 1 H).

**5-(2,4-Dimethoxybenzyl)-2-formyl-8-hydroxy-1-methyl-6-oxo-1,5,6,9-tetrahydropyrido[3′,2′:4,5]cyclopenta[1,2-f]indole-7-carboxylic acid (27a).** Compound 27a was prepared from 26a according to the procedure used to prepare 27c (72%, dark red foam). LC−MS \(m / z = 473.0\) [M-H]−.

**2-((Ethylamino)methyl)-8-hydroxy-1-methyl-6-oxo-1,5,6,9-tetrahydropyrido[3′,2′:4,5]cyclopenta[1,2-f]indole-7-carboxylic acid hydrochloride (4a).** Compound 4a was prepared from 27a and a solution of ethylamine according to the procedure used to prepare 6a (6%, white solid). LC−MS \(m / z = 354.1\) [M+H]+; \(^1\)H NMR (500 MHz, DMSO-d\(_6\)) \(\delta 1.22 - 1.38\) (m, 3 H), 2.54 (s, 2 H), 3.00 - 3.13 (m, 2 H), 3.83 - 3.90 (m, 3 H), 4.42 (br. s, 2 H), 6.89 (br. s, 1 H), 7.84 (s, 1 H), 8.41 (s, 1 H), 9.35 (br. s, 2 H), 13.59 (br. s, 1 H), 13.66 (br. s, 1 H), 16.03 (br. s, 1 H).
1-(2,4-Dimethoxybenzyl)-9-formyl-4-hydroxy-8-methyl-2-oxo-2,5,6,8-tetrahydro-1H-indolo[6,5-h]quinoline-3-carboxylic acid (27b). Compound 27b was prepared from 26b according to the procedure used to prepare 27c (69%, red foam). LC−MS m/z = 487.0 [M−H].

4-Hydroxy-8-methyl-9-((methylamino)methyl)-2-oxo-2,5,6,8-tetrahydro-1H-indolo[6,5-h]quinoline-3-carboxylic acid hydrochloride (5a). Compound 5a was prepared from 27b and a solution of methylamine according to the procedure used to prepare 6a (24%, white solid). LC−MS m/z = 354.1 [M+H]; 1H NMR (500 MHz, DMSO-d6) δ 2.63 (br. s, 3 H), 2.68 (d, J=7.6 Hz, 2 H), 2.98 (t, J=7.6 Hz, 2 H), 3.82 (s, 3 H), 4.40 (br. s, 2 H), 6.79 (s, 1 H), 7.53 (s, 1 H), 8.34 (s, 1 H), 9.26 (br. s, 2 H), 12.70 (br. s, 1 H), 13.66 (br. s, 1 H).

1-(2,4-Dimethoxybenzyl)-11-formyl-4-hydroxy-10-methyl-2-oxo-2,5,6,7,8,10-hexahydro-1H-pyrido[3',2':7,8]cycloocta[1,2-f]indole-3-carboxylic acid (27d). Compound 27d was prepared from 26d according to the procedure used to prepare 27c (73%, red foam). LC−MS m/z = 517.2 [M+H].

11-((Ethylamino)methyl)-4-hydroxy-10-methyl-2-oxo-2,5,6,7,8,10-hexahydro-1H-pyrido[3',2':7,8]cycloocta[1,2-f]indole-3-carboxylic acid hydrochloride (7a). Compound 7a was prepared from 27d and a solution of ethylamine according to the procedure used to prepare 6a (53%, white solid). LC−MS m/z = 394.8 [M-H]; 1H NMR (500 MHz, DMSO-d6) δ 1.27 (t, J=7.3 Hz, 3 H), 1.33 - 1.53 (m, 3 H), 1.90 (br. s, 1 H), 2.13 (br. s, 1 H), 2.34 (t, J=12.9 Hz, 1 H), 2.80 (dd, J=7.7 Hz, 1 H), 2.97 (dd, J=13.1, 7.7 Hz, 1 H), 3.08 (tq, J=7.6, 5.0 Hz, 2 H), 3.84 (s, 3 H), 4.42 (t, J=5.4 Hz, 2 H), 6.75 (s, 1 H), 7.54 (s, 1 H), 7.65 (s, 1 H), 9.14 (br. s, 2 H), 12.79 (s, 1 H), 13.91 (s, 1 H).

Scheme A.\(^a\)
Reagents and conditions: (a) NIS (1.1 equiv), AcOH, CH₂Cl₂, rt, overnight, 38%; (b) propargyl alcohol (1.2 equiv), Et₃N (2 equiv), Pd(PPh₃)₂Cl₂ (0.02 equiv) and CuI (0.04 equiv), CH₃N 70 °C, 2 h 77%; (c) t-BuOK (2.2 equiv), 50 °C, 1 h; (d) TBSCI (1.0 equiv), imidazole (1.05 equiv), CH₂Cl₂, 0 °C to rt, 30 min, 52% over 2 steps; (e) NaH (1.2 equiv), MeI (1.5 equiv), DMF, 0 °C to rt, 30 min, 85%; (f) n-BuLi (1.2 equiv), DMF (2.5 equiv), THF, −78 °C, 15 min, 64%; (g) potassium vinyltrifluoroborate (2.0 equiv), Pd(OAc)₂ (0.03 equiv), SfPhos ligand (0.06 equiv), K₂CO₃ (3.0 equiv), dioxane/H₂O, 85 °C, 2 h, 65%; (h) 3fbutenylmagnesium bromide (1.2 equiv), THF, −78 °C to rt, 10 min, 77%; (i) Grubbs second generation catalyst (0.05 equiv), toluene, 75 °C, 40 min, 62%; (j) 10% Pd/C, H₂ (1 atm), EtOAc, rt, 1 h, 83%; (k) Dess-Martin periodinane (1.3 equiv), NaHCO₃ (10.3 equiv), CH₂Cl₂, 0 °C to rt, 72%; (l) 2,4-dimethoxybenzyl amine (1.15 equiv), Et₃N, (2.9 equiv), TiCl₄ (0.65 equiv), CH₂Cl₂, 0 °C to rt, 16 h, then trimethyl methanetricarboxylate, (1.7 equiv), diphenyl ether, 230 °C, 10 min; 50% over 2 steps; (m) TBAF (2.9 equiv), THF, rt, 1 h, 91%; (n) LiI (3.0 equiv), EtOAc, 60 °C, 1.5 h, 97%; (o) MnO₂ (25 equiv in three portions over 1 h), CH₂Cl₂, 72%; (p) amine (3 equiv), DCE, rt, 10 min, then AcOH (1.8 equiv) and NaBH(OAc)₃ (1.8 equiv), 2 h; (q) i-Pr₂SiH, TFA, 60 °C, 2 h, then HCl/Et₂O (54-75% over 2 steps).

4-Bromo-3-chloro-2-iodoaniline (A1). To a solution of 4-f bromof3-chloroaniline (10.30 g, 49.89 mmol) in CH₂Cl₂ (100 mL) was added AcOH (9 mL, 150 mmol) followed NIS (12.50 g, 55.60 mmol). The reaction was stirred overnight and then washed well with NaHCO₃ (aq. satd., ~100 mL) until the pH was neutral. The organic layer was washed with brine (50 mL) and dried over Na₂SO₄. Upon removal of the solvent, two products (~3:2 ratio by LCfMS) were separated by column chromatography (EtOAc/hexanes, 0f10% gradient) affording 4-f bromof5-chlorof2-iodoaniline (9.17 g, 55%) and 4-f bromof3-chlorof2-iodoaniline (A1) (6.25 g, 38%) as tan solids. 4-f bromof3-chlorof2-iodoaniline was taken forward into the next step. LC−MS m / z = 330.8, 332.8 [M+H]+; 1H NMR (500 MHz, CDCl₃) δ 4.35 (br. s, 2 H), 6.53 (d, J=8.5 Hz, 1 H), 7.37 (d, J=8.5 Hz, 1 H).

3-(6-Amino-3-bromo-2-chlorophenyl)prop-2-yn-1-ol (A2). To solution of 4-f bromof3-chlorof2-iodoaniline (A1) (15.74 g, 47.36 mmol) in CH₃CN (50 mL) was added propargyl alcohol (3.40 mL, 57.01 mmol) and NEt₃ (13.2 mL, 94.71 mmol). The mixture was degassed with argon before Pd(PPh₃)₂Cl₂ (0.65 g, 0.93 mmol, 0.02 equiv) and CuI (0.36 g, 1.89 mmol, 0.04 equiv) were added. The reaction was heated at 70 °C for 2 h. The reaction mixture was cooled to room temperature and concentrated. EtOAc (200 mL) was added to the residue and the solid was filtered and washed with EtOAc. After concentration of the mother liquor, A2 (6.189 g, 50%) and starting material (6.131 g, 39%) was obtained after silica gel chromatography (EtOAc/hexanes, 0-10% gradient) affording 3-(6-amino-3-bromo-2-chlorophenyl)prop-2-yn-1-ol (A2) (15.74 g, 55%) and 4-bromo-3-chloro-2-iodoaniline (A1) (6.25 g, 38%) as tan solids. 4-bromo-3-chloro-2-iodoaniline was taken forward into the next step. LC−MS m / z = 330.8, 332.8 [M+H]+; 1H NMR (500 MHz, DMSO-δ₆) δ 4.39 (d, J=6.0 Hz, 2 H), 5.34 (t, J=6.0 Hz, 1 H), 5.88 (br. s, 2 H), 6.61 (d, J=8.5 Hz, 1 H), 7.37 (d, J=8.5 Hz, 1 H).

(5-Bromo-4-chloro-1H-indol-2-yl)methanol (A3). To a solution of A2 (9.48 g, 36.39 mmol) in DMF (75 mL) was added t-BuOK (9.0 g, 80.21 mmol). The mixture was heated at 50 °C for 1 h under an argon atmosphere. Upon cooling to 0 °C, the reaction was quenched by addition of NH₄Cl (aq. satd., 50 mL) and H₂O (150 mL). The product was extracted with EtOAc (100 mL X 3). The combined organic phases were washed with brine (100 mL) and dried over Na₂SO₄. The solvent was concentrated and the residue was purified by column chromatography. 3-(6-Amino-3-bromo-2-chlorophenyl)prop-2-yn-1-ol (A2). To solution of 4-bromo-3-chloroaniline (10.30 g, 49.89 mmol) in CH₂Cl₂ (100 mL) was added AcOH (9 mL, 150 mmol) followed NIS (12.50 g, 55.60 mmol). The reaction was stirred overnight and then washed well with NaHCO₃ (aq. satd., ~100 mL) until the pH was neutral. The organic layer was washed with brine (50 mL) and dried over Na₂SO₄. Upon removal of the solvent, two products (~3:2 ratio by LCfMS) were separated by column chromatography (EtOAc/hexanes, 0f10% gradient) affording 4-bromo-5-chloro-2-iodoaniline (9.17 g, 55%) and 4-bromo-3-chloro-2-iodoaniline (A1) (6.25 g, 38%) as tan solids. 4-bromo-3-chloro-2-iodoaniline was taken forward into the next step. LC−MS m / z = 330.8, 332.8 [M+H]+; 1H NMR (500 MHz, CDCl₃) δ 4.35 (br. s, 2 H), 6.53 (d, J=8.5 Hz, 1 H), 7.37 (d, J=8.5 Hz, 1 H).

(5-Bromo-4-chloro-1H-indol-2-yl)methanol (A3). To a solution of A2 (9.48 g, 36.39 mmol) in DMF (75 mL) was added t-BuOK (9.0 g, 80.21 mmol). The mixture was heated at 50 °C for 1 h under an argon atmosphere. Upon cooling to 0 °C, the reaction was quenched by addition of NH₄Cl (aq. satd., 50 mL) and H₂O (150 mL). The product was extracted with EtOAc (100 mL X 3). The combined organic phases were washed with brine (100 mL) and dried over Na₂SO₄. The solvent was concentrated and the residue was purified by column chromatography.
(EtOAc/hexanes, 0-50% gradient) to afford A3 which was used directly in the next step. LC−MS
m / z = 260.1, 262.1 [M+H]+; 1H NMR (500 MHz, DMSO-d6) δ 4.62 (d, J=5.7 Hz, 2 H), 5.41 (t, J=5.7 Hz, 1 H), 6.34 (s, 1 H), 7.27 (d, J=8.5 Hz, 1 H), 7.32 (d, J=8.5 Hz, 1 H), 11.58 (br. s, 1 H).

5-Bromo-2-((tert-butyldimethylsilyloxy)methyl)-4-chloro-1H-indole (A4). To a solution of A3 in CH2Cl2 (125 mL) was added imidazole (2.6 g, 38.19 mmol). The mixture was cooled to 0°C and TBSCl (5.50 g 36.49 mmol) was added in portions. The reaction was stirred at room temperature for 30 min and LCfMS indicated complete consumption of starting material. The mixture was washed with H2O (100 mL) and the organic phase was separated, washed brine (50 mL) and dried over Na2SO4. The solvent was concentrated and the residue was purified by column chromatography (EtOAc/hexanes, 0f15% gradient) to afford A4 (7.127 g, 52% over 2 steps) as a solid. LC−MS m / z = 374.2, 376.2 [M+H]+; 1H NMR (500 MHz, CDCl3) δ 0.13 (s, 6 H), 0.95 (s, 9 H), 4.89 (d, J=0.9 Hz, 2 H), 6.40 (dd, J=2.2, 0.9 Hz, 1 H), 7.16 (dd, J=8.5, 0.9 Hz, 1 H), 7.34 (d, J=8.5 Hz, 1 H), 8.48 (br. s, 1 H).

5-Bromo-2-((tert-butyldimethylsilyloxy)methyl)-4-chloro-1-methyl-1H-indole (A5). To a solution of A4 (7.10 g, 18.94 mmol) in DMF (55 mL) at 0°C was added NaH (60%, 0.91 g, 22.75 mmol) in portions. Upon completion of the addition, the reaction mixture was warmed to room temperature, stirred for 10 min and then cooled to 0°C and MeI (1.8 mL, 28.91 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 30 min and then cooled to 0°C and quenched by the addition of NH4Cl (aq. satd.). The precipitate that formed was filtered, washed with H2O, dried under N2, then purified by column chromatography (EtOAc/hexanes, 0-15% gradient) to afford A5 (6.25 g, 85% yield) as a solid. LC−MS m / z = 388.2, 390.2 [M+H]+; 1H NMR (500 MHz, CDCl3) δ 0.08 (s, 6 H), 0.91 (s, 9 H), 3.77 (s, 3 H), 4.82 (s, 2 H), 6.47 (s, 1 H), 7.09 (d, J=8.8 Hz, 1 H), 7.38 (d, J=8.8 Hz, 1 H).

2-((tert-butyldimethylsilyloxy)methyl)-4-chloro-1-methyl-1H-indole-5-carbaldehyde (A6). To solution of A5 (0.493 g, 1.27 mmol) in THF (5 mL) at −78°C was added n-BuLi (2.5M in hexanes, 0.60 mL, 1.50 mmol) dropwise over ~5 min. The reaction was stirred at this temperature 10 min before DMF (0.25 mL, 3.21 mmol) was added. The mixture was stirred at −78°C for 15 min and then quenched with NH4Cl (aq. satd.). The precipitate that formed was filtered, washed with H2O, dried under N2, then purified by column chromatography (EtOAc/hexanes, 0-10% gradient) to afford A6 (0.274 g, 64%) as a solid. LC−MS m / z = 338.2, 340.2 [M+H]+; 1H NMR (500 MHz, CDCl3-d6) δ 0.10 (s, 6 H), 0.92 (s, 9 H), 3.83 (s, 3 H), 4.85 (s, 2 H), 6.66 (s, 1 H), 7.27 (d, J=8.5 Hz, 1 H), 7.81 (d, J=8.5 Hz, 1 H), 10.58 (s, 1 H).

2-((tert-butyldimethylsilyloxy)methyl)-1-methyl-4-vinyl-1H-indole-5-carbaldehyde (A7). Compound A6 (0.274 g, 0.81 mmol), potassium vinyltrifluoroborate (0.22 g, 1.64 mmol), Pd(OAc)2 (5.5 mg, 0.02 mmol, 0.03 equiv), S-Phos ligand (20 mg, 0.05 mmol, 0.06 equiv) and K2CO3 (0.34 g, 2.46 mmol) were mixed together in a vial that was evacuated and backfilled with argon before dioxane (3.2 mL) and H2O (0.5 mL) were added. The reaction was heated at 85°C for 2 h and then cooled to room temperature. Water (5 mL) was added to the reaction mixture and the product was
extracted with CH₂Cl₂ (15 mL X 2). The combined organic phases were washed with brine (10 mL) and dried over Na₂SO₄. Upon concentration of the solvent, the residue was purified by column chromatography (EtOAc/hexanes, 0-10% gradient) affording A7 as a white solid (0.170 g, 65%). LC−MS *m/z* = 330.3 [M+H]+; ¹H NMR (500 MHz, acetone-d₆) δ ppm 0.12 (s, 6 H), 0.92 (s, 9 H), 3.89 (s, 3 H), 4.97 (d, *J*= 0.6 Hz, 2 H), 5.70 (dd, *J*= 17.5, 1.6 Hz, 1 H), 5.76 (dd, *J*= 11.2, 1.6 Hz, 1 H), 6.77 (s, 1 H), 7.49 (d, *J*= 8.8 Hz, 1 H), 7.60 (dd, *J*= 17.5, 11.2 Hz, 1 H), 7.74 (d, *J*= 8.8 Hz, 1 H), 10.34 (s, 1 H).

1-(2-(((tert-Butyldimethylsilyl)oxy)methyl)-1-methyl-4-vinyl-1H-indol-5-yl)pent-4-en-1-ol (A8). To a solution of A7 (0.17 g, 0.52 mmol) in THF (1 mL) at −78 °C was added 3-butylmagnesium bromide (0.5M in THF, 1.25 mL, 0.63 mmol) dropwise over ~10 min. The reaction was stirred at this temperature for 10 min, then slowly warmed up to 0 °C and quenched with NH₄Cl (aq. satd., 2 mL). The product was extracted with EtOAc (10 mL X 3). The combined organic phases were washed with brine (50 mL) and dried over Na₂SO₄. Upon removal of the solvent, the product was purified by column chromatography (EtOAc/hexanes, 0-15% gradient) affording A8 (0.152 g, 77%) as an oil. LC−MS *m/z* = 386.3 [M+H]+; ¹H NMR (500 MHz, CDCl₃) δ ppm 0.07 (s, 3 H), 0.08 (s, 3 H), 0.91 (s, 9 H), 1.81 f 1.91 (m, 1 H), 1.93 f 2.01 (m, 1 H), 2.07 f 2.17 (m, 1 H), 2.18 f 2.28 (m, 1 H), 3.79 (s, 3 H), 4.83 (s, 2 H), 4.97 (ddt, *J*= 10.2, 2.1, 1.1 Hz, 1 H), 5.05 (dq, *J*= 17.0, 1.7 Hz, 1 H), 5.16 (dd, *J*= 7.9, 5.4 Hz, 1 H), 5.60 (dd, *J*= 11.3, 1.9 Hz, 1 H), 5.68 (dd, *J*= 17.7, 1.9 Hz, 1 H), 5.86 (ddt, *J*= 17.0, 10.2, 6.6 Hz, 1 H), 6.55 (s, 1 H), 7.13 (dd, *J*= 17.7, 11.3 Hz, 1 H), 7.26 (d, *J*= 8.5 Hz, 1 H), 7.39 (d, *J*= 8.5 Hz, 1 H).

2-((tert-Butyldimethylsilyloxy)methyl)-3-methyl-3,6,7,8-tetrahydrocyclohepta[e]indol-6-ol (A9). To a solution of A8 (1.668 g, 4.32 mmol) in toluene (170 mL, 0.025 M) under an argon atmosphere was added Grubbs second generation catalyst (186 mg, 0.22 mmol, 0.05 equiv). The reaction was heated at 75 °C for 40 min until starting material was completely consumed. After cooling the reaction to room temperature, toluene was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/hexanes, 0-20% gradient) to provide A9 (0.964 g, 62%) as a solid. LC−MS *m/z* = 358.3 [M+H]+; ¹H NMR (500 MHz, CDCl₃) δ ppm 0.08 (s, 6 H), 0.91 (s, 9 H), 1.91 (br. s, 1 H), 2.11 f 2.20 (m, 1 H), 2.25 f 2.36 (m, 1 H), 2.45 f 2.54 (m, 1 H), 2.60 f 2.73 (m, 1 H), 3.78 (s, 3 H), 4.84 (s, 2 H), 5.05 (br. d, *J*= 7.6 Hz, 1 H), 6.12 (ddd, *J*= 12.0, 5.4, 3.8 Hz, 1 H), 6.50 (s, 1 H), 6.90 (dt, *J*= 12.0, 1.8 Hz, 1 H), 7.17 (d, *J*= 8.2 Hz, 1 H), 7.29 (d, *J*= 8.2 Hz, 1 H).

2-((tert-Butyldimethylsilyloxy)methyl)-3-methyl-3,6,7,8,9,10-hexahydrocyclohepta[e]indol-6-ol (A10). A solution of A9 (0.964 g, 2.70 mmol) in EtOAc (10 mL) was hydrogenated over 10% Pd/C (Degussa type, 100 mg) with a H₂-filled balloon (1 atm) until complete consumption of starting material as indicated by TLC. After ~1 h, the catalyst was filtered and washed with EtOAc. The solvent was concentrated and the residue was purified by column chromatography (EtOAc/hexanes, 0-20% gradient) to provide A10 (0.808 g, 83%) as a solid. LC−MS *m/z* = 360.3 [M+H]+; ¹H NMR (500 MHz, CDCl₃) δ ppm 0.08 (s, 3 H), 0.09 (s, 3 H), 0.91 (s, 9 H), 1.60 - 1.68 (m, 1 H), 1.70 - 1.98 (m, 4 H), 2.09 - 2.20 (m, 1 H), 2.93 (ddd, *J*= 14.4, 9.5, 1.6 Hz, 1 H), 3.26 (ddd, *J*= 14.4, 9.1, 1.9 Hz, 1 H), 3.76 (s, 3 H), 4.83 (s, 2 H), 5.07 (dd, *J*= 6.8, 3.0 Hz, 1 H), 6.42 (s, 1 H), 7.12 (d, *J*= 8.2 Hz, 1 H), 7.30 (d, *J*= 8.2 Hz, 1 H).

2-((tert-Butyldimethylsilyloxy)methyl)-3-methyl-7,8,9,10-tetrahydrocyclohepta[e]indol-6(3H)-one (A11). To a solution of A10 (0.791 g, 2.20 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added solid NaHCO₃ (1.90 g, 22.61 mmol) followed by Dess-
Martin periodinane (1.20 g, 2.83 mmol). The reaction was stirred at 0 °C. Upon complete conversion of starting material, the reaction mixture was diluted with CH2Cl2, washed with NaHCO3 (aq. satd., 10 mL), Na2S2O3 (10% aq., 10 mL) and brine (10 mL). The organic phase was dried over Na2SO4. After removal of the solvent, the residue was purified by column chromatography (EtOAc/hexanes, 0-15% gradient) affording A11 (0.5687 g, 72%) as a colorless solid. LC−MS m/z = 358.3 [M+H]+; 1H NMR (500 MHz, CDCl3) δ ppm 0.10 (s, 6 H), 0.92 (s, 9 H), 1.77 - 1.89 (m, 2 H), 1.91 - 1.99 (m, 2 H), 2.80 (t, J=6.0 Hz, 2 H), 3.21 (t, J=6.6 Hz, 2 H), 3.80 (s, 3 H), 4.84 (s, 2 H), 6.55 (s, 1 H), 7.21 (d, J=8.2 Hz, 1 H), 7.74 (d, J=8.2 Hz, 1 H).

Methyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-10-(2,4-dimethoxybenzyl)-7-hydroxy-1-methyl-9-oxo-1,4,5,6,9,10-hexahydropyrido[2',3':3,4]cyclohepta[1,2-e]indole-8-carboxylate (A12). To a solution of A11 (0.6187 g, 1.73 mmol) in CH2Cl2 (5 mL) was added 2,4-dimethoxybenzylamine (0.30 mL, 2.00 mmol) and NEt3 (0.70 mL, 5.02 mmol). The mixture was cooled to 0 °C before TiCl4 (1M in CH2Cl2, 1.15 mL, 1.15 mmol) was added dropwise via syringe pump over 30 min. The reaction was warmed to room temperature and then stirred overnight. The mixture was diluted with CH2Cl2 (10 mL) and then quenched with NaHCO3 (aq. satd., 5 mL). Upon vigorous shaking, the organic phase was separated using a PTFE phase separator and dried over Na2SO4. Removal of the solvent afforded the crude imine (0.858 g, ~quant) as a yellow oil, which was taken directly into the next step without purification.

Crude imine (0.858 g, 1.69 mmol) and trimethyl methanetricarboxylate (0.55 g, 2.89 mmol) were mixed together in Ph2O (4 mL). The stirred mixture was placed onto a pre-heated heat block at 230 °C and heated for 10 min after initial bubbling of MeOH was observed (occurs at ~160 °C internal reaction temperature). The reaction mixture was cooled to room temperature, loaded directly on a silica gel column, eluted with hexanes to remove Ph2O and followed by an EtOAc/hexanes gradient (0-70%) to yield A12 as a yellow foam (0.5425 g, 50% over 2 steps). LC−MS m/z = 633.5 [M+H]+; 1H NMR (500 MHz, CDCl3) δ ppm 0.09 (s, 3 H), 0.12 (s, 3 H), 0.92 (s, 9 H), 1.49 (td, J=13.6, 7.3 Hz, 1 H), 1.97 - 2.17 (m, 2 H), 2.41 (td, J=12.9, 7.9 Hz, 1 H), 2.99 (dd, J=13.9, 6.0 Hz, 2 H), 3.48 (s, 3 H), 3.75 (s, 3 H), 3.78 (s, 3 H), 3.99 (s, 3 H), 4.84 (d, J=13.2 Hz, 1 H), 4.84 (d, J=13.2 Hz, 1 H), 5.18 (br. s, 2 H), 6.27 (d, J=2.4 Hz, 1 H), 6.35 (dd, J=8.2, 2.4 Hz, 1 H), 6.45 (s, 1 H), 6.82 (d, J=8.2 Hz, 1 H), 7.00 (d, J=8.8 Hz, 1 H), 7.11 (d, J=8.8 Hz, 1 H), 13.68 (s, 1 H).

Methyl 10-(2,4-dimethoxybenzyl)-7-hydroxy-2-(hydroxymethyl)-1-methyl-9-oxo-1,4,5,6,9,10-hexahydropyrido[2',3':3,4]cyclohepta[1,2-e]indole-8-carboxylate (A13). To a solution of A12 (0.5424 g, 0.86 mmol) in THF (3 mL) was added TBAF solution (1M THF, 2.40 mL, 2.40 mmol). The reaction mixture was stirred at room temperature for 1 h until starting material was completely consumed. THF was concentrated and the residue was purified by column chromatography (EtOAc/CH2Cl2, 0-80% gradient). Compound A13 was obtained as a yellow solid (0.4048 g, 91%). LC−MS m/z = 519.2 [M+H]+; 1H NMR (500 MHz, CDCl3) δ 1.49 (dt, J=13.6, 6.8 Hz, 1 H), 1.96 - 2.18 (m, 2 H), 2.42 (td, J=12.8, 7.7 Hz, 1 H), 2.99 (dt, J=13.6, 4.5 Hz, 2 H), 3.49 (s, 3 H), 3.75 (s, 3 H), 3.81 (s, 3 H), 3.99 (s, 3 H), 4.83 (s, 2 H), 5.17 (br. s, 2 H), 6.28 (d, J=2.4 Hz, 1 H), 6.36 (dd, J=8.4, 2.4 Hz, 1 H), 6.54 (s, 1 H), 6.82 (d, J=8.4 Hz, 1 H), 7.02 (d, J=8.8 Hz, 1 H), 7.13 (d, J=8.8 Hz, 1 H), 13.68 (br. s, 1 H).
10-(2,4-Dimethoxybenzyl)-7-hydroxy-2-(hydroxymethyl)-1-methyl-9-oxo-1,4,5,6,9,10-hexahydropyrido[2',3':3,4]cyclohepta[1,2-e]indole-8-carboxylic acid (A14). To a suspension of A13 (0.4048 g, 0.78 mmol) in EtOAc (2.5 mL) was added LiI (0.31 g, 2.32 mmol). The reaction mixture was heated at 60 °C for 1.5 h until complete consumption of starting material was observed. The mixture was then cooled to room temperature and acidified with aqueous 1M HCl (3 mL). The product was extracted with CH$_2$Cl$_2$ (10 mL X 3). The organic phase was washed with brine (10 mL) and dried over Na$_2$SO$_4$. Upon removal of the solvent, A14 was obtained as a yellow solid (0.3814 g, 97%). LC−MS m / z = 505.2 [M+H]$^+$; $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ 1.41 (td, $J$=13.5, 7.1 Hz, 1 H), 1.86 f 2.15 (m, 2 H), 2.38 (td, $J$=12.8, 8.0 Hz, 1 H), 2.88 (dd, $J$=13.6, 5.7 Hz, 1 H), 3.01 (dd, $J$=13.6, 6.0 Hz, 1 H), 3.33 (br. s, 1 H), 3.53 (s, 3 H), 3.69 (s, 3 H), 3.75 (s, 3 H), 4.64 (s, 2 H), 5.12 f 5.32 (m, 2 H), 6.37 (dd, $J$=8.4, 2.4 Hz, 1 H), 6.43 (d, $J$=2.4 Hz, 1 H), 6.57 (s, 1 H), 6.64 (d, $J$=8.4 Hz, 1 H), 7.10 (d, $J$=8.5 Hz, 1 H), 7.36 (d, $J$=8.5 Hz, 1 H), 13.82 (s, 1 H), 16.17 (s, 1 H).

10-(2,4-Dimethoxybenzyl)-2-formyl-7-hydroxy-1-methyl-9-oxo-1,4,5,6,9,10-hexahydropyrido[2',3':3,4]cyclohepta[1,2-e]indole-8-carboxylic acid (A15). To a solution of A14 (0.3814 g, 0.76 mmol) in CH$_2$Cl$_2$ (10 mL) was added activated MnO$_2$ (1.85 g, 19.1 mmol) in 3 portions with 30 min intervals between additions. Upon complete consumption of the starting material, the excess MnO$_2$ was filtered and washed with CH$_2$Cl$_2$. The solvent was concentrated affording A15 as a dark red foam (0.2742 g, 72%) which is used in the next step without further purification. LC−MS m / z = 501.1 [M+H].

7-Hydroxy-1-methyl-2-((methylamino)methyl)-9-oxo-1,4,5,6,9,10-hexahydropyrido[2',3':3,4]cyclohepta[1,2-e]indole-8-carboxylic acid hydrochloride (8a). To a solution of A15 (139.1 mg, 0.28 mmol) in dichloroethane (2.2 mL) was added MeNH$_2$ solution (2M THF, 0.42 mL, 0.84 mmol) followed by AcOH (30 µL, 0.50 mmol). After stirring at room temperature for 10 min, NaBH(OAc)$_3$ (105 mg, 0.50 mmol) was added. The reaction was stirred at room temperature ~2 h and monitored by LC/MS until the starting aldehyde was completely consumed. The solvent was concentrated and the residue was dissolved in MeOH (6 mL) and several drops of TFA to generate a homogeneous mixture that was filtered through a PTFE micron filter and purified directly by preparative HPLC. To the intermediate reductive amination product (94.2 mg, 54%), obtained as a TFA salt, was added i-Pr$_3$SiH (0.90 mL) followed by TFA (0.90 mL). The mixture was heated at 60 °C for 2 h until complete consumption of starting material was observed. TFA was concentrated under reduced pressure and addition of an HCl solution (2M Et$_2$O, 1.5 mL) to the oily residue resulted in precipitate formation. The mixture was diluted with Et$_2$O and the solid was filtered and washed well with Et$_2$O. Compound 8a was obtained as a colorless solid (45.2 mg, 75%) as an HCl salt. LC−MS m / z = 368.2 [M+H]; $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ ppm 1.28 (t, $J$=7.3 Hz, 3 H), 2.12 - 2.35 (m, 4 H), 2.84 (br. s, 2 H), 3.86 (s, 3 H), 4.43 (br. s, 2 H), 6.93 (s, 1 H), 7.38 (d, $J$=8.5 Hz, 1 H), 7.56 (d, $J$=8.5 Hz, 1 H), 9.25 (br. s, 2 H), 12.90 (br. s, 1 H), 13.87 (s, 1 H).

2-((Ethylamino)methyl)-7-hydroxy-1-methyl-9-oxo-1,4,5,6,9,10-hexahydropyrido[2',3':3,4]cyclohepta[1,2-e]indole-8-carboxylic acid hydrochloride (8b). Compound 8b was prepared from A15 and ethyl amine according to the procedure used to prepare 8a (54%) as a colorless solid. LC−MS m / z = 382.2 [M+H]; $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$ ppm 1.28 (t, $J$=7.3 Hz, 3 H), 2.12 - 2.35 (m, 4 H), 2.84 (br. s, 2 H), 3.01 - 3.16 (m, 2 H), 3.86 (s, 3 H), 4.43 (t, $J$=5.0 Hz, 2 H), 6.93 (s, 1 H), 7.38 (d, $J$=8.5 Hz, 1 H), 7.56 (d, $J$=8.5 Hz, 1 H), 9.21 (br. s, 2 H), 12.89 (s, 1 H), 13.87 (s, 1 H).
Scheme B.\(^d\)

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**Reagents and conditions:**
- (a) tert-butyl carbamate (1.5 equiv), Pd(OAc)\(_2\) (0.03 equiv), S-Phos (0.05 equiv), Cs\(_2\)CO\(_3\) (1.5 equiv), dioxane, 100 °C, 4 h, 94%.
- (b) NaH (1.5 equiv), allyl iodide (2 equiv), DMF, rt, 15 min, 90%.
- (c) 1-propenylmagnesium bromide (1.4 equiv), THF, −78 °C to rt, 1 h, 87%.
- (d) Grubbs second generation catalyst (0.05 equiv), CH\(_2\)Cl\(_2\), 40 °C, 3 h, 66%.
- (e) MnO\(_2\) (6.1 equiv), CH\(_2\)Cl\(_2\), rt, 2 h.
- (f) Pd-C (0.1 equiv by wt), H\(_2\) (1 atm), EtOAc, rt, 3 h, 90% over 2 steps.
- (g) 2,4-dimethoxybenzyl amine (1.1 equiv), Et\(_3\)N, (3.0 equiv), TiCl\(_4\) (0.65 equiv), CH\(_2\)Cl\(_2\), 0 °C to rt, 16 h.
- (h) trimethyl methanetricarboxylate, (1.7 equiv), diphenyl ether, 210 °C, 10 min; 63% over 2 steps.
- (i) TBAF (2.5 equiv), THF, rt, 2 h, 80%.
- (j) LiI (3 equiv), EtOAc, 60 °C, 2 h, 92%.
- (k) MnO\(_2\) (30 equiv in three portions over 1 h, CH\(_2\)Cl\(_2\), 80%).
- (l) amine (2 equiv), DCE, rt, 10 min, then AcOH (2 equiv) and NaBH(OAc)\(_3\) (2.2 equiv), 1.5 h.
- (m) i-Pr\(_3\)SiH, TFA, 60 °C, 2 h, then HCl/Et\(_2\)O (29-30% over 2 steps).

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**tert-Butyl (2-(((tert-butyldimethylsilyl)oxy)methyl)-5-formyl-1-methyl-1H-indol-6-yl)carbamate (B1).** A round bottomed flask was charged with 2-(((tert-butyldimethylsilyl)oxy)methyl)-6-chloro-1-methyl-1H-indole-5-carbaldehyde (compound 20 in manuscript, 3.0 g, 8.87 mmol), tert-butyl carbamate (1.56 g, 13.31 mmol), palladium acetate (60 mg, 0.27 mmol), S-Phos (182 mg, 0.44 mmol) and Cs\(_2\)CO\(_3\) (4.33 g, 13.31 mmol). The flask was purged with argon for 10 minutes and dioxane (30 mL) was added via cannula. The mixture was heated at 100 °C for 4 h. Upon cooling to room temperature, the mixture was filtered through a plug of silica gel, washed with EtOAc (250 mL) and concentrated under reduced pressure. Purification by column chromatography (0-15% EtOAc in hexanes) gave 3.55 g (94%) of the desired product as an off-white solid. \(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta -0.13\) - 0.21 (m, 6 H), 0.72 - 1.04 (m, 9 H), 1.57 (s, 9 H), 3.79 (s, 3 H), 4.81 (s, 2 H), 6.43 (d, \(J=0.6\) Hz, 1 H), 7.81 (s, 1 H), 8.36 (s, 1 H), 9.87 (s, 1 H), 10.63 (s, 1 H).
**tert-Butyl allyl(2-(((tert-butylidimethylsilyl)oxy)methyl)-5-formyl-1-methyl-1H-indol-6-yl)carbamate (B2).** A round bottomed flask containing **B1** (4.95 g, 11.82 mmol) was purged with argon for 10 minutes and DMF (60 mL) was added via cannula. Solid NaH (710 mg, 17.74 mmol, 60 wt %) was added in one portion, and the suspension was stirred at room temperature. After 10 min, allyl iodide (2.2 mL, 23.64 mmol) was added via syringe. The solution was stirred for 15 min before being poured into H$_2$O (250 mL). The product was then extracted with EtOAc (150 mL X 2), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (0-20% EtOAc in hexanes) gave 4.87 g (90%) of **B2** as a yellow solid. LC−MS $m / z$ = 359.1 [M+H]$^+$ (loss of Boc group); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.02 - 0.16 (m, 6 H), 0.77 - 1.04 (m, 9 H), 1.26 - 1.62 (m, 9 H), 3.79 (s, 3 H), 4.20 - 4.45 (m, 2 H), 4.83 (s, 2 H), 5.04 - 5.19 (m, 2 H), 5.89 - 6.07 (m, 1 H), 6.51 (s, 1 H), 7.03 - 7.17 (m, 1 H), 8.15 (s, 1 H), 10.07 (s, 1 H).

**tert-Butyl (E)-allyl(2-(((tert-butylidimethylsilyl)oxy)methyl)-5-(1-hydroxybut-2-en-1-yl)-1-methyl-1H-indol-6-yl)carbamate (B3).** A round bottomed flask containing **B2** (4.86 g, 10.59 mmol) was purged with argon for 10 minutes and THF (50 mL) was added via cannula. The solution was cooled to −78 ºC using a dry ice/acetone bath. At −78 ºC, prop-1-en-1-ylmagnesium bromide (30.0 mL, 14.83 mmol, 0.5M in THF) was added dropwise. Upon completion of the addition, the cooling bath was removed and the reaction was warmed to room temperature over 1 h. The reaction was then quenched by the addition of saturated aqueous NH$_4$Cl (100 mL). The product was extracted with EtOAc (150 mL X 2), dried over Na$_2$SO$_4$, filtered and then concentrated under reduced pressure. The desired product was obtained as a glassy yellow solid (4.60 g, 87%) which was carried on directly into the ring-closing metathesis step.

**tert-Butyl 2-(((tert-butylidimethylsilyl)oxy)methyl)-5-hydroxy-1-methyl-5,8-dihydroazepino[3,2-f]indole-9(1H)-carboxylate (B4).** To a round bottomed flask was added crude **B3** (2.7 g, 5.40 mmol). The flask was purged with argon for 10 min and CH$_2$Cl$_2$ (100 mL) was added via cannula. Under argon, solid (1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium (230 mg, 0.27 mmol) was added and the mixture was stirred at 40 ºC for 3 hours. Upon consumption of the starting material, the reaction was concentrated and purified by column chromatography (0-35% EtOAc in hexanes) to give 1.63 g (66%) of the desired product as tan solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.05 (d, $J$=4.1 Hz, 6 H), 0.77 - 0.95 (m, 9 H), 1.21 - 1.56 (m, 9 H), 3.36 - 3.49 (m, 1 H), 3.71 (s, 3 H), 4.56 - 4.75 (m, 1 H), 4.84 (s, 2 H), 5.21 - 5.41 (m, 1 H), 5.46 - 5.77 (m, 3 H), 6.39 (s, 1 H), 7.23 (br. s, 1 H), 7.52 (s, 1 H).

**tert-Butyl 2-(((tert-butylidimethylsilyl)oxy)methyl)-1-methyl-5-oxo-5,6,7,8-tetrahydroazepino[3,2-f]indole-9(1H)-carboxylate (B5).** To a round bottomed flask was added **B4** (2.0 g, 4.40 mmol). The flask was purged with argon for 10 minutes and CH$_2$Cl$_2$ (25 mL) was added via cannula. Under argon, solid MnO$_2$ (2.3 g, 27 mmol) was added and the mixture was stirred at room temperature for 2 h. Upon consumption of the starting material, the reaction was filtered through a plug of silica gel (eluting with EtOAc) and concentrated under reduced pressure. The unsaturated ketone intermediate (2.0 g, quant.) was isolated as yellow crystals which required no additional purification. LC−MS $m / z$ = 357.2 [M+H]$^+$ (loss of Boc group).

To the unsaturated ketone intermediate (2.0 g, 4.4 mmol) was added EtOAc (20 mL) via syringe. To the stirring solution was added 10% Pd/C (200 mg) and the reaction was hydrogenated under an atmosphere of H$_2$. The suspension was stirred vigorously at room
temperature for 3 h. After completion by LC−MS, the mixture was filtered through a short plug of silica gel, eluting with EtOAc. The solution was concentrated under reduced pressure. Purification by column chromatography (0-40% EtOAc in hexanes) gave 1.81 g (90%) of the desired product as a light yellow foam. 

**1H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 0.06 (s, 6 H), 0.68 - 1.01 (m, 9 H), 1.20 - 1.61 (m, 9 H), 1.79 - 2.11 (m, 2 H), 2.51 - 2.64 (m, 2 H), 3.54 - 3.84 (m, 5 H), 4.86 (s, 2 H), 6.55 (s, 1 H), 7.39 (s, 1 H), 7.81 - 8.05 (m, 1 H).

**7-tert-Butyl 3-methyl 10-(((tert-butyl(dimethyl)silyl)oxymethyl)-1-(2,4-dimethoxybenzyl)-4-hydroxy-9-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',3':4,5]azepino[3,2-f]indole-3,7(9H)-dicarboxylate (B6).** To a solution of B5 (1.76 g, 3.84 mmol) in CH\(_2\)Cl\(_2\) (13 mL) was added 2,4-dimethoxybenzylamine (640 µL, 4.22 mmol) and NEt\(_3\) (1.6 mL, 11.52 mmol). The mixture was cooled to 0 °C before a solution of TiCl\(_4\) (1.0 M CH\(_2\)Cl\(_2\), 2.5 mL, 2.49 mmol) was added dropwise via syringe pump over 30 minutes. The reaction was warmed to room temperature and stirred overnight. The resultant mixture was diluted with CH\(_2\)Cl\(_2\) (20 mL) and then quenched with NaHCO\(_3\) (sat. aq., 10 mL). Following vigorous shaking, the organic phase was separated using a PTFE phase separator, dried over Na\(_2\)SO\(_4\) and filtered. Removal of the solvent afforded the crude imine intermediate (2.11 g, ~91 %, LC−MS m / z = 608.3 [M+H]\(^+\)) as a yellow solid.

The imine intermediate (2.11 g, 3.46 mmol) and trimethyl methanetricarboxylate (1.12 g, 5.89 mmol) were mixed together in Ph\(_2\)O (7.0 mL). The stirred mixture was placed into a preheated heat block at 210 °C and heated for 10 minutes under a blanket of argon. The reaction mixture was cooled to room temperature and loaded directly onto a silica cartridge and purified (100% hexanes to elute the Ph\(_2\)O, followed by 0f85% EtOAc in hexanes) to give 1.75 g (69%) of B6 as burnt orange crystals which were used directly in the next step. LC−MS m / z = 734.2 [M+H]\(^+\).

**7-tert-Butyl 3-methyl 1-(2,4-dimethoxybenzyl)-4-hydroxy-10-(hydroxymethyl)-9-methyl-2-oxo-1,2,5,6-tetrahydropyrido[2',3':4,5]azepino[3,2-f]indole-3-carboxylic acid (B7).** To a suspension of B7 (1.16 g, 1.87 mmol) in THF (10 mL) was added LiI (750 mg, 5.62 mmol). The reaction mixture was stirred with heating at 60 ºC until complete consumption of starting material was observed (~2 h). The mixture was then cooled to room temperature and quenched with 1M HCl (10 mL) and diluted with H\(_2\)O. The product was extracted with EtOAc (100 mL X 2) and the combined organic phase was washed with 10% aq. Na\(_2\)S\(_2\)O\(_3\) (40 mL), brine (100 mL) and then dried over Na\(_2\)SO\(_4\). Upon removal of the solvent, the product (1.04 g, 92%) was obtained as a yellow solid that was used directly in the next step. LC−MS m / z = 604.6 [M-H], 606.6 [M+H]\(^+\).

**7-(tert-Butoxycarbonyl)-1-(2,4-dimethoxybenzyl)-4-hydroxy-10-(hydroxymethyl)-9-methyl-2-oxo-1,2,5,6,7,9-hexahydropyrido[2',3':4,5]azepino[3,2-f]indole-3-carboxylic acid (B8).** To a solution of B8 (1.16 g, 1.87 mmol) in EtOAc (6.0 mL) was added LiCl (750 mg, 5.62 mmol). The reaction mixture was stirred with heating at 60 °C until complete consumption of starting material was observed (~2 h) and the combined organic phase was washed with 10% aq. Na\(_2\)S\(_2\)O\(_3\) (40 mL), brine (100 mL) and then dried over Na\(_2\)SO\(_4\). Upon removal of the solvent, the product (1.04 g, 92%) was obtained as a yellow solid that was used directly in the next step. LC−MS m / z = 604.6 [M-H], 606.6 [M+H]\(^+\).

**7-(tert-Butoxycarbonyl)-1-(2,4-dimethoxybenzyl)-10-formyl-4-hydroxy-9-methyl-2-oxo-1,2,5,6,7,9-hexahydropyrido[2',3':4,5]azepino[3,2-f]indole-3-carboxylic acid (B9).** To a
solution of B8 (1.04 g, 1.73 mmol) in CH₂Cl₂ (9.0 mL) was added activated MnO₂ (3.70 g, 43.1 mmol). Upon complete consumption of the starting material, MnO₂ was filtered and washed with CH₂Cl₂. The mother liquor was concentrated to afford the product (833 mg, 80%) as an off-white foam that required no further purification. LC–MS m/z = 602.5 [M-H], 604.5 [M+H].

General procedure for reductive amination and deprotection of B9. To a solution of B9 (200 mg, 0.33 mmol) in dichloroethane (3.5 mL) was added a solution of amine (0.66 mmol, 2.0 equiv.) followed by AcOH (47 µL, 0.66 mmol, 2.0 equiv.). After stirring at room temperature for 10 min, NaBH(OAc)₃ (147 mg, 0.70 mmol) was added. The reaction was stirred at room temperature for 1.5 h until the starting aldehyde was consumed. Dichloroethane was then concentrated and the residue was dissolved in MeOH (10 mL) and several drops of TFA to generate a homogeneous mixture which was filtered through a PTFE micron filter and purified directly by preparative HPLC. The crude reductive amination product was obtained as a TFA salt. To the crude intermediate was added i-Pr₃SiH (1.0 mL) followed by TFA (1.5 mL). The resultant mixture was heated at 60 °C for 2 h. Upon complete consumption of the starting material, TFA was concentrated under reduced pressure. Addition of an HCl solution (2.0 M Et₂O, 2.0 mL) to the oily residue led to a precipitate. The mixture was diluted with Et₂O, and the solid was filtered and washed thoroughly with Et₂O to obtain the amine HCl salts.

4-Hydroxy-9-methyl-10-((methylamino)methyl)-2-oxo-1,2,5,6,7,9-hexahydropyrido[2',3':4,5]azepino[3,2-f]indole-3-carboxylic acid hydrochloride (6d). Obtained as a pale pink solid (41 mg, 29%). LC–MS m/z = 367.3 [M-H]; ¹H NMR (500 MHz, DMSO-d₆) δ ppm 2.64 (t, J=5.0 Hz, 2 H), 3.69 - 3.78 (m, 2 H), 3.86 (s, 5 H), 4.46 (t, J=5.0 Hz, 2 H), 6.93 (s, 1 H), 7.80 - 7.93 (m, 1 H), 8.00 (s, 1 H), 9.26 - 9.61 (m, 2 H), 13.15 (s, 1 H), 13.89 (s, 1 H), 16.07 (s, 1 H).

10-((Ethylamino)methyl)-4-hydroxy-9-methyl-2-oxo-1,2,5,6,7,9-hexahydropyrido[2',3':4,5]azepino[3,2-f]indole-3-carboxylic acid hydrochloride (6g). The desired product was obtained as a pale pink solid (43 mg, 30%). LC–MS m/z = 381.4 [M-H]; ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.29 (t, J=7.3 Hz, 3 H), 2.98 - 3.16 (m, 2 H), 3.64 - 3.81 (m, 4 H), 3.86 (s, 3 H), 4.46 (t, J=5.5 Hz, 2 H), 6.93 (s, 1 H), 7.78 - 7.91 (m, 1 H), 8.00 (s, 1 H), 9.21 - 9.55 (m, 2 H), 13.02 - 13.40 (m, 1 H), 13.69 - 14.10 (m, 1 H).

4-Hydroxy-10-((isopropylamino)methyl)-9-methyl-2-oxo-1,2,5,6,7,9-hexahydropyrido[2',3':4,5]azepino[3,2-f]indole-3-carboxylic acid hydrochloride (6l). The desired product was obtained as a pale pink solid (43 mg, 30%). LC–MS m/z = 395.3 [M-H]; ¹H NMR (500 MHz, DMSO-d₆) δ ppm 1.37 (d, J=6.6 Hz, 6 H), 3.36 - 3.55 (m, 1 H), 3.71 - 3.82 (m, 2 H), 3.87 (s, 2 H), 4.36 - 4.54 (m, 4 H), 6.96 (s, 1 H), 7.90 (s, 1 H), 8.01 (s, 1 H), 9.43 (br. s, 2 H), 13.21 (s, 1 H), 13.92 (s, 1 H).
Scheme C.a

Reagents and conditions: (a) NaH (1.2 equiv), ethyl 4-bromobutanoate (1.2 equiv), DMF, 0 °C to rt, 16 h; (b) PPA, 120 °C, 2 h, 59% over 2 steps; (c) 2,4-dimethoxybenzyl amine (1.1 equiv), Et3N (3 equiv), TiCl4 (0.5 equiv), CH2Cl2, 0 °C to rt, 16 h; (d) CH(CO2Me)3 (2 equiv), Ph2O, 230 °C, 15 min, 64% over 2 steps; (e) TFA, CH2Cl2, rt, 1 h; (f) BnOH (4.2 equiv), Ph3P (3.8 equiv), DIAD (3.8 equiv), THF, 0 °C to rt, 4 h, 61% over 2 steps; (g) BocNH2 (2 equiv), K2CO3 (2.5 equiv), CuI (0.1 equiv), N, N'-dimethylcyclohexane-1,2-diamine (0.2 equiv), toluene, 110 °C, 92%; (h) NaH (1.5 equiv), Mel (1.5 equiv), DMF, 0 °C to rt, 2 h, 94%; (i) Ph2O, 200 °C, 2 h, 95%; (j) NIS (1.5 equiv), DMF, rt, 3 h; (k) prop-2-yn-1-ol (2 equiv), CuI 0.05 equiv), Pd(Ph3P)2Cl2 (0.05 equiv), Et3N (2 equiv), CH3CN, rt, 5 h, 38% over 2 steps; (l) CuI (1.2 equiv), DMF, 100 °C, 16 h, 87%; (m) MnO2 (5 equiv), CH2Cl2, rt, overnight, 72%; (n) amine (3 equiv), NaBH(OAc)3 (2.6 equiv), AcOH, DCE, rt, 1 h; (o) TMSI (20 equiv), rt, 3 d, 32-64%.

8-Bromo-3,4-dihydrobenzo[b]thiepin-5(2H)-one (C1). To a solution of 3-bromothiophenol (50 g, 265 mmol) in dry DMF (500 mL) at 0 °C was added NaH (12.7 g, 318 mmol, 60% in mineral oil). The mixture was stirred for 10 min, followed by the addition of ethyl 4-bromobutanoate (45.5 mL, 318 mmol). The cooling bath was removed and the mixture was stirred overnight. This was then diluted with water (1.5 L) and extracted with ethyl ether (300 mL X 3). The extracts were combined and washed with water (100 mL X 2), brine (100 mL) and dried over anhydrous Na2SO4. The volatiles were removed under vacuum to furnish ethyl 4-((3-bromophenyl)thio)butanoate as a light brown oil, which was used directly in the next step. 1H NMR (CDCl3) δ 1.27 (t, J=1.0 Hz, 3 H), 1.97 (quintet, J=7.2 Hz, 2 H), 2.47 (t, J=7.3 Hz, 2 H), 2.98 (t, J=7.3 Hz, 2 H), 4.15 (q, J=7.3 Hz, 2 H), 7.15 (t, J=1.0 Hz, 1 H), 7.23-7.27 (m, 1 H), 7.29-7.32 (m, 1 H), 7.46 (t, J=1.9 Hz, 1 H).

To preheated PPA (600 g) at 120 °C was added the intermediate obtained above. The mixture was well mixed and heated at 120 °C for 2 h and then poured onto ice (1000 mL) and stirred for 0.5 h. The organic phase was extracted with CH2Cl2 (300 mL X 3). The CH2Cl2 extracts were combined, washed with water (200 mL X 2), satd. aqueous NaHCO3 (300 mL) and dried over Na2SO4. The solvent was then removed by rotary evaporation and the residue was chromatographed (silica gel, EtOAc in hexanes, 0-30% gradient) to provide C1 as a light brown oil (39.9 g, 59% yield over two steps). 1H NMR (CDCl3) δ 2.28 (quintet, J=6.8 Hz, 2 H), 2.99 (t,
Methyl 9-bromo-1-(2,4-dimethoxybenzyl)-4-hydroxy-2-oxo-1,2,5,6-tetrahydrobenzo[2,3]thiepino[4,5-b]pyridine-3-carboxylate (C2). To a stirred solution of C1 (36.2 g, 141 mmol), (2,4-dimethoxybenzyl amine (25.9 g, 23.3 mL, 155 mmol), and triethylamine (42.7 g, 58.7 mL, 423 mmol) in CH₂Cl₂ (300 mL) at 0 ºC was added TiCl₄ (1M CH₂Cl₂, 71 mL, 71 mmol) dropwise. After the addition, the mixture was brought to room temperature and stirred overnight. The reaction was quenched with satd. NaHCO₃ solution (3 mL) and the mixture was diluted with CH₂Cl₂ (120 mL). The CH₂Cl₂ layer was separated using a phase separator cartridge and the aqueous layer was extracted with CH₂Cl₂ (30 mL X 2). The combined organic phases were evaporated to dryness followed by the addition of trimethyl methanetricarboxylate (53.6 g, 282 mmol) and diphenyl ether (280 mL). This was then stirred at 230 ºC for 15 min. After cooling, the reaction was chromatographed (ethyl acetate in hexanes 0-100%) to furnish C2 as a light brown solid (47.6 g, 64%). LC−MS m / z = 532.0, 534.0 [M+H]+.

Methyl 2,4-bis(benzyloxy)-9-bromo-5,6-dihydrobenzo[2,3]thiepino[4,5-b]pyridine-3-carboxylate (C3). A mixture of C2 (47.6 g, 89.5 mmol) was dissolved in CH₂Cl₂ (100 mL) and treated with TFA (100 mL) for 1 h at room temperature. The volatiles were removed by rotary evaporation and the residue was triturated with water (~1 L). The precipitate was collected by filtration, washed with water and dried. The material was then dissolved in THF (600 mL) at 0 ºC, followed by the addition of benzyl alcohol (40.6 g, 38.9 mL, 376 mmol), Ph₃P (90.3 g, 344.4 mmol) and DIAD (69.6 g, 68.2 mL, 344.4 mmol). After the addition, the cooling bath was removed and the mixture was stirred for 4 h at room temperature. Chromatography (silica gel, EtOAc in hexanes, 0-50%) provided C3 (30.8 g, 61%) as a colorless oil. LC−MS m / z = 562.3, 564.3 [M+H]+; ¹H NMR (CDCl₃) δ: 2.71 (t, J=6.5 Hz, 2 H), 3.24 (t, J=6.6 Hz, 2 H), 5.13 (s, 2 H), 3.93 (s, 3 H), 5.48 (s, 2 H), 7.28-7.51 (m, 11 H), 7.59 (dd, J=8.4, 2.0 Hz, 1 H), 7.78 (d, J=1.9 Hz, 1 H).

Methyl 2,4-bis(benzyloxy)-9-((tert-butoxycarbonyl)amino)-5,6-dihydrobenzo[2,3]thiepino[4,5-b]pyridine-3-carboxylate (C4). A mixture of C3 (30.8 g, 54.8 mmol), BocNH₂ (12.8 g, 110 mmol), K₂CO₃ (18.9 g, 137 mmol), CuI (1.05 g, 5.5 mmol), N, N’-dimethylcyclohexane-1,2-diamine (1.56 g, 1.73 mL, 11.0 mmol) and toluene (100 mL) was heated at 110 ºC under a nitrogen atmosphere for 24 h. The reaction was then diluted with ethyl acetate (200 mL) and filtered. The precipitate was washed with ethyl acetate and the filtrate was concentrated to dryness. The residue was chromatographed (silica gel, ethyl acetate in hexanes, 0-70 %) to provide C4 (30.3 g, 92%). LC−MS m / z = 599.2 [M+H]+; ¹H NMR (CDCl₃) δ: 1.55 (s, 9 H), 2.71 (t, J=6.6 Hz, 2 H), 3.23 (t, J=6.6 Hz, 2 H), 3.92 (s, 3 H), 5.12 (s, 2 H), 5.50 (s, 2 H), 6.56 (s, 1 H), 7.28-7.32 (m, J=7.3 Hz, 1 H), 7.33-7.51 (m, 10 H), 7.55 (d, J=8.4, 2.0 Hz, 1 H), 7.78 (d, J=1.9 Hz, 1 H).

Methyl 2,4-bis(benzyloxy)-9-((tert-butoxycarbonyl)(methyl)amino)-5,6-dihydrobenzo[2,3]thiepino[4,5-b]pyridine-3-carboxylate (C5). To a solution of C4 (1.20 g, 2.0 mmol) in DMF (5.0 mL) was added NaH (0.12 g, 3.0 mmol, 60% in mineral oil) at room temperature. The mixture was stirred for 30 min followed by the addition of MeI (0.43 g, 0.19 mL, 3.0 mmol). The reaction was then stirred for an additional 2 h. Water (5 mL) was added and the product was extracted with CH₂Cl₂ (25 mL X 2), washed with water and dried over Na₂SO₄. Chromatography of the crude material (silica gel, ethyl acetate in hexanes 0-20%) furnished C5 (1.13 g, 94%) as a white powder. LC−MS m / z = 613.2 [M+H]+; ¹H NMR (CDCl₃) δ: 1.50 (s, 9
H), 2.74 (t, J=6.3 Hz, 2 H), 3.25 (t, J=6.5 Hz, 2 H), 3.31 (s, 3 H), 3.92 (s, 3 H), 5.13 (s, 2 H), 5.50 (s, 2 H), 7.29-7.33 (m, J=7.3 Hz, 1 H), 7.35-7.47 (m, 10 H), 7.53 (d, J=2.2 Hz, 1 H), 7.58 (d, J=8.5 Hz, 1 H).

Methyl 2,4-bis(benzyloxy)-9-(methylamino)-5,6-dihydrobenzo[2,3]thiepino[4,5-b]pyridine-3-carboxylate (C6). Compound C5 (1.13 g, 1.85 mmol) was heated in diphenyl ether (20 mL) at 200 ºC for 2 h under a nitrogen atmosphere. After cooling, the mixture was loaded on a silica gel column and eluted with ethyl acetate in hexanes (0-70%) to furnish C6 (0.90 g, 95%) as a colorless oil. ¹H NMR (CDCl₃) δ 2.75 (t, J=6.6 Hz, 2 H), 2.92 (s, 3 H), 3.25 (t, J=6.6 Hz, 2 H), 3.91 (s, 3 H), 5.11 (s, 2 H), 5.50 (s, 2 H), 6.78-6.84 (m, 1 H), 6.97 (br. s, 1 H), 7.28-7.33 (m, 1 H), 7.34-7.47 (m, 10 H), 7.51 (d, J=8.5 Hz, 1 H).

Methyl 2,4-bis(benzyloxy)-10-(3-hydroxyprop-1-yn-1-yl)-9-(methylamino)-5,6-dihydrobenzo[2,3]thiepino[4,5-b]pyridine-3-carboxylate (C7). A mixture of C6 (0.90 g, 1.76 mmol), NIS (0.59 g, 2.64 mmol) and DMF (5.0 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water (30 mL) and the precipitate was collected by filtration, washed with water and dried. Column chromatography (silica gel, ethyl acetate in hexanes 0-50%) provided 0.85 g of the desired iodide intermediate (LC−MS m / z = 639.5 [M+H]+) mixed with ~33% of the undesired iodide isomer. The mixture of the iodide intermediates (0.85 g, 1.33 mmol), CuI (0.013 g, 0.07 mmol), Pd(Ph₃P)₂Cl₂ (0.095 g, 0.07 mmol), triethylamine (0.27 g, 2.66 mmol), prop-2-yn-1-ol (0.15 g, 0.155 mL, 2.66 mmol) and acetonitrile (5.0 mL) was stirred at room temperature for 5 h under an argon atmosphere. The volatiles were removed by rotary evaporation and the residue was treated with water (5 mL) and ethyl acetate (10 mL). The organic phase was separated and the aqueous layer was extracted with ethyl acetate (5 mL X 2). The combined organic phases were washed with water (5 mL), brine (5 mL) and dried over anhydrous Na₂SO₄. The solvent was removed in vacuo and the residue was chromatographed (silica gel, ethyl acetate in CH₂Cl₂ 0-60%) to furnish C7 (0.38 g, 38%) as a white solid. LC−MS m / z = 567.5 [M+H]+.

Methyl 2,4-bis(benzyloxy)-10-(hydroxymethyl)-9-methyl-5,9-dihydro-6H-pyrido[2',3':4,5]thiepino[3,2-f]indole-3-carboxylate (C8). Compound C7 (380 mg, 0.67 mmol) was dissolved in DMF (2.0 mL) and stirred at 100 ºC overnight in the presence of CuI (154 mg, 0.81 mmol). After cooling, the mixture was diluted with saturated NH₄Cl (5.0 mL) and the precipitate was collected by filtration, washed with water, dried, and chromatographed (silica gel, ethyl acetate in CH₂Cl₂ 0-50%) to furnish C8 as an oil (330 mg, 87%). LC−MS m / z = 567.6 [M+H]⁺; ¹H NMR (CDCl₃) δ: 2.73 (br. s, 2 H), 3.21 (br. s, 2 H), 3.85 (s, 3 H), 3.92 (s, 3 H), 4.85 (s, 2 H), 5.13 (s, 2 H), 5.55 (s, 2 H), 6.54 (s, 1 H), 7.29-7.50 (m, 10 H), 7.62 (s, 1 H), 7.83 (d, J=0.6 Hz, 1 H).

Methyl 2,4-bis(benzyloxy)-10-formyl-9-methyl-5,9-dihydro-6H-pyrido[2',3':4,5]thiepino[3,2-f]indole-3-carboxylate (C9). Compound C8 (1.67 g, 2.95 mmol) was treated with activated MnO₂ (1.31 g, 15 mmol) in CH₂Cl₂ (20 mL) at room temperature overnight. The solid material was filtered and washed thoroughly with CH₂Cl₂. The filtrate was concentrated and chromatographed (silica gel, ethyl acetate in CH₂Cl₂, 0-10 %) to provide C9 (1.2 g, 72%) as a solid. LC−MS m / z = 565.4 [M+H]⁺; ¹H NMR (CDCl₃) δ: 2.76 (br. s, 2 H), 3.21 (br. s, 2 H), 3.94 (s, 3 H), 4.13 (s, 3 H), 5.14 (s, 2 H), 5.54 (s, 2 H), 7.31-7.51 (m, 11 H), 7.72 (s, 1 H), 7.96 (s, 1 H), 9.94 (s, 1 H).
General procedure for reductive amination and deprotection of C9. To a solution of C9 (0.15 mmol) in DCE was added amine (0.45 mmol, 3 equiv.), NaBH(OAc)$_3$ (0.39 mmol) and one drop of acetic acid. The mixture was stirred at room temperature for 1 h, diluted with CH$_2$Cl$_2$ (4 mL) and neutralized with NaHCO$_3$. The organic layer was dried and loaded onto a silica column and eluted with MeOH in CH$_2$Cl$_2$ (0-20%) to provide the reductive amination intermediate. The intermediate was dissolved in CH$_2$Cl$_2$ (1.0 mL) and treated with TMSI (600 mg, 0.43 mL, 3.0 mmol) at room temperature for 3 days. The reaction mixture was cooled in an ice-water bath and quenched with HCl in methanol (1.0 mL, 1.25 M) and diluted with ethyl ether (1.5 mL). The precipitate was collected by filtration and purified by reverse phase preparative HPLC (0.2% TFA in acetonitrile / 0.2% TFA in water). Treatment with HCl in ethyl ether (1.0 mL, 2.0 M) at room temperature for 3 h provided the desired amine HCl salt.

4-Hydroxy-9-methyl-10-((methylamino)methyl)-2-oxo-2,5,6,9-tetrahydro-1H-pyrido[2',3':4,5]thiepin[3,2-f]indole-3-carboxylic acid hydrochloride (6e). Obtained 31 mg (49%) as a white powder. LC−MS m / z = 384.3 [M-H]; $^1$H NMR (DMSO-$d_6$) δ 1.86-1.99 (m, 1 H), 2.61-2.69 (m, 3 H), 3.01-3.14 (m, 1 H), 3.16-3.27 (m, 1 H), 3.50-3.60 (m, 1 H), 3.87 (s, 3 H), 4.45 (br. t, $J=5.20$ Hz, 2 H), 6.84 (s, 1 H), 7.92 (s, 1 H), 7.93 (s, 1 H), 9.15 (br. s, 2 H), 13.02 (s, 1 H), 13.83 (s, 1 H), 16.20 (br. s, 1 H).

10-((Ethylamino)methyl)-4-hydroxy-9-methyl-2-oxo-2,5,6,9-tetrahydro-1H-pyrido[2',3':4,5]thiepin[3,2-f]indole-3-carboxylic acid hydrochloride (6h). Obtained 42 mg (64%) as a white powder. LC−MS m / z = 398.3 [M-H]; $^1$H NMR (DMSO-$d_6$) δ: 1.27 (t, $J=7.3$ Hz, 3 H), 1.86-1.98 (m, 1 H), 3.00-3.14 (m, 2 H), 3.15-3.26 (m, 1 H), 3.50-3.59 (m, 1 H), 3.87 (s, 3 H), 4.45 (t, $J=5.4$ Hz, 2 H), 6.85 (s, 1 H), 7.92 (s, 1 H), 7.93 (s, 1 H), 9.12 (br. s, 2 H), 13.02 (br. s, 1 H), 13.82 (br. s, 1 H), 16.19 (br. s, 1 H).

4-Hydroxy-10-((isopropylamino)methyl)-9-methyl-2-oxo-2,5,6,9-tetrahydro-1H-pyrido[2',3':4,5]thiepin[3,2-f]indole-3-carboxylic acid hydrochloride (6m). Obtained 37 mg (55%) as a white powder. LC−MS m / z = 412.4 [M-H]; $^1$H NMR (DMSO-$d_6$) δ: 1.34 (d, $J=6.31$ Hz, 6 H), 1.83-1.99 (m, 1 H), 3.00-3.26 (m, 2 H), 3.42-3.62 (m, 2 H), 3.87 (s, 3 H), 4.39-4.52 (m, 2 H), 6.85 (s, 1 H), 7.92 (s, 1 H), 7.93 (s, 1 H), 9.01 (br. s, 2 H), 13.03 (br. s, 1 H), 13.82 (br. s, 1 H), 16.40 (br. s, 1 H).

10-((Dimethylamino)methyl)-4-hydroxy-9-methyl-2-oxo-2,5,6,9-tetrahydro-1H-pyrido[2',3':4,5]thiepin[3,2-f]indole-3-carboxylic acid hydrochloride (6u). Obtained 21 mg (32%) as a white powder. LC−MS m / z = 398.4 [M-H]; $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 1.93 (br. s, 1 H), 3.09 (br. s, 1 H), 3.21 (br. s, 1 H), 3.55 (br. s, 1 H), 3.60 (br. s, 6 H, obscured by H$_2$O), 3.91 (s, 3 H), 4.60 (br. s, 2 H), 6.96 (s, 1 H), 7.94 (s, 2 H), 10.55 (br. s, 1 H), 13.01 (br. s, 1 H), 13.83 (br. s, 1 H), 16.18 (br. s, 1 H).

4-Hydroxy-9-methyl-2-oxo-10-(pyrrolidin-1-ylmethyl)-2,5,6,9-tetrahydro-1H-pyrido[2',3':4,5]thiepin[3,2-f]indole-3-carboxylic acid hydrochloride (6y). Obtained 25 mg (36%) as white powder. LC−MS m / z = 424.4 [M-H]; $^1$H NMR (500 MHz, DMSO-$d_6$) δ: 1.85-2.24 (m, 5 H), 3.03-3.29 (m, 3 H), 3.45-3.74 (m, 4 H), 3.85-4.05 (m, 3 H), 4.69 (br. s, 1 H), 4.93 (s, 1 H), 6.94-7.11 (m, 1 H), 7.87-8.04 (m, 2 H), 10.68 (br. s, 1 H), 12.92-13.17 (m, 1 H), 13.85 (br. s, 1 H), 16.19 (br. s, 1 H).
Scheme D.\textsuperscript{a}

\[ \text{Scheme D.} \]

\[ \text{D1} \xrightarrow{\text{a}} \text{D2} \xrightarrow{\text{b}} \text{D7} \xrightarrow{\text{c}} \text{D12} \xrightarrow{\text{d}} \text{D8} \xrightarrow{\text{e}} \text{D9} \xrightarrow{\text{f}} \text{D3} \xrightarrow{\text{g}} \text{D4} \xrightarrow{\text{h}} \text{D5} \]

\( ^a \text{Reagents and conditions: (a) Boc}_2\text{O (1.05 equiv), DMAP (0.1 equiv), CH}_{2}\text{Cl}_2, \text{rt, 2 h, 88%}; (b) 10\% \text{Pd-C, H}_2, (1 \text{ atm}) \text{MeOH/} \text{Et}_3\text{N (10/1), 98%}; (c) \text{TBSCl (1.5 equiv), imidazole (2.0 equiv), CH}_2\text{Cl}_2, \text{rt, 91%}; (d) \text{NBS (1.1 equiv), CH}_2\text{Cl}_2, \text{rt, overnight, 90%}; (e) \text{MnO}_2 (49 \text{ equiv), CH}_2\text{Cl}_2, \text{overnight, 90%}; (f) \text{LDA (1.5 equiv), THF, −78 °C to rt, 1 h, then ClCO}_2\text{Et (2.0 equiv), −78 °C to rt, 74%}; (g) \text{Ph}_2\text{O, 180-190 °C, 15 min; 81%}; (h) \text{NaH (1.5 equiv), DMF, 0 °C then MeI (1.2 equiv), 0 °C to rt, 91%}; (i) \text{DIBAL-H (2.5 equiv), CH}_2\text{Cl}_2, −78 °C, 1 h}; (j) \text{MnO}_2, (19 \text{ equiv), CH}_2\text{Cl}_2, 1 \text{ h, 90%}}; (k) \text{Pin}_2\text{B} (1.5 \text{ equiv), Pd(dppf)Cl}_2 (0.1 \text{ equiv); KOAc (3.0 equiv), dioxane 90 °C, overnight, 73%}; (l) \text{D11 (1.2 equiv), D12 (1.0 equiv), Pd}_2\text{dba}_3 (0.1 \text{ equiv), } t\text{-Bu}_3\text{PHBF}_4 (0.2 \text{ equiv), K}_2\text{CO}_3 (3.0 \text{ equiv), dioxane, 90 °C, overnight, 56%}; (m) \text{TBAF (4 equiv), THF, 0 °C, 1 h, 98%}}; (n) \text{Deoxo-Fluor (2.5 equiv), CH}_2\text{Cl}_2, −78 °C to rt, 1 h, 76%}; (o) \text{amine (3 equiv), NaBH(OAc)}_3 (1.8 \text{ equiv), DCE, then AcOH (1.8 equiv), 2 h (p) TIPS-H, TFA, 60 °C, 2 h, then } \text{HCl/Et}_2\text{O, 27-87% (2 steps).}

**1-(tert-Butoxycarbonyl)-1H-indole-6-carboxaldehyde (D1).** To a solution of 1H-indole-6-carboxaldehyde (3.0 g, 20.7 mmol) and di-tert-butyl dicarbonate (4.8 g, 1.05 eq.) in 20 mL of dry dichloromethane was added N,N-dimethylaminopyridine (244 mg, 0.1 equiv) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was diluted with ethyl acetate. The solution was washed with 1N HCl, saturated aq. NaHCO\textsubscript{3}, brine, and dried over MgSO\textsubscript{4}. After filtration, the filtrate was concentrated in vacuo to obtain D1 as a yellow gum (4.45 g, 88%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta = 1.67 \text{ (s, 9 H)}, 6.67 \text{ (dd, } J=0.63, 3.78 \text{ Hz, 1 H)}, 7.69 \text{ (d, } J=7.88 \text{ Hz, 1 H)}, 7.78-7.85 \text{ (m, 2 H)}, 8.70 \text{ (br. s, 1 H)}, 10.10 \text{ (s, 1 H)}. \)

**tert-Butyl 6-(hydroxymethyl)indoline-1-carboxylate (D2).** 1-(tert-butoxycarbonyl)-1H-indole-6-carboxaldehyde (1.0 g, 4.08 mmol) was dissolved in 30 mL of methanol. Triethylamine
(3 mL), and 10% palladium on carbon (200 mg) were added to the solution under nitrogen. After the vessel was purged and filled with hydrogen, the reaction mixture was stirred under 1 atm of hydrogen overnight. After the vessel was purged with nitrogen, the catalyst was removed by filtration. After concentration in vacuo, the crude product (1.0 g, 98%) was used in the next step without further purification.

**tert-Butyl 6-[[tert-butyldimethylsilyl]oxymethyl]indoline-1-carboxylate (D3).** To a solution of D2 (1.0 g, 4.01 mmol) and imidazole (552 mg, 8.02 mmol, 2.0 eq.) in dichloromethane (20 mL) was added tert-butyldimethylchlorosilane (6.0 mL, 1.0 M in CH$_2$Cl$_2$, 1.5 equiv) slowly at room temperature. The reaction was stirred at room temperature for 2 h, and then quenched with satd. NaHCO$_3$. The aqueous layer was extracted with CH$_2$Cl$_2$ (2X) and the combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel eluting with 0-20% EtOAc in hexanes to provide D3 (1.33 g, 91%). $^1$H NMR (500 MHz, CDCl$_3$) δ 0.06 (s, 6 H), 0.84 (s, 9 H), 1.54 (s, 9 H), 3.06 (t, $J$=8.67 Hz, 2 H), 3.98 (br. s, 2 H), 4.71 (s, 2 H), 6.95 (br. s, 1 H), 7.10 (d, $J$=7.57 Hz, 1 H), 7.64 (br. s, 1 H).

**tert-Butyl 5-bromo-6-[[tert-butyldimethylsilyl]oxymethyl]indoline-1-carboxylate (D4).** A mixture of D3 (1.33 g, 3.66 mmol) and NBS (723 mg, 1.10 eq.) in CH$_2$Cl$_2$ (20 mL) was stirred at room temperature overnight. Aqueous K$_2$CO$_3$ (15 mL) was added and the mixture was extracted with CH$_2$Cl$_2$. The organic extracts were combined, washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate and concentrated to dryness under reduced pressure. The residue was purified by column chromatography (0-20% CH$_2$Cl$_2$ in hexanes) to give D4 (1.45 g, 90 %) as a light pink solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 0.11 (s, 6 H), 0.82 (s, 9 H), 1.53 (s, 9 H), 3.05 (t, $J$=8.67 Hz, 2 H), 3.99 (br. t, $J$=8.51 Hz, 2 H), 4.71 (s, 2 H), 7.19 (d, $J$=8.5 Hz, 1 H), 7.70 (br. s, 1 H).

**tert-Butyl 5-bromo-6-[[tert-butyldimethylsilyl]oxymethyl]indole-1-carboxylate (D5).** A mixture of D4 (1.45 g, 3.28 mmol) and MnO$_2$ (14 g, 49 eq.) in CH$_2$Cl$_2$ (60 mL) was stirred at room temperature overnight, then filtered and washed with CH$_2$Cl$_2$. The filtrate was combined and evaporated to provide D5 (1.3 g, 90%) as a white solid, which was used in the next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 0.11 (s, 6 H), 0.93 (s, 9 H), 1.56 (s, 9 H), 4.83 (s, 2 H), 6.49 (d, $J$=3.73 Hz, 1 H), 7.59 (d, $J$=3.47 Hz, 1 H), 7.71 (s, 1 H), 8.34 (s, 1 H).

**1-tert-Butyl 2-ethyl 5-bromo-6-[[tert-butyldimethylsilyl]oxymethyl]indole-1,2-dicarboxylate (D6).** To a stirred solution of D5 (410 mg, 0.93 mmol) in anhydrous THF (5 mL) under argon at $-78^\circ$C was added LDA (0.70 mL, 2.0M in THF, 1.5 equiv) dropwise. The mixture was stirred for 10 min at $-78^\circ$C before warming to 0 °C slowly over 1 h. After recooling to $-78^\circ$C, ethyl carbonochloridate (0.18 mL, 2.0 equiv) was added. The reaction mixture was stirred at $-78^\circ$C for 15 min, then warmed to room temperature over 1 h. The mixture was quenched by the addition of saturated ammonium chloride solution at 0 °C and extracted with ethyl acetate. The combined organic layers were washed with water, dried over sodium sulfate and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel eluting with 0-30% EtOAc in hexanes to provide D6 (355 mg, 74%). $^1$H NMR (500 MHz, CDCl$_3$) δ 0.17 (s, 6 H), 0.95 (s, 9 H), 1.22 (d, $J$=6.94 Hz, 3 H), 1.60 (s, 9 H), 4.39 (q, $J$=7.25 Hz, 2 H), 4.85 (d, $J$=0.95 Hz, 2 H), 7.01 (d, $J$=0.63 Hz, 1 H), 7.75 (s, 1 H), 8.29 (s, 1 H).

**Ethyl 5-bromo-6-[[tert-butyldimethylsilyl]oxymethyl]-1H-indole-2-carboxylate**
Compound D6 (1.4 g, 2.7 mmol) was mixed with Ph$_2$O (3 mL) and heated at 180°C for 15 min under Ar. After cooling, the crude product was purified by flash column chromatography on silica gel eluting with 0-30% EtOAc in hexanes to provide D7 (910 mg, 81%). $^1$H NMR (500 MHz, acetone-$d_6$) δ 0.16 (s, 6 H), 0.97 (s, 9 H), 1.36 (t, $J$=7.09 Hz, 3 H), 4.36 (q, $J$=7.04 Hz, 2 H), 4.85 (d, $J$=0.95 Hz, 2 H), 7.15 (dd, $J$=0.95, 2.21 Hz, 1 H), 7.82 (s, 1 H), 7.90 (s, 1 H), 11.10 (br. s, 1 H).

Ethyl 5-bromo-6-[[tert-butyl(dimethyl)silyl]oxymethyl]-1-methyl-indole-2-carboxylate (D8). To a solution of D7 (1.1 g, 2.7 mmol) in DMF (6 mL), cooled to 0 °C, was added NaH (60% in oil, 140 mg, 1.50 equiv). Gas evolution was observed and the mixture was stirred for 30 min at which point iodomethane (460 mg, 1.2 equiv) was added. The solution was warmed to room temperature and stirred for 2 h. Saturated NH$_4$Cl was added and the mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over MgSO$_4$, then filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel eluting with 0-100% CH$_2$Cl$_2$ in hexanes to provide D8 (1.03 g, 91%) as white foam. $^1$H NMR (500 MHz, acetone-$d_6$) δ 0.17 (s, 6 H), 0.99 (s, 9 H), 1.38 (t, $J$=7.09 Hz, 3 H), 4.07 (s, 3 H), 4.37 (q, $J$=7.25 Hz, 2 H), 4.89 (s, 2 H), 7.24 (d, $J$=0.95 Hz, 1 H), 7.73 (s, 1 H), 7.91 (s, 1 H).

[5-Bromo-6-[[tert-butyl(dimethyl)silyl]oxymethyl]-1-methyl-indol-2-yl]methanol (D9). To a solution of D8 (1.0 g, 2.35 mmol) in CH$_2$Cl$_2$ (10 mL) at −78 ºC was added DIBAL-H (5.9 mL, 1.0M in CH$_2$Cl$_2$, 2.5 equiv) dropwise. The mixture was stirred at −78 ºC for 1 h, then quenched by addition of a saturated solution of Rochelle salt (10 mL) at −78 ºC. The mixture was warmed to room temperature, and then diluted with CH$_2$Cl$_2$. After stirring at room temperature for 30 min, the mixture was extracted with CH$_2$Cl$_2$. The organic extracts were combined, dried over sodium sulfate and evaporated to give D9 (900 mg, 100%), which was used in the next step without further purification. $^1$H NMR (500 MHz, acetone-$d_6$) δ 0.15 (s, 6 H), 0.97 (s, 9 H), 3.82 (s, 3 H), 4.77 (d, $J$=5.67 Hz, 2 H), 4.87 (d, $J$=0.95 Hz, 2 H), 6.36 (s, 1 H), 7.58 (s, 1 H), 7.69 (s, 1 H).

5-Bromo-6-[[tert-butyl(dimethyl)silyl]oxymethyl]-1-methyl-indole-2-carbaldehyde (D10). A mixture of D9 (900 mg, 2.34 mmol) and MnO$_2$ (4.0 g, 19 equiv) in CH$_2$Cl$_2$ (20 mL) was stirred at room temperature for 1 h. The mixture was then filtered through a pad of Celite® and washed with CH$_2$Cl$_2$. The filtrate was evaporated to provide D10 (810 mg, 90%), which was used in the next step without further purification. $^1$H NMR (500 MHz, acetone-$d_6$) δ 0.13 (s, 6 H), 0.93 (s, 9 H), 4.11 (s, 3 H), 4.89 (d, $J$=1.26 Hz, 2 H), 7.38 (d, $J$=0.95 Hz, 1 H), 7.75 (s, 1 H), 8.00 (s, 1 H), 9.95 (s, 1 H).

6-[[tert-Butyl(dimethyl)silyl]oxymethyl]-1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indole-2-carbaldehyde (D11). A solution of D10 (810 mg, 2.12 mmol), KOAc (623 mg, 3.0 equiv), bis(pinnacolato)diboron (807 mg, 1.5 equiv) and Pd(dppf)Cl$_2$ (173 mg, 0.1 equiv) in anhydrous dioxane (8 mL) was heated at 90 °C under an argon atmosphere overnight. The reaction was cooled to room temperature, filtered, and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica gel eluting with 0-50% dichloromethane in hexanes to provide D11 (668 mg, 73%) as a yellow solid. $^1$H NMR (500 MHz, acetone-$d_6$) δ 0.08 (s, 6 H), 0.93 (s, 9 H), 1.37 (s, 12 H), 4.10 (s, 3 H), 5.18 (d, $J$=1.26 Hz, 2 H), 7.42 (d, $J$=0.95 Hz, 1 H), 7.72 (s, 1 H), 8.21 (s, 1 H), 9.93 (s, 1 H).

Benzyl 2,4-dibenzyloxy-5-[[tert-butyl(dimethyl)silyl]oxy]methy]-6-[[tert-
butyl(dimethyl)silyl]oxymethyl]-2-formyl-1-methyl-indol-5-yl]pyridine-3-carboxylate (D13). A mixture of benzyl 2,4-dibenzoyloxy-5-[[tert-butyl(dimethyl)silyl]oxymethyl]-6-chloropyridine-3-carboxylate[^1] (D12, 970 mg, 1.61 mmol), D11 (830 mg, 1.2 equiv), Pd(dba)$_3$ (152 mg, 0.1 equiv), t-Bu$_3$P HBF$_4$ (96 mg, 0.2 equiv) and K$_2$CO$_3$ (672 mg, 3.0 equiv) in dioxane (5.2 mL) and water (1.3 mL) was stirred at 90 ºC for 1 h under an argon atmosphere. The reaction was then cooled, diluted with water and extracted with ethyl acetate. The organic phases were combined, dried over sodium sulfate and evaporated. The residue was purified by silica gel column chromatography with 0-100% dichloromethane in hexanes to give D13 (793 mg, 56%).

**Benzyl 2,4-dibenzyloxy-6-[2-formyl-6-(hydroxymethyl)-1-methyl-indol-5-yl]-5-(hydroxymethyl)pyridine-3-carboxylate (D14).** To a solution of D13 (230 mg, 0.26 mmol) in THF (5 mL) was added TBAF (1.06 mL, 1.0M in THF, 4.0 equiv) at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 min before it was warmed to room temperature over 1 h. The solvent was concentrated and the crude reaction mixture was purified by flash column chromatography (0-50% EtOAc/CH$_2$Cl$_2$) to afford D14 (167 mg, 98%). MS m / z 643.3 [M+H]$^+$; $^1$H NMR (500 MHz, acetone-$d_6$) δ 4.17 (s, 3 H), 4.37-4.46 (m, 2 H), 4.57 (br. s, 2 H), 5.26 (s, 2 H), 5.37-5.42 (m, 4 H), 7.30-7.47 (m, 16 H), 7.73 (s, 1 H), 7.76 (s, 1 H), 9.96 (s, 1 H).

**Benzyl 2,4-bis(benzyloxy)-10-formyl-9-methyl-7,9-dihydro-5H-pyrido[2',3':5,6]oxepino[4,3-f]indole-3-carboxylate (D15).** To a solution of D14 (167 mg, 0.26 mmol) in CH$_2$Cl$_2$ (25 mL) cooled at −78 ºC was added a 1.0M solution of deoxofluor in CH$_2$Cl$_2$ (145 mg, 2.5 equiv). After 1 h, the cooling bath was removed and the temperature was warmed to 0 ºC (~ 1 h). The mixture was diluted with CH$_2$Cl$_2$ and treated with saturated aqueous sodium bicarbonate and extracted with CH$_2$Cl$_2$ (3X). The organic extracts were combined, washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography with ethyl acetate in hexanes (5 to 50% gradient) to provide D15 (123 mg, 76%). MS m / z 625.2 [M+H]$^+$; $^1$H NMR (500 MHz, acetone-$d_6$) δ 4.20 (s, 3 H), 4.39 (s, 2 H), 4.60 (s, 2 H), 5.22 (s, 2 H), 5.38 (s, 2 H), 5.61 (s, 2 H), 7.31-7.46 (m, 13 H), 7.51 (d, $J$=7.50 Hz, 2 H), 7.59 (d, $J$=0.95 Hz, 1 H), 7.73 (s, 1 H), 8.37 (s, 1 H), 10.02 (s, 1 H).

**4-Hydroxy-9-methyl-2-oxo-10-(pyrrolidin-1-ylmethyl)-1,5,7,9-tetrahydro-2H-pyrido[2',3':5,6]oxepino[4,3-f]indole-3-carboxylic acid hydrochloride (6x).** Following the procedure used to prepare 8a, compound D15 and pyrrolidine gave 6x (75% yield). MS m / z 410.3 [M+H]$^+$; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.92 (br. s, 2 H), 2.05 (br. s, 2 H), 3.20 (br. s, 2 H), 3.92 (s, 3 H), 4.14 (s, 2 H), 4.52 (s, 2 H), 4.69 (s, 2 H), 6.88 (s, 1 H), 7.84 (br. s, 1 H), 8.05 (s, 1 H), 8.85 (br. s, 1 H), 13.18 (s, 1 H), 13.87 (br. s, 1 H).

**4-Hydroxy-10-((isopropylamino)methyl)-9-methyl-2-oxo-1,5,7,9-tetrahydro-2H-pyrido[2',3':5,6]oxepino[4,3-f]indole-3-carboxylic acid hydrochloride (6k).** Following the procedure used to prepare 8a, compound D15 and isopropylamine gave 6k (27% yield). MS m / z 396.3 [M-H]$^-$; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.35 (d, $J$=6.62 Hz, 6 H), 3.41 (br. s, 1 H), 3.88 (s, 3 H), 4.14 (s, 2 H), 4.51 (s, 2 H), 4.67 (s, 2 H), 6.87 (s, 1 H), 7.82 (s, 1 H), 8.04 (s, 1 H), 8.78-8.99 (br. s, 2 H), 13.18 (s, 1 H), 13.91 (br. s, 1 H).

**10-((Dimethylamino)methyl)-4-hydroxy-9-methyl-2-oxo-1,5,7,9-tetrahydro-2H-pyrido[2',3':5,6]oxepino[4,3-f]indole-3-carboxylic acid hydrochloride (6t).** Following the
procedure used to prepare 8a, compound D15 and a solution of dimethylamine gave 6t (79% yield). LC–MS $m/z$ = 382.1 [M-H]; $^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.83 (s, 6 H), 3.90 (s, 3 H), 4.15 (s, 2 H), 4.53 (s, 2 H), 4.61 (s, 2 H), 6.95 (s, 1 H), 7.83 (s, 1 H), 8.07 (s, 1 H), 13.13 (s, 1 H), 13.94 (br. s, 1 H).
LC-MS trace for 6a
LC-MS trace for 6i
LC-MS trace for 6o
LC-MS trace for 6q
LC-MS trace for 6r
Sample Report:

Sample 1 Vial 2:9 ID 1283_165_1 File marnoid5421-1 Date 16-Mar-2012 Time 10:47:39 Description

Peak Number | Time | Area %Total | Mass Found
--- | --- | --- | ---
1 | 0.92 | 100.00 |

Peak ID | Compound | Time | Mass Found |
--- | --- | --- | ---
1 | 3: UV Detector | 0.92 | 100.00 |

1: MS ES+ 7.6e+006
2: MS ES- 3.1e+005

LC-MS trace for 6s
LC-MS trace for 6v
**Supplemental Table 1.** Enzymatic data for selected compounds from Tables 6 and 7 from the manuscript.

| Compd | E. coli DNA gyrase<sup>a</sup> IC<sub>50</sub> (µM) | E. coli Topo II<sup>a</sup> IC<sub>50</sub> (µM) | Human Topo II<sup>b</sup> IC<sub>50</sub> (µM) |
|-------|---------------------------------|---------------------------------|---------------------------------|
| 6a    | 1.4                             | 2.8                             | >100                            |
| 6i    | 2.7                             | 2.0                             | >100                            |
| 6o    | 0.11                            | 8.4                             | >100                            |
| 6p    | n.d.<sup>c</sup>                | n.d.<sup>c</sup>                | n.d.<sup>c</sup>                |
| 6q    | 0.73                            | 6.1                             | >100                            |
| 6r    | 0.41                            | 9.6                             | >100                            |
| 6s    | 0.49                            | 5.4                             | >100                            |
| 6v    | 0.21                            | 5.1                             | >100                            |
| 6w    | 0.28                            | 2.5                             | >100                            |

<sup>a</sup> Wild-type E. coli (ATCC 25922).  <sup>b</sup>Human topoisomerase II.  <sup>c</sup>Not determined.

**Supplemental Table 2.** In vitro antibacterial activity of reference antibiotics.

| Compd | MIC (µg/mL)<sup>a</sup> |
|-------|-------------------------|
|       | E. coli<sup>WT</sup> | E. coli<sup>R1</sup> | E. coli<sup>R2</sup> | A. bau<sup>WT</sup> | A. bau<sup>R</sup> | K. pneu<sup>WT</sup> |
| ciprofloxacin | 0.012 | >250 | >250 | 0.19 | >25 | 0.19 |
| cefepime | 0.05 | 0.05 | n.d.<sup>b</sup> | 0.78 | 0.78 | 0.02 |
| tigecycline | 0.13 | 0.25 | 0.13 | 0.78 | 0.78 | 0.13 |

<sup>a</sup>Minimum inhibitory concentration. E. coli<sup>WT</sup> = E. coli ATCC 25922; E. coli<sup>R1</sup> = E. coli SKM18; E. coli<sup>R2</sup> = E. coli ELZ4251; A. bau<sup>WT</sup> = A. baumannii ATCC BAA-747; A. bau<sup>R</sup> = A. baumannii MMX2240; K. pneu<sup>WT</sup> = K. pneumoniae ATCC 35657.  <sup>b</sup>Not determined.
Figure 1. Time-kill kinetics plots for ciprofloxacin against *E. coli* WT (1a) and *A. baumannii* WT (1b).
**Bacterial time kill curves.** The time kill kinetics for *E. coli* and *A. baumannii* were performed in accordance with NCCLS guidelines. Briefly, aliquots from the compound treated bacterial cultures at the indicated time points were serially diluted in sterile PBS (phosphate buffered saline) to produce 10-fold dilutions ($10^1$, $10^2$, $10^3$, $10^4$, $10^5$, $10^6$) which were then spotted onto agar plates and CFU/mL (colony forming units per mL) was determined in duplicate by counting colonies on the agar plate after 24 hours of incubation. The kill kinetics are then represented graphically by plotting the log$_{10}$ CFUs versus time at each compound concentration.

**DNA gyrase mutant expression and purification.** Site directed mutagenesis to generate mutant gyrase A subunit (gyrase$^{SD-LY}$) was carried out using the Invitrogen’s GeneArt site directed mutagenesis PLUS kit according to the manufacturer’s protocol. Primers were generated using Invitrogen’s “Oligo Designer”. Accuprime pfx DNA polymerase was used for increased fidelity of the pcr reactions. Plasmid DNA pET15b containing the wild-type *E. coli* DNA gyrase was used as the template. After sequence verification (Genewiz) of the mutation in the pcr product, the NdeI/XmaI restriction digested fragment containing the gyrase A mutant sequence was ligated into a similarly digested plasmid pET15b. The plasmid DNA containing the mutant gyrase A subunit was then transformed into competent BL21 (λDE3) pLysS cells for expression and purification of the mutant gyrase A subunit.

Purification of the histidine tagged gyrase A subunit (WT or mutant), was carried out by modification of a combination of methods. Briefly, 1L cultures of the *E. coli* BL21(λDE3) pLysS containing the plasmid of interest (WT or mutant gyrase subunit A) was grown in Luria-Bertani (LB) medium containing the selective antibiotic. Induction of the protein was carried out by adding 0.5 mM IPTG to log phase culture and allowing additional growth overnight at 18 °C. The bacterial cell pellet was allowed to incubate for 30 min on ice in 40 mL of buffer containing 20mM Tris-HCl (pH 7.9), 300 mM NaCl, 0.1% triton x-100, 10% glycerol and 0.1% (weight/vol.) lysozyme for lysis. The lysate was then briefly sonicated (2 x 10 sec bursts) to reduce viscosity and then centrifuged at 20,000 x g for 30 minutes. The soluble fraction was then mixed with 5 mL of a 50% Ni-NTA slurry which was pre-equilibrated with buffer N (20 mM Tris-HCl (pH7.9), 300 mM NaCl, 0.1% triton x-100, 10% glycerol) and allowed to equilibrate for a minimum of 1 h after which the slurry was poured into a column and the unbound proteins were collected in the flow through fraction. The Ni-NTA column was then washed with 15 to 20 column volumes of buffer N with added 50 mM imidazole and washes were collected in column volume fractions to assess the protein content by a gel electrophoresis. The gyrase subunit A was then eluted with buffer N containing 200 mM imidazole in column volume fractions. The various fractions collected were examined by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and those containing the gyrase subunit A were pooled and dialyzed against 4L of TED (50 mM Tris pH 8.0, 1 mM EDTA, and 2 mM dithiothreitol). The dialysate was then subjected to anion exchange chromatography on a Mono Q HR 10/10 column (run by a FPLC system) which was equilibrated in TED buffer. The gyrase subunit A was eluted using a 1M NaCl gradient in the same buffer. Peak fractions containing the protein were pooled and concentrated using centrifugal concentrators (Millipore), and then subjected to desalting and buffer exchange by size exclusion chromatography on a Superdex 200 column equilibrated in 10 mM Tris pH 7.5, 50 mM KCl, 0.1 mM EDTA and 2 mM DTT. Peak fractions containing the protein were pooled and concentrated and stored at -80 °C in the presence of 25% glycerol.

The purified mutant gyrase A$^{SD-LY}$ was then reconstituted with WT gyrase B subunit (purchased from Topogen) in a 1:1 molar ratio at 15 micromolar concentration in a storage
buffer (50 mM Tris-Cl pH 7.5, 100 mM KCl, 2 mM dithiotreitol, 1 mM EDTA, and 50% glycerol) before use in the enzymatic assay. For experiments comparing gyrase\textsuperscript{WT} and gyrase\textsuperscript{SD-LY}, gyrase\textsuperscript{WT} holoenzyme used was also reconstituted using a similarly purified WT gyrase subunit A, along with gyrase subunit B.

**DNA gyrase assay.** Microtitre plate based supercoiling assay for *E. coli* DNA gyrase WT or mutant was carried out as described.\textsuperscript{5} Briefly, black streptavidin coated 96-well microplates (Pierce) were rehydrated and washed three times in wash buffer (20 mM Tris-HCl, pH 8.0, 137 mM NaCl, 0.01% bovine serum albumin, 0.05% Tween-20). 100 µL of 500 nM biotinylated TFO1 (triplex forming oligonucleotide) was immobilized onto the streptavidin plate. Excess oligonucleotide was washed off using the wash buffer. 30 µL enzyme reactions containing 1 µg relaxed plasmid DNA (pNO1 from Inspiralis) in 35 mM Tris-HCl (pH 7.5), 24 mM KCl, 4mM MgCl\textsubscript{2}, 2mM DTT, 1.8 mM spermidine, 1mM ATP, 6.5% glycerol, 0.1 mg/ml albumin, and 1 U of *E. coli* DNA gyrase (Topogen) was incubated at 37° C for 30 minutes. 100 µL of TF buffer (50 mM sodium acetate, pH 5.5, 50 mM NaCl, 50 mM MgCl\textsubscript{2}\cdot6 H\textsubscript{2}O) was then added to the reaction and the entire mixture was transferred to the microplate wells after the TFO1 immobilization process. The microplate was incubated at room temperature for 30 min to allow triplex formation. Any unbound plasmid was washed off using 3 X 200 µL of TF buffer, then 200 uL of 1X SYBR Gold in 10 mM Tris-HCl (pH 8.0), 1 mM EDTA was added and allowed to stain for 20 min. Fluorescence was read using the EnVision plate reader.

**Topoisomerase IV activity.** Decatenation assays using purified topoisomerase IV protein were performed using the DNA topo IV assay kit (Profoldin) according to the manufacturer’s protocol. Decatenation of kinetoplast concatenated DNA (Profoldin) was assayed in a total reaction volume of 20 µl containing 40 mM Tris pH 7.5, 6 mM MgCl\textsubscript{2}, 10 mM DTT, 100 mM potassium glutamate, 50 mg/ml acetylated BSA, 1 mM ATP, and 0.2 mg kDNA substrate. Compound titrations in DMSO were added and the reactions were initiated with 2 units of *E. coli* topoIV (Topogen) that were incubated in a 96 well plate with shaking for 30 min at 37°C. Upon quenching the reaction with EDTA, the assay mixture was filtered using a 96 well filterplate (Millipore) to separate the decatenated DNA product from the substrate kDNA. The decatenated product was then quantified using picogreen fluorescence on an EnVision plate reader.

Human Topoisomerase II decatenation activity was assayed similar to that described for the *E. coli* topoisomerase IV in a 96-well plate based format, except that 1 unit of human topoisomerase II (Topogen) was used.
All animal studies were performed under IACUC approved protocols at AAALAC-certified animal facilities.

**Pharmacokinetic studies in mice**

The pharmacokinetics of test compounds was evaluated in CD-1 mice. Compounds were dosed at 10 mg/kg IV in 10% DMSO and 1% Tween 80 in pH 8.0 phosphate buffer in CD-1 mice. Blood was collected by terminal cardiac puncture (3 mice per time point) at 0.083, 0.25, 1, 2, 4, 7, 16, and 24 hours after dosing. Plasma drug levels were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Briefly, the plasma samples were treated with acetonitrile-methanol mixture containing an internal standard that is a close analog of the test compounds. Pharmacokinetic parameters were calculated using a noncompartmental model using WinNonlin (Phoenix, Pharsight; St. Louis MO).

**Mouse model of bacterial-induced lethality**

The mice were made neutrophil-deficient with the use of cyclophosphamide IP administration at 150 mg/kg Day -4 and 100 mg/kg cyclophosphamide on Day -1. CD-1 mice were inoculated with Gram negative bacteria (*E. coli*, 1x10⁶ CFU/mouse) mixed with 5% mucin and injected intraperitoneally. Morbidity and mortality was monitored twice per day. Moribund mice were euthanized.

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