Supporting Information

Development of Highly Potent and Selective Steroidal Inhibitors and Degraders of CDK8.

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Content

Molecular overlay and Docking Studies

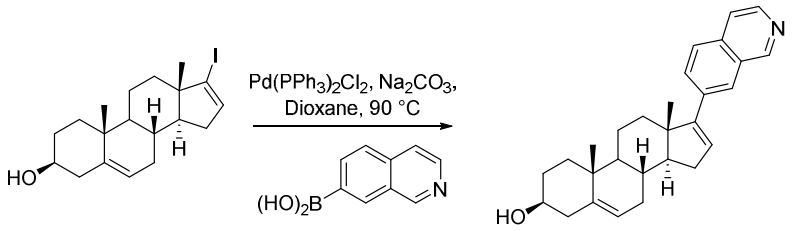
The molecular overlay shown in figure 1 of the manuscript was constructed based on the co-crystal structure of Cortistatin A with CDK8 (PDB: 4CRL). Compound 19 was energy minimized using ChemOffice 2016 Chem3D with MM2 energy minimization to minimum RMS gradient of 0.010. Once the energy minimized structure was obtained, it was imported into the co-crystal structure of Cortistatin A with CDK8 and pair fitted to Cortistatin A using 8 points.

Experimental Procedures and Compounds Characterization

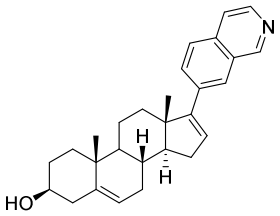
General

All reactions were monitored by thin layer chromatography (TLC) with 0.25 mm E. Merck pre-coated silica gel plates (60 F_{254}) and Waters LCMS system (Waters 2489 UV/Visible Detector, Waters 3100 Mass, Waters 515 HPLC pump, Waters 2545 Binary Gradient Module, Waters Reagent Manager, Waters 2767 Sample Manager) using SunFire™ C18 column (4.6 x 50 mm, 5 μm particle size): solvent gradient = 100% A at 0 min, 1% A at 5 min; solvent A = 0.035% TFA in Water; solvent B = 0.035% TFA in MeOH; flow rate : 2.5 mL/min. Purification of reaction products was carried out by flash chromatography using CombiFlash®Rf with Teledyne Isco Redi*Sep*®Rf High Performance Gold or Silicycle Silia*Sep*™ High Performance columns (4 g, 12 g, 24 g, 40 g or 80 g). The purity of all compounds was over 95% and was analyzed with Waters LCMS system. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker (500 MHz for ^{1}H, and 100 MHz for ^{13}C) spectrometer. Chemical shifts are reported relative to chloroform (δ = 7.24) for ^{1}H NMR or dimethyl sulfoxide (δ = 2.50) for ^{1}H NMR and dimethyl sulfoxide (δ = 39.51) for ^{13}C NMR. Data are reported as (*br* = broad, *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet). Purified compounds were greater than 95% pure based on LCMS analysis. All enzyme IC50's were obtained from Invitrogen using a Lanthascreen binding assay.

Representative Synthetic Scheme for the preparation of compounds **1**-**8**



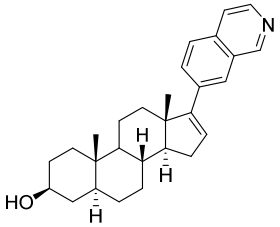
17 1



(3S,8R,10R,13S,14S)-17-(isoquinolin-7-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol (1)

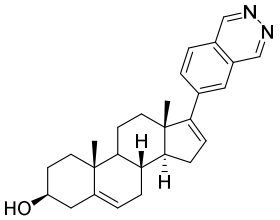
To a solution of (3S,8R,10R,13S,14S)-17-iodo-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol (50 mg, 0.13 mmol) in 1,4-dioxane (5mL) and Na_2CO_3 2M aq. (0.32 mL, 0.63 mmol) was added isoquinolin-7-ylboronic acid (25 mg, 0.14 mmol). The solution was thoroughly degassed and then $Pd(PPh_3)_2Cl_2$ (5 mg, 0.006 mmol) was added and the mixture was heated to 90 °C for 1 hour. The reaction was quenched with H_2O and extracted with EtOAc (3 X 50 mL), dried over $MgSO_4$ and condensed to give a brown oil that was purified by reverse phase chromatography using a gradient of 1-90% ACN in H_2O to give the title compound as a beige solid (40 mg, 80% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 9.66 (s, 1H), 8.55 (d, *J* = 5Hz, 1H), 8.35 (s, 1H), 8.20 (d, *J* = 6Hz, 1H), 8.13 (s, 2H), 6.39 (s, 1H), 5.33 (s, 1H), 3.28 (m, 1H), 3.17 (s, 1H), 2.38-1.99 (m, 6H), 1.81-1.52 (m, 8H), 1.45-1.33 (m, 3H), 1.15 (s, 3H), 1.03 (s, 3H). MS m/z 400.39 $[M+H]^+$.

The following compounds were prepared using the method above from either 5α-Androst-16-en-3β-ol, 17-iodo-(Compound **2**) or Androsta-5,16-dien-3-ol, 17-iodo-, (3β)- (Compounds **1**, and **3**-**8**) and the appropriate boronic ester/acid.



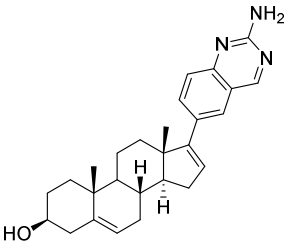
(3S,5S,8R,10S,13S,14S)-17-(isoquinolin-7-yl)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol (2)

(76% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 9.65 (s, 1H), 8.56 (d, *J* = 5Hz, 1H), 8.32 (s, 1H), 8.17 (d, *J* = 6Hz, 1H), 8.12 (s, 2H), 6.37 (s, 1H), 3.38 (m, 1H), 3.17 (s, 1H), 2.41-2.22 (m, 3H), 1.75-1.14 (m, 17H), 1.11 (s, 3H), 0.84 (s, 3H). MS m/z 401.74 $[M+H]^+$.



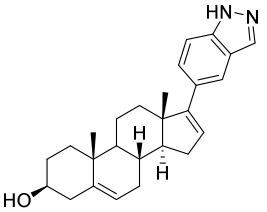
(3S,8R,10R,13S,14S)-10,13-dimethyl-17-(phthalazin-6-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol (3)

(68% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 9.86 (s, 1H), 9.80 (s, 1H), 8.28 (s, 1H), 8.24 (d, *J* = 6Hz, 2H), 6.51 (s, 1H), 5.34 (s, 1H), 3.26 (m, 1H), 3.17 (s, 1H), 2.41-1.87 (m, 6H), 1.83-1.54 (m, 8H), 1.41-1.30 (m, 3H), 1.11 (s, 3H), 1.01 (s, 3H). MS m/z 400.86 $[M+H]^{+}$.



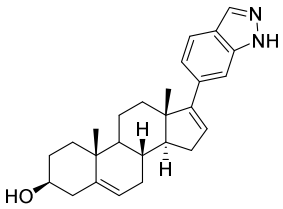
(3S,8R,10R,13S,14S)-17-(2-aminoquinazolin-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol (4)

(60% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 9.38 (s, 1H), 8.06 (br, 2H), 7.89 (s, 1H), 7.80 (d, *J* = 6Hz, 1H), 7.54 (d, *J* = 6Hz, 1H) 6.34 (s, 1H), 5.32 (s, 1H), 3.29 (m, 1H), 3.17 (s, 1H), 1.83-1.21 (m, 17H), 0.93 (s, 3H), 0.44 (s, 3H). MS m/z 416.37 $[M+H]^{+}$.



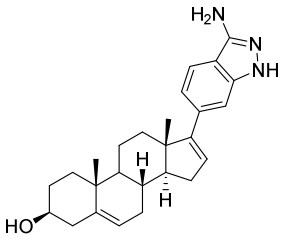
(3S,8R,10R,13S,14S)-17-(1H-indazol-5-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol (5)

(58% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 12.91 (s, 1H), 7.98 (s, 1H), 7.58 (s, 1H), 7.43 (d, *J* = 6Hz, 1H), 7.21 (d, *J* = 6Hz, 1H), 6.38 (s, 1H), 5.30 (s, 1H), 4.63 (s, 1H), 3.27 (m, 1H), 2.22-1.20 (m, 18H), 0.93 (s, 3H), 0.43 (s, 3H). MS m/z 389.48 $[M+H]^{+}$.



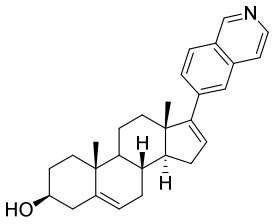
(3S,8R,10R,13S,14S)-17-(1H-indazol-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol (6)

(53% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 12.91 (s, 1H), 7.97 (s, 1H), 7.46 (s, 1H), 7.31 (d, *J* = 6Hz, 1H), 7.18 (d, *J* = 6Hz, 1H), 6.39 (s, 1H), 5.30 (s, 1H), 4.63 (s, 1H), 3.27 (m, 1H), 2.22-1.20 (m, 19H), 0.93 (s, 3H), 0.43 (s, 3H). MS m/z 389.48 $[M+H]^{+}$.



(3S,8R,10R,13S,14S)-17-(3-amino-1H-indazol-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol (7)

(54% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 12.96 (s, 1H), 7.94 (s, 1H), 7.48 (s, 1H), 7.40 (d, *J* = 6Hz, 1H), 7.19 (d, *J* = 6Hz, 1H), 6.39 (s, 1H), 5.30 (s, 1H), 5.12 (s, 1H), 4.63 (s, 1H), 3.27 (m, 1H), 2.22-1.20 (m, 18H), 0.93 (s, 3H), 0.43 (s, 3H). MS m/z 403.61 $[M+H]^{+}$.



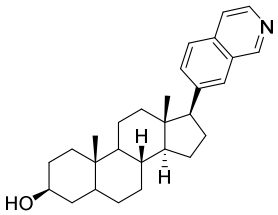
(3S,8R,10R,13S,14S)-17-(isoquinolin-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol (8)

(64% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 9.47 (s, 1H), 8.44 (s, 1H), 8.20 (s, 2H), 8.11 (d, *J* = 6Hz, 1H), 7.95 (d, *J* = 6Hz, 1H), 6.40 (s, 1H), 5.30 (s, 1H), 3.29 (m, 1H), 2.97 (t, *J* = 10Hz, 1H), 2.30-1.96 (m, 5H), 1.85-1.26 (m, 12H), 0.91 (s, 3H), 0.43 (s, 3H). MS m/z: 400.56 $[M+H]^{+}$.

Representative Synthetic Scheme for the preparation of compounds **9**-**16**

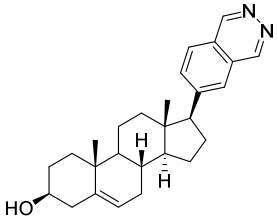
(3S,8S,10R,13S,14S,17S)-17-(isoquinolin-7-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol (9)

To a solution of (3S,8R,10R,13S,14S)-17-(isoquinolin-7-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol (10 mg, 0.025 mmol) in DMSO/THF (1:1) (3 mL) was added potassium diazene-1,2-dicarboxylate (109 mg, 0.50 mmol) and AcOH (64 µL, 1 mmol) in 3 portions over 2 hours. The mixture was stirred at rt overnight. An additional 109 mg of diazene-1,2-dicarboxylate and 64 µL of AcOH was added and the mixture stirred 2 hours. Quenched with sat. aq. $NaHCO_3$ and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and condensed to give a yellow oil that was purified by reverse phase HPLC using a gradient of 1-80% ACN in H_2O to give the title compound as a brown oil (6 mg, 60 % yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 9.66 (s, 1H), 8.57 (s, 1H), 8.29 (s, 2H), 8.16 (d, *J* = 6Hz, 1H), 7.99 (d, *J* = 6Hz, 1H), 5.32 (s, 1H), 3.28 (m, 1H), 2.98 (t, *J* = 10Hz, 1H), 2.35-1.98 (m, 5H), 1.87-1.29 (m, 12H), 0.93 (s, 3H), 0.46 (s, 3H). MS m/z 402.39 $[M+H]^+$.



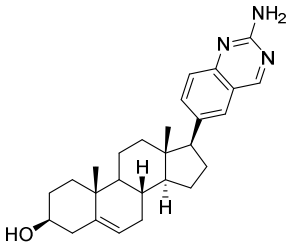
(3S,8R,10S,13S,14S,17S)-17-(isoquinolin-7-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-ol (10)

(71% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 9.68 (s, 1H), 8.54 (d, *J* = 5Hz, 1H), 8.37 (d, *J* = 6Hz, 1H), 8.31 (s, 1H), 8.19 (d, *J* = 6Hz, 1H), 8.04 (d, *J* = 6Hz, 1H), 3.36 (m, 1H), 3.17 (s, 1H), 2.97 (t, *J* = 10Hz, 1H), 2.41-2.22 (m, 3H), 1.78-1.12 (m, 17H), 0.72 (s, 3H), 0.41 (s, 3H). MS m/z 404.76 $[M+H]^+$.



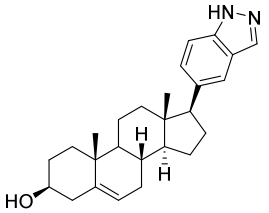
(3S,8S,10R,13S,14S,17S)-10,13-dimethyl-17-(phthalazin-6-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol (11)

(64% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 9.86 (s, 1H), 9.80 (s, 1H), 8.28 (s, 1H), 8.24 (d, *J* = 6Hz, 2H), 5.31 (s, 1H), 4.87 (s, 1H) 3.26 (m, 1H), 3.17 (s, 1H), 2.41-1.87 (m, 6H), 1.83-1.54 (m, 10H), 1.41-1.30 (m, 3H), 1.09 (s, 3H), 0.98 (s, 3H). MS m/z 403.38 $[M+H]^+$.



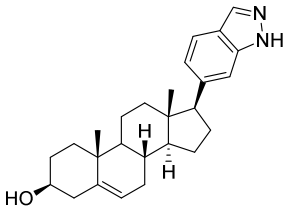
(3S,8S,10R,13S,14S,17S)-17-(2-aminoquinazolin-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol (12)

(52% yield). ^{1}H NMR (500 MHz, DMSO-d6) δ 9.36 (s, 1H), 8.14 (br, 2H), 7.91 (s, 1H), 7.86 (d, *J* = 6Hz, 1H), 7.57 (d, *J* = 6Hz, 1H), 5.33 (s, 1H), 4.72 (s, 1H), 3.29 (m, 1H), 3.17 (s, 1H),), 2.97 (t, *J* = 10Hz, 1H), 1.85-1.20 (m, 18H), 0.72 (s, 3H), 0.41 (s, 3H). MS m/z 417.96 $[M+H]^+$.



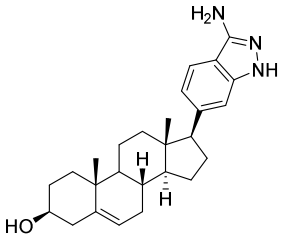
(3S,8S,10R,13S,14S,17S)-17-(1H-indazol-5-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol (13)

(50% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 12.91 (s, 1H), 7.98 (s, 1H), 7.58 (s, 1H), 7.43 (d, *J* = 6Hz, 1H), 7.21 (d, *J* = 6Hz, 1H), 5.31 (s, 1H), 4.67 (s, 1H), 3.27 (m, 1H), 2.22-1.20 (m, 20H), 0.92 (s, 3H), 0.44 (s, 3H). MS m/z: 391.28 $[M+H]^+$.



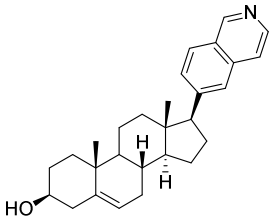
(3S,8S,10R,13S,14S,17S)-17-(1H-indazol-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol (14)

(53% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 12.91 (s, 1H), 7.97 (s, 1H), 7.46 (s, 1H), 7.31 (d, *J* = 6Hz, 1H), 7.18 (d, *J* = 6Hz, 1H), 5.32 (s, 1H), 4.63 (s, 1H), 3.27 (m, 1H), 2.22-1.20 (m, 20H), 0.91 (s, 3H), 0.46 (s, 3H). MS m/z: 391.34 $[M+H]^+$.



(3S,8S,10R,13S,14S,17S)-17-(3-amino-1H-indazol-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol (15)

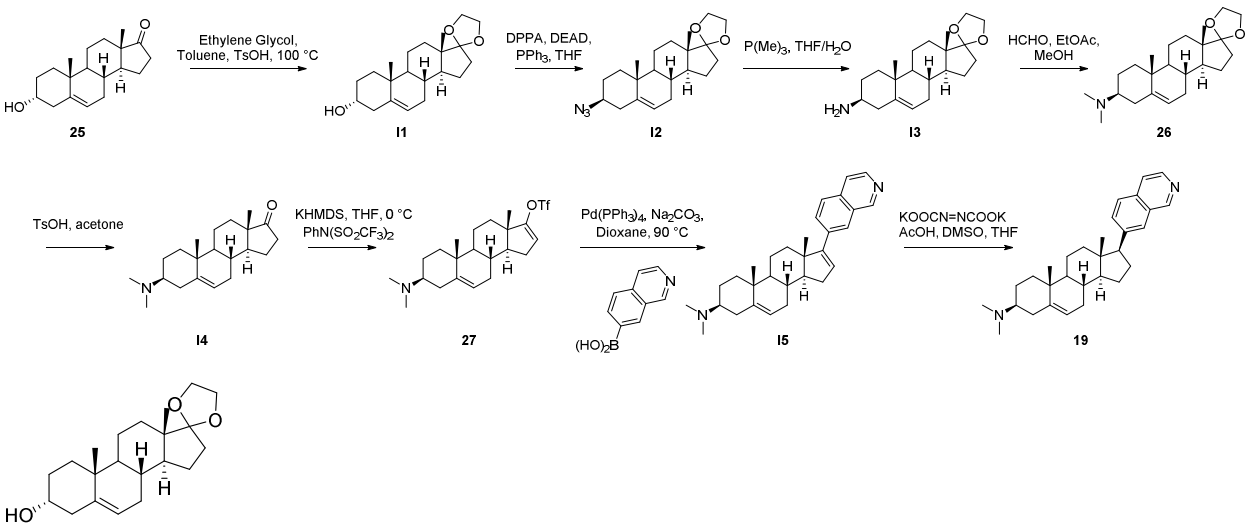
(48% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 12.96 (s, 1H), 7.94 (s, 1H), 7.48 (s, 1H), 7.40 (d, *J* = 6Hz, 1H), 7.19 (d, *J* = 6Hz, 1H), 5.32 (s, 1H), 4.66 (s, 1H), 3.27 (m, 1H), 2.22-1.20 (m, 20H), 0.93 (s, 3H), 0.43 (s, 3H). MS m/z: 405.83 $[M+H]^+$.



(3S,8S,10R,13S,14S,17S)-17-(isoquinolin-6-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol (16)

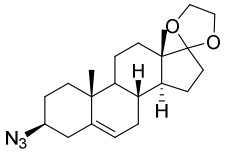
(68% yield). ^{1}H NMR (500 MHz, DMSO-d6): δ 9.36 (s, 1H), 8.14 (br, 2H), 7.91 (s, 1H), 7.86 (d, *J* = 6Hz, 1H), 7.57 (d, *J* = 6Hz, 1H), 5.33 (s, 1H), 3.29 (m, 1H), 3.17 (s, 1H),), 2.98 (t, *J* = 10Hz, 1H), 1.85-1.20 (m, 19H), 0.72 (s, 3H), 0.41 (s, 3H). MS m/z: 402.83 $[M+H]^+$.

Compounds **18** - **20** were prepared according to literature procedure using the route depicted below[1] starting from either 3α-Androsterone (compound **18**), 3β-Androsterone (compound **20**) or 3α-Hydroxy-5-androsten-17-one (compound **19**) With the exception of compound **I3**, which was prepared using the procedure shown below. Compounds **I1**, **26, I4** & **27** were used without further purification. Characterization data was identical to that reported in the literature[1].



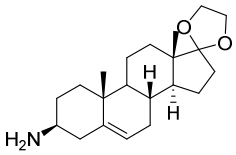
(3R,8R,10R,13S,14S)-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolan]-3-ol (I1)

Prepared according to literature procedure starting from cis-DHEA. Characterization was identical to that reported in the literature.[2]



(3S,8R,10R,13S,14S)-3-azido-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolane] (I2).

Prepared according to literature procedure starting from I1.[1] ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.36 (s, 1H), 3.94-3.83 (m, 4H), 2.25 (m, 2H), 2.06-1.97 (m, 2H), 1.95-1.81 (m, 4H), 1.72- 1.63 (m, 1H), 1.62-1.35 (m, 9H), 1.31-1.24 (m, 1H), 1.15-1.07 (m, 1H), 1.01 (s, 3H), 0.87 (s, 3H).

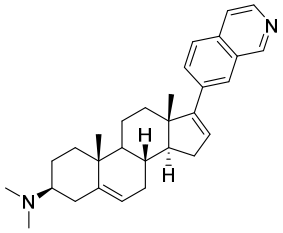


(3S,8R,10R,13S,14S)-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolan]-3-amine (I3)

(3S,8R,10R,13S,14S)-3-azido-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolane] (2 g, 5.59 mmol) was dissolved in anhydrous THF (50 mL). H_2O (503 µL, 28 mmol) was added followed by Me_3P (1.15 mL, 11.2 mmol) was added and stirred for 6 hours. The reaction was quenched with H_2O and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and condensed to give a yellow oil that was purified by flash chromatography using a gradient of 1-10% MeOH in DCM to

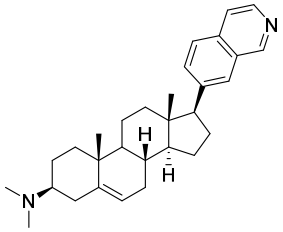
give the title compound as a white solid (1.58 g, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.39 (s, 1H), 3.97-3.86 (m, 4H), 3.47 (br, 2H), 2.81 (m, 1H), 2.28 (m, 2H), 2.05-1.98 (m, 2H), 1.92-1.78 (m, 3H), 1.74-1.67 (m, 1H), 1.64-1.38 (m, 9H), 1.32-1.24 (m, 1H), 1.15-1.07 (m, 1H), 1.03 (s, 3H), 0.88 (s, 3H). MS m/z 332.47 $[M+H]^+$.

Compounds I4, 26 and 27 were prepared according to literature procedure[1]. Characterization was identical to that reported in the literature[1].



(3S,8R,10R,13S,14S)-17-(isoquinolin-7-yl)-N,N,10,13-tetramethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-amine (I5)

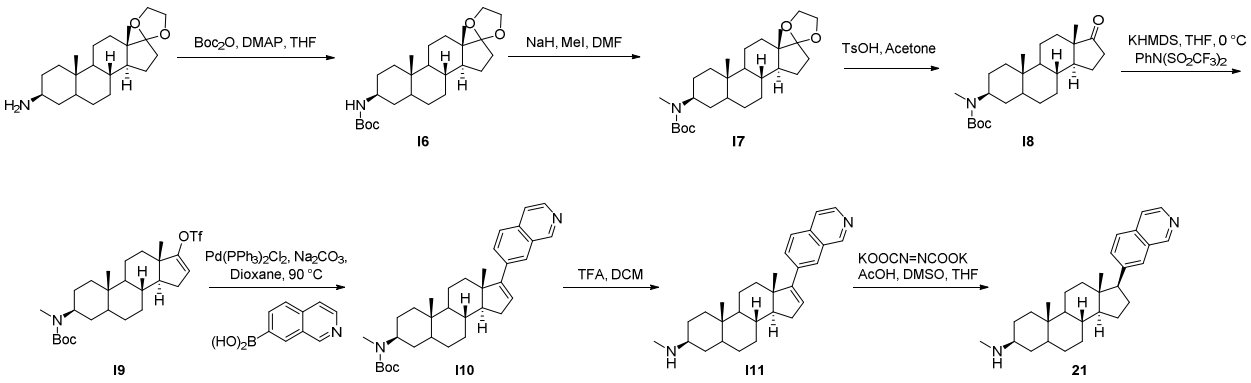
Prepared according to literature procedure.[1] ^{1}H NMR (500 MHz, DMSO-d6): δ 9.65 (s, 1H), 8.57 (d, *J* = 6Hz, 1H), 8.33 (s, 1H), 8.17 (d, *J* = 6Hz, 1H), 8.12 (s, 2H), 6.39 (s, 1H), 5.49 (s, 1H), 3.17 (s, 1H), 3.04 (m, 4H), 2.78 (s, 6H), 2.45-2.26 (m, 5H), 1.98-1.88 (m, 3H), 1.81-1.55 (m, 6H), 1.49-1.41 (m, 1H), 1.17 (s, 3H), 1.06 (s, 3H). MS m/z: 427.29 $[M+H]^+$.

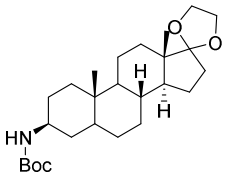


(3S,8S,10R,13S,14S,17S)-17-(isoquinolin-7-yl)-N,N,10,13-tetramethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-amine (19)

Prepared according to literature procedure.[1] ^{1}H NMR (500 MHz, DMSO-d6): δ 9.72 (s, 1H), 8.61 (d, *J* = 6Hz, 1H), 8.35 (d, *J* = 6Hz, 1H), 8.33 (s, 1H), 8.20 (d, *J* = 6Hz, 1H), 8.03 (d, *J* = 6Hz, 1H), 5.47 (s, 1H), 3.44 (m, 1H), 3.0 (t, *J* = 10Hz, 1H), 2.77 (s, 6H), 2.44-2.27 (m, 5H), 1.68-1.28 (m, 12H), 1.16-1.00 (m, 4H), 0.96 (s, 3H), 0.47 (s, 3H). MS m/z: 429.58 $[M+H]^+$.

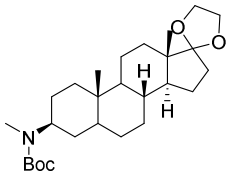
Compound **21** was prepared according to the following route:





tert-butyl ((3S,8R,10S,13S,14S)-10,13-dimethylhexadecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolan]-3-yl)carbamate (I6)

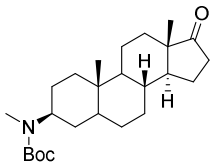
To a solution of (3S,8R,10S,13S,14S)-10,13-dimethylhexadecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolan]-3-amine (500 mg, 1.50 mmol) in THF (25 mL) was added Boc_2O (393 mg, 1.80 mmol) followed by DMAP (37 mg, 0.3 mmol). The mixture was stirred for 3 hours. The reaction was quenched with H_2O and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and condensed to give a yellow oil that was purified by flash chromatography using a gradient of 5-20% EtOAc in Hexanes to give the title compound as a white solid (602 mg, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 (br, 1H), 3.92-3.81 (m, 4H), 2.06-1.89 (m, 1H), 1.80-1.52 (m, 10H), 1.46 (s, 9H), 1.41-1.18 (m, 10H), 1.08-0.90 (m, 2H), 0.81 (s, 3H), 0.79 (s, 3H). MS m/z 434.58 $[M+H]^+$



tert-butyl ((3S,8R,10S,13S,14S)-10,13-dimethylhexadecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolan]-3-yl)(methyl)carbamate (I7)

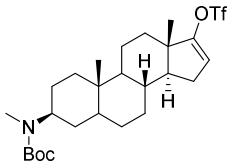
To a solution of tert-butyl ((3S,8R,10S,13S,14S)-10,13-dimethylhexadecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolan]-3-yl)carbamate (602 mg, 1.39 mmol) in DMF (10 mL) was added NaH 60% in mineral oil (83 mg, 2.08 mmol). The mixture was stirred for 30 minutes, then MeI (208 µL, 3.34 mmol) was added and stirred overnight. The reaction was quenched with H_2O and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and condensed to give a yellow oil that was purified by flash chromatography using a gradient of 5-30% EtOAc in Hexanes to give the title compound as a white solid (602 mg, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.95-3.82 (m, 4H), 2.75 (s, 3H), 2.02-1.93 (m, 1H), 1.84-

1.50 (m, 10H), 1.48 (s, 9H), 1.45-1.18 (m, 10H), 1.10-0.90 (m, 2H), 0.86 (s, 3H), 0.82 (s, 3H). MS m/z 448.83 $[M+H]^+$.



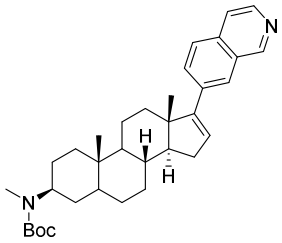
tert-butyl ((3S,8R,10S,13S,14S)-10,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)(methyl)carbamate (I8)

Prepared using the same procedure used for compound **I4** and used without further purification. MS m/z 404.31 $[M+H]^+$.



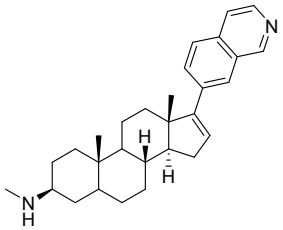
(3S,8R,10S,13S,14S)-3-((tert-butoxycarbonyl)(methyl)amino)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (I9)

Prepared using the same procedure used for compound **27** and used without further purification. MS m/z 536.78 $[M+H]^+$.



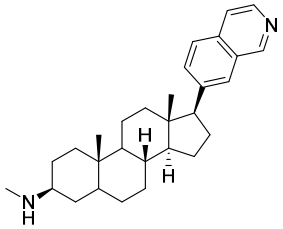
tert-butyl ((3S,8R,10S,13S,14S)-17-(isoquinolin-7-yl)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)(methyl)carbamate (I10)

Prepared using the same procedure used for compound **1**. ^{1}H NMR (500 MHz, DMSO): δ 9.70 (s, 1H), 8.50 (d, *J* = 6Hz, 1H), 8.25 (s, 1H), 8.19 (d, *J* = 6Hz, 1H), 8.14 (d, *J* = 6Hz, 1H), 8.04 (d, *J* = 8Hz, 1H), 6.32 s, 1H), 2.77 (s, 3H), 2.40-2.33 (m, 1H), 2.21-2.10 (m, 2H), 1.82-1.59 (m, 8H), 1.49 (s, 9H), 1.44-1.24 (m, 8H), 1.15 (s, 3H), 1.12-1.05 (m, 2H), 0.90 (s, 3H). MS m/z 515.63 $[M+H]^+$



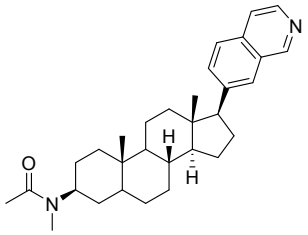
(3S,8R,10S,13S,14S)-17-(isoquinolin-7-yl)-N,10,13-trimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-amine (I11)

To a solution of tert-butyl ((3S,8R,10S,13S,14S)-17-(isoquinolin-7-yl)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)(methyl)carbamate (50 mg, 0.1 mmol) in DCM (10 mL) was added TFA (1 mL). The mixture was stirred for 30 minutes and the solvent removed in vacuo to give the title compound as a beige solid that was used without further purification. (40 mg, 98% yield). MS m/z 415.57 $[M+H]^+$



(3S,8R,10S,13S,14S,17S)-17-(isoquinolin-7-yl)-N,10,13-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-amine (21)

Prepared using the same procedure used for compound **9**. MS m/z: 417.37 $[M+H]^+$. 91% yield

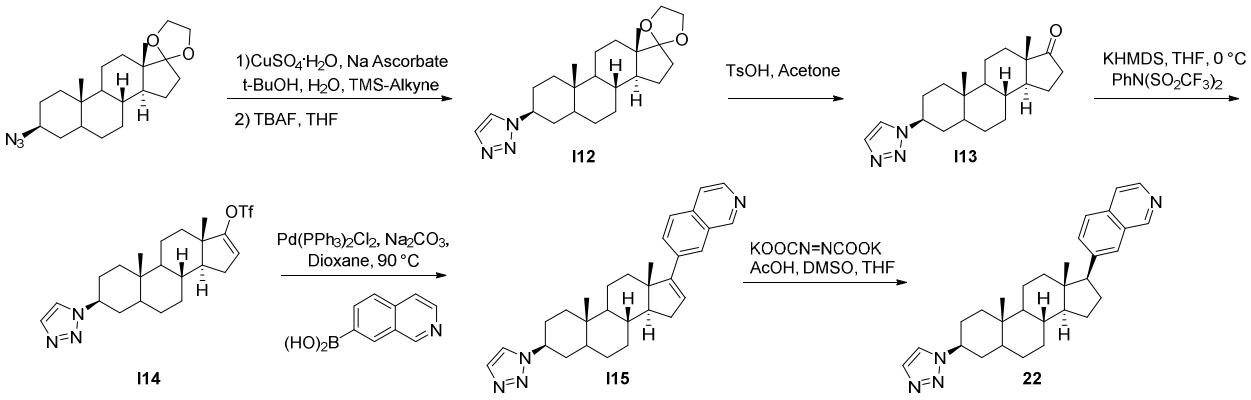


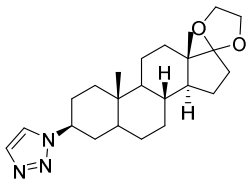
N-((3S,8R,10S,13S,14S,17S)-17-(isoquinolin-7-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)-N-methylacetamide (24)

To a solution of (3S,8R,10S,13S,14S,17S)-17-(isoquinolin-7-yl)-N,10,13-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-amine (20 mg, 0.048 mmol) in THF (3 mL) and sat. aq. $NaHCO_3$ soln (2mL) was added acetyl chloride (4µL, 0.058 mmol). The mixture was stirred for 30 minutes and then the reaction was quenched with H_2O and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and condensed to give a yellow oil that was purified by reverse phase HPLC using a gradient of 1-80% ACN in H_2O to give the title compound as a brown solid (12 mg, 57% yield). δ 9.70 (s, 1H), 8.62 (d, *J* = 6Hz, 1H), 8.33 (d, *J* = 6Hz, 1H), 8.31 (s, 1H), 8.22 (d, *J* = 6Hz,

1H), 8.01 (d, *J* = 6Hz, 1H), 3.54 (m, 1H), 3.21 (s, 3H), 3.1 (t, *J* = 10Hz, 1H), 2.70 (s, 3H), 2.44-2.27 (m, 6H), 1.68-1.28 (m, 12H), 1.16-1.00 (m, 4H), 0.94 (s, 3H), 0.44 (s, 3H). MS m/z: 459.72 $[M+H]^+$.

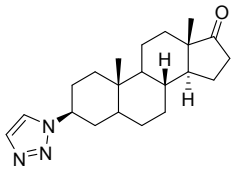
Compound **22** was prepared according to the following route:





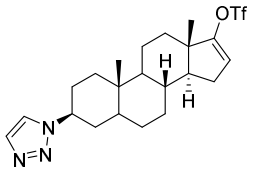
1-((3S,8R,10S,13S,14S)-10,13-dimethylhexadecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolan]-3-yl)-1H-1,2,3-triazole (I12)

To a solution of (3S,8R,10S,13S,14S)-3-azido-10,13-dimethylhexadecahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolane] (500 mg, 1.39 mmol) in t-BuOH (10 mL) and H_2O (3 mL) was added $CuSO_4 \cdot 5H_2O$ (18 mg, 0.07 mmol) and sodium ascorbate (6 mg, 0.03 mmol) followed by TMS-alkyne (231 µL, 1.67 mmol). The reaction mixture was heated to 70 °C for 1 hour. The reaction was quenched with H_2O and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and condensed to give a yellow oil that was dissolved in THF (20 mL). TBAF 1M in THF (6.95 mL, 6.95 mmol) was added and stirred for 30 minutes. The reaction was quenched with H_2O and extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and condensed to give a brown oil that was purified by flash chromatography using a gradient of 10-60% EtOAc in hexanes to give the title compound as a white solid (348 mg, 65 % yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (q, *J* = 10Hz, 2H), 4.31 (m, 1H), 3.95-3.82 (m, 4H), 2.83 (m, 3H), 2.27 (m, 1H), 2.03-1.95 (m, 2H), 1.90-1.75 (m, 3H), 1.71-1.63 (m, 1H), 1.67-1.39 (m, 10H), 1.35-1.26 (m, 1H), 1.13-1.07 (m, 1H), 0.97 (s, 3H), 0.78 (s, 3H). MS m/z: 386.76 $[M+H]^+$.



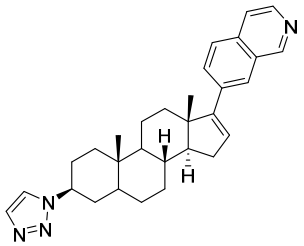
(3S,8R,10S,13S,14S)-10,13-dimethyl-3-(1H-1,2,3-triazol-1-yl)hexadecahydro-17H-cyclopenta[a]phenanthren-17-one (I13)

Prepared using the same procedure used for compounds **I4** and used without further purification. MS m/z 341.86 $[M+H]^+$.



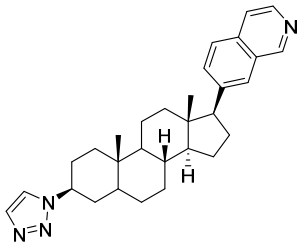
(3S,8R,10S,13S,14S)-10,13-dimethyl-3-(1H-1,2,3-triazol-1-yl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (I14)

Prepared using the same procedure used for compounds **27** and used without further purification. MS m/z 474.45 $[M+H]^+$.



7-((3S,8R,10S,13S,14S)-10,13-dimethyl-3-(1H-1,2,3-triazol-1-yl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)isoquinoline (I15)

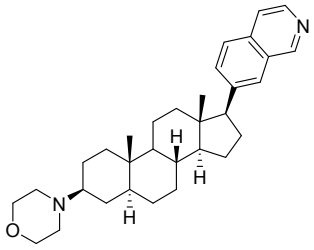
Prepared using the same procedure used for compound **1**. ^{1}H NMR (500 MHz, DMSO): δ 9.74 (s, 1H), 8.53 (d, *J* = 6Hz, 1H), 8.17 (s, 2H), 8.03 (q, *J* = 10Hz, 2H), 7.90 (s, 1H), 7.69 (s, 1H), 6.38 (s, 1H), 4.52 (m, 1H), 2.33-2.11 (m, 3H), 2.12-1.85 (m, 5H), 1.72-1.40 (m, 8H), 1.30-1.20 (m, 2H), 1.15-1.08 (m, 1H), 0.97 (s, 3H), 0.92-0.87 (m, 1H), 0.51 (s, 3H). MS m/z 453.51 $[M+H]^+$



7-((3S,8R,10S,13S,14S,17S)-10,13-dimethyl-3-(1H-1,2,3-triazol-1-yl)hexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)isoquinoline (22)

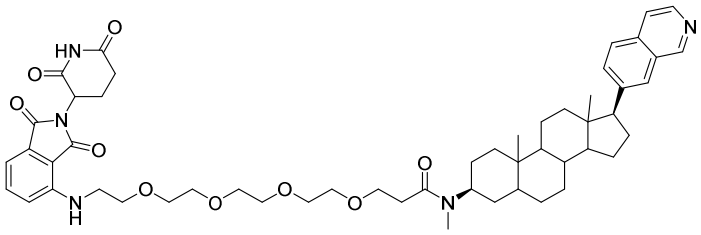
Prepared using the same procedure used for compound **9**. ^{1}H NMR (500 MHz, DMSO): δ 9.76 (s, 1H), 8.57 (d, *J* = 6Hz, 1H), 8.21 (s, 2H), 8.06 (q, *J* = 10Hz, 2H), 7.92 (s, 1H), 7.72 (s, 1H), 4.58 (m, 1H), 3.02 (t, *J* =

10Hz, 1H), 2.33-2.11 (m, 3H), 2.06-1.82 (m, 5H), 1.69-1.37 (m, 10H), 1.33-1.22 (m, 2H), 1.13-1.04 (m, 1H), 0.95 (s, 3H), 0.92-0.87 (m, 1H), 0.53 (s, 3H). MS m/z 455.68 $[M+H]^+$.



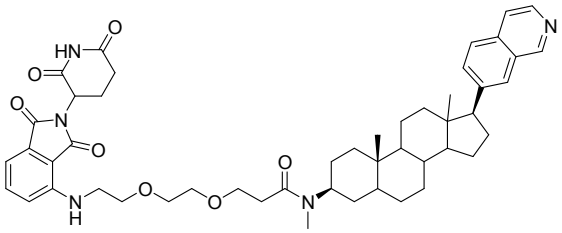
4-((3S,5S,8R,10S,13S,14S,17S)-17-(isoquinolin-7-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)morpholine (23)

Prepared according to literature procedure[1].



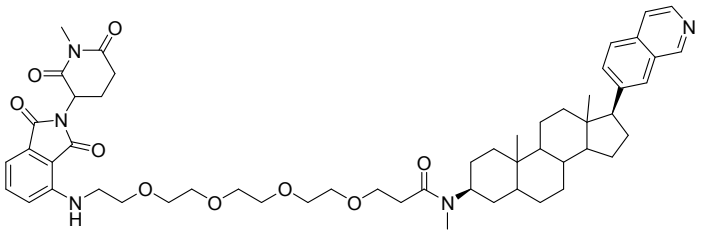
1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-N-((3S,17S)-17-(isoquinolin-7-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)-N-methyl-3,6,9,12-tetraoxapentadecan-15-amide (29)

To a solution of (3S,8R,10S,13S,14S,17S)-17-(isoquinolin-7-yl)-N,10,13-trimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-amine (20 mg, 0.048 mmol) in DMF was added HATU (37 mg, 0.096 mmol) and 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-oic acid (28 mg, 0.053 mmol) followed by DIEA (42 µL, 0.24 mmol). The reaction was stirred for 30 minutes and then inJected directly onto the HPLC and purified using a gradient of 1-90% ACN in H_2O to give the title compound as a yellow solid (8 mg, 18% yield). ^{1}H NMR (500 MHz, DMSO): δ 11.09 (s, 1H), 9.71 (s, 1H), 8.60 (s, 1H), 8.36-8.29 (m, 3H), 8.19-8.16 (m, 1H), 7.99 (t, *J* = 5Hz, 1H), 7.60-7.54 (m, 1H), 7.15 (dd, *J* = 5Hz, 8Hz, 1H), 7.04 (d, *J* = 6Hz, 1H), 5.12- 5.03 (m, 1H), 4.27 (m, 1H), 3.64-3.59 (m, 4H), 3.54-3.45 (m, 14H), 2.99-2.84 (m, 2H), 2.79 (s, 3H), 2.06-1.95 (m, 3H), 1.83-0.91 (m, 24H), 0.77 (s, 3H), 0.43 (s, 3H). MS m/z: 921.49 $[M+H]^+$.



3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)-N-((3S,10S,17S)-17-(isoquinolin-7-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)-N-methylpropanamide (30)

^{1}H NMR (500 MHz, DMSO): δ 11.10 (s, 1H), 9.67 (s, 1H), 8.59 (s, 1H), 8.31-8.24 (m, 3H), 8.15 (d, *J* = 7 Hz, 1H), 7.96 (t, *J* = 5Hz, 1H), 7.76 (dd, *J* = 5Hz, 8Hz, 1H), 7.66-7.52 (m, 1H), 7.24-7.12 (m, 1H), 5.12 (m, 1H), 4.25 (m, 1H), 3.68 (m, 8H), 3.00-2.84 (m, 4H), 2.77 (s, 3H), 2.26 (m, 2H), 1.71-0.91 (m, 25H), 0.79 (s, 3H), 0.46 (s, 3H). MS m/z: 832.79 $[M+H]^+$.



N-((3S,17S)-17-(isoquinolin-7-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-3-yl)-N-methyl-1-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-amide (31)

^{1}H NMR (500 MHz, DMSO): δ 9.71 (s, 1H), 8.60 (s, 1H), 8.35-8.29 (m, 3H), 8.19-8.16 (m, 1H), 7.99 (t, *J* = 5Hz, 1H), 7.61-7.57 (m, 1H), 7.16 (dd, *J* = 5Hz, 8Hz, 1H), 7.04 (d, *J* = 6Hz, 1H), 5.12- 5.03 (m, 1H), 4.27 (m, 1H), 3.64-3.45 (m, 18H), 3.01 (s, 3H), 2.99-2.91 (m, 2H), 2.80 (s, 3H), 2.06-1.95 (m, 3H), 1.83-0.91 (m, 24H), 1.16 (s, 3H), 1.06 (s, 3H), 0.76 (s, 3H). MS m/z: 935.71 $[M+H]^+$.

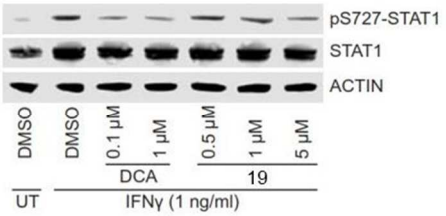


Figure S1. Immunoblots for pS727-STAT1 and total STAT1 from lysates from HepG2 cells treated with interferon gamma (IFNγ) and Compound 19 and DCA as indicated for 18h.

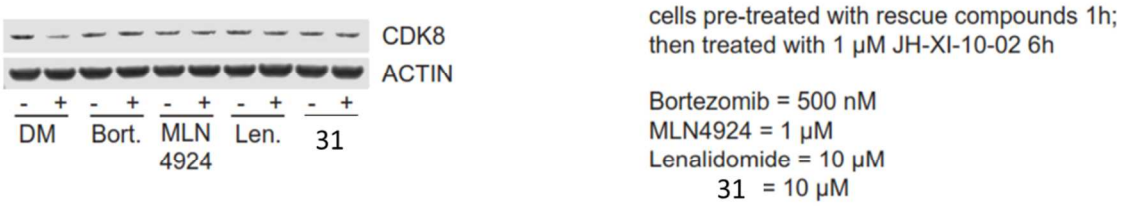


Figure S2. Rescue experiments with Bortezamib, MLN4924, Lenalidomide and **31**

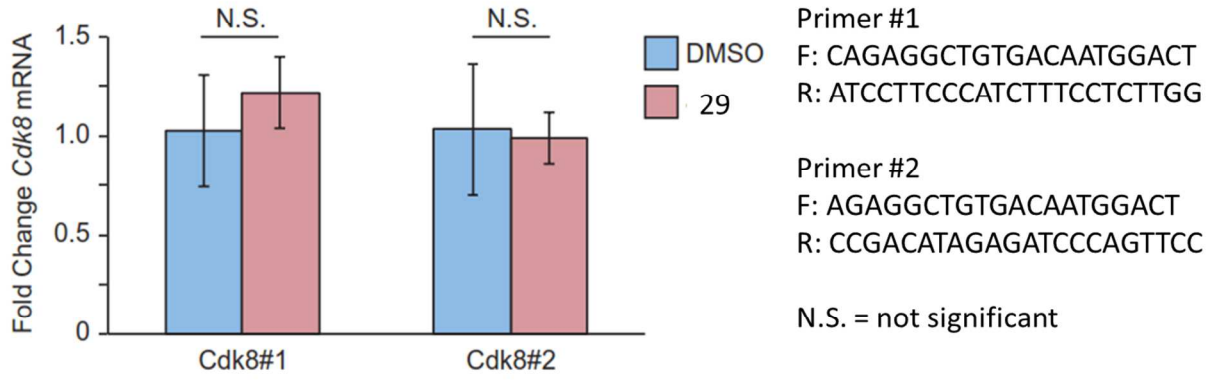


Figure S3. Q-PCR using two different primer sets for Cdk8 (relative to Actin) from Jurkat cells treated with **29** (1 μM) or vehicle control for 24h.

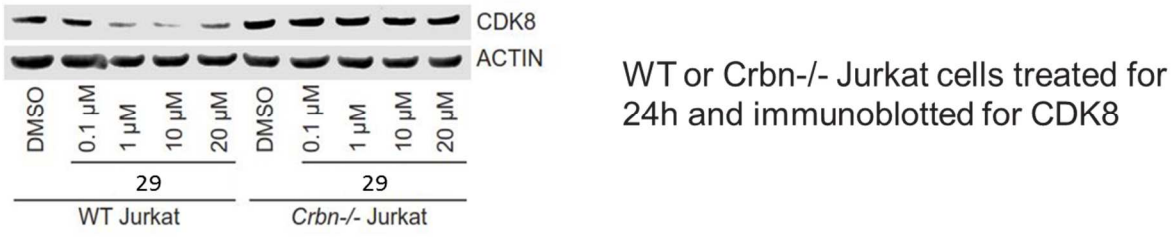
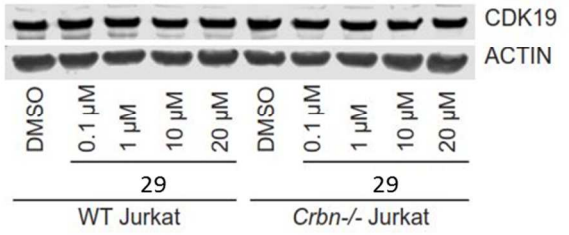


Figure S4. Treatment of Jurkat cells with multiple concentrations of **29** for 24h



WT or Crbn-/- Jurkat cells treated for 24h and immunoblotted for CDK19

Figure S5. Degradation of CDK19 in Jurkat cells treated with **29** for 24h

KinomeScan analysis[3] (% Control at 10µM)

Compound Concentration (uM)	10
CDK11 (CDK19)	0.4
CDK8	2.9
PIKFYVE	8.5
NEK1	8.7
RIOK2	11
PRKG1	14
PKAC-beta	19
HASPIN	24
NEK5	24
MRCKA	25
PAK3	26
TTK	27
CDKL2	30
SRPK1	33
MEK6	36
ASK1	37
PKN2	37
ALK	38
LRRK2	38
ACVR2B	39
PKAC-alpha	40
PIP5K1A	43
LKB1	44
DYRK1B	45
LTK	45

DMPK2	46
RIPK1	47
TESK1	47
ICK	49
ROS1	49
MAK	50
NEK3	50
TRKA	50
CHEK2	51
EGFR(L747-S752del, P753S)	51
ERK3	52
LIMK2	52
PRKCE	52
ZAK	52
NEK2	53
PRKCQ	53
PIM2	54
RIOK1	54
TXK	54
HUNK	55
RSK4(Kin.Dom.1-N-terminal)	55
SIK	55
ADCK4	56
NLK	56
SIK2	56
SRPK3	56
AKT3	58
FLT3	58
GSK3A	58
TNK1	58
MET(Y1235D)	59
ABL1-nonphosphorylated	60
PIK3CA(I800L)	60
RSK2(Kin.Dom.1-N-terminal)	60
ALK(C1156Y)	61
DRAK2	61
MYLK	61
TIE1	61
CLK1	62
EGFR	62
EGFR(E746-A750del)	62
FLT3(D835V)	62
MAPKAPK2	62

MERTK	62
FLT3(N841I)	63
KIT(L576P)	63
WEE1	63
MAP3K4	64
STK33	64
DMPK	65
HIPK4	65
MAP4K3	65
MELK	65
PLK3	65
QSK	65
TRKC	65
DCAMKL1	66
NEK7	66
PKNB(M.tuberculosis)	66
TBK1	66
WNK2	66
ABL1(H396P)-nonphosphorylated	67
CSNK1G3	67
EGFR(L858R)	67
ARK5	68
EPHB4	68
FLT3(D835H)	68
INSRR	68
JNK1	68
MET(M1250T)	68
MLK1	68
MUSK	68
AXL	69
MARK3	69
MEK5	69
YANK2	69
CDK3	70
CDKL1	70
CLK3	70
CSNK1G2	70
KIT(V559D,V654A)	70
TRKB	70
TSSK3	70
CLK4	71
EGFR(L747-E749del, A750P)	71
EGFR(T790M)	71

KIT	71
MAP3K2	71
PAK2	71
PLK4	71
SRPK2	71
TNIK	71
ULK1	71
BLK	72
FER	72
FGFR3(G697C)	72
FLT4	72
NEK9	72
RIOK3	72
RPS6KA4(Kin.Dom.1-N-terminal)	72
RSK3(Kin.Dom.1-N-terminal)	72
S6K1	72
ABL1-phosphorylated	73
LCK	73
PDGFRB	73
PIK3C2G	73
RIPK4	73
SLK	73
STK35	73
WNK4	73
BRSK1	74
CDK2	74
EPHA6	74
PKN1	74
RIPK5	74
STK36	74
TRPM6	74
CSNK1D	75
JNK2	75
MYO3A	75
p38-delta	75
RSK1(Kin.Dom.2-C-terminal)	75
AMPK-alpha2	76
BMPR1A	76
CDK4	76
EPHB3	76
PIP5K2C	76
RET	76
ROCK1	76

BUB1	77
HPK1	77
MLK3	77
NEK6	77
PDPK1	77
ABL1(T315I)-nonphosphorylated	78
ACVR1B	78
DYRK2	78
EPHA3	78
PIK3CA(E542K)	78
PRKCH	78
ULK3	78
AURKB	79
DCAMKL3	79
FYN	79
HIPK2	79
IKK-beta	79
IRAK3	79
LZK	79
PFCDPK1(P.falciparum)	79
PIK3CA(H1047Y)	79
TEC	79
AKT1	80
CDK5	80
FAK	80
MEK3	80
MRCKB	80
PFTAIRE2	80
YSK1	80
ERK8	81
GRK4	81
HIPK1	81
INSR	81
IRAK4	81
MEK2	81
BMX	82
CAMK2B	82
DAPK1	82
DDR1	82
DRAK1	82
EPHA1	82
EPHA5	82
NDR1	82

PCTK2	82
PRKG2	82
PRKX	82
ABL1(F317L)-nonphosphorylated	83
ADCK3	83
CSNK2A2	83
PFTK1	83
TSSK1B	83
AURKC	84
BRK	84
EPHA8	84
ERBB2	84
FLT3(ITD)	84
GCN2(Kin.Dom.2,S808G)	84
JNK3	84
MYO3B	84
PAK1	84
PIM1	84
PYK2	84
SRC	84
ABL1(F317I)-nonphosphorylated	85
BIKE	85
BRSK2	85
CASK	85
ERK2	85
FGFR4	85
HIPK3	85
KIT(V559D,T670I)	85
LYN	85
MST1	85
PIK4CB	85
RAF1	85
TGFBR1	85
ABL1(F317I)-phosphorylated	86
ABL2	86
CDK4-cyclinD1	86
EPHB2	86
JAK1(JH1domain-catalytic)	86
MAP4K4	86
MEK4	86
MLCK	86
PCTK3	86

PHKG1	86
PRKCD	86
SBK1	86
TIE2	86
ACVR1	87
JAK3(JH1domain-catalytic)	87
KIT(V559D)	87
LOK	87
PAK7	87
SgK110	87
AMPK-alpha1	88
CSF1R	88
CSNK1A1L	88
EGFR(L861Q)	88
EPHB6	88
FGFR3	88
FLT3(ITD,D835V)	88
MET	88
MST3	88
MYLK4	88
p38-beta	88
PIK3CA(E545A)	88
PRKD2	88
RET(V804L)	88
RIPK2	88
ROCK2	88
SYK	88
TNNI3K	88
WEE2	88
ALK(L1196M)	89
CTK	89
DLK	89
EGFR(G719S)	89
EGFR(S752-I759del)	89
EPHA4	89
FRK	89
PIK3CD	89
RET(M918T)	89
RPS6KA5(Kin.Dom.1-N-terminal)	89
STK16	89
ABL1(E255K)-phosphorylated	90
ABL1(T315I)-phosphorylated	90
ERBB4	90

IKK-epsilon	90
LRRK2(G2019S)	90
MAP4K5	90
MYLK2	90
OSR1	90
PIK3CG	90
RSK1(Kin.Dom.1-N-terminal)	90
RSK4(Kin.Dom.2-C-terminal)	90
AKT2	91
CAMK1	91
CDK7	91
CDK9	91
CSNK1A1	91
KIT(D816V)	91
MINK	91
PFPK5(P.falciparum)	91
VRK2	91
CAMK1G	92
EGFR(L747-T751del,Sins)	92
ERK4	92
FGFR2	92
MAP3K3	92
MLK2	92
PLK1	92
RSK2(Kin.Dom.2-C-terminal)	92
TAK1	92
ZAP70	92
ABL1(Q252H)-nonphosphorylated	93
ITK	93
PIK3CA(E545K)	93
PIK3CA(Q546K)	93
PRKCI	93
RET(V804M)	93
RSK3(Kin.Dom.2-C-terminal)	93
TAOK1	93
WNK1	93
WNK3	93
CDKL5	94
DYRK1A	94
FLT1	94
GAK	94
LIMK1	94
MKK7	94

PRKD3	94
YSK4	94
AURKA	95
CDC2L1	95
CDC2L2	95
CSNK2A1	95
HCK	95
IRAK1	95
LATS1	95
MARK4	95
PAK4	95
PIK3CA(M1043I)	95
TLK2	95
AAK1	96
ABL1(Q252H)-phosphorylated	96
BRAF	96
CAMK1D	96
CAMK2A	96
ERBB3	96
ERK1	96
ERK5	96
FLT3(K663Q)	96
JAK1(JH2domain-pseudokinase)	96
MARK1	96
MARK2	96
PAK6	96
PIK3CA(C420R)	96
TLK1	96
TYK2(JH2domain-pseudokinase)	96
CDKL3	97
EGFR(G719C)	97
GRK1	97
IGF1R	97
MAP3K15	97
MAST1	97
MEK1	97
NEK11	97
NEK4	97
p38-gamma	97
PIK3CB	97
PIM3	97
PRP4	97
YANK3	97

ACVRL1	98
DCAMKL2	98
FGFR1	98
MKNK2	98
NIM1	98
PIK3CA	98
TAOK2	98
TGFBR2	98
ABL1(H396P)-phosphorylated	99
CHEK1	99
IKK-alpha	99
MST2	99
PIP5K2B	99
ABL1(F317L)-phosphorylated	100
ABL1(M351T)-phosphorylated	100
ABL1(Y253F)-phosphorylated	100
ACVR2A	100
ANKK1	100
ASK2	100
BMPR1B	100
BMPR2	100
BRAF(V600E)	100
BTK	100
CAMK1B	100
CAMK2D	100
CAMK2G	100
CAMK4	100
CAMKK1	100
CAMKK2	100
CDC2L5	100
CDK4-cyclinD3	100
CIT	100
CLK2	100
CSF1R-autoinhibited	100
CSK	100
CSNK1E	100
CSNK1G1	100
DAPK2	100
DAPK3	100
DDR2	100
EGFR(L858R,T790M)	100
EIF2AK1	100
EPHA2	100

EPHA7	100
EPHB1	100
ERN1	100
FES	100
FGR	100
FLT3(D835Y)	100
FLT3(ITD,F691L)	100
FLT3(R834Q)	100
FLT3-autoinhibited	100
GRK2	100
GRK3	100
GRK7	100
GSK3B	100
JAK2(JH1domain-catalytic)	100
KIT(A829P)	100
KIT(D816H)	100
KIT-autoinhibited	100
LATS2	100
MAP3K1	100
MAP4K2	100
MAPKAPK5	100
MKNK1	100
MST1R	100
MST4	100
MTOR	100
NDR2	100
NEK10	100
NIK	100
p38-alpha	100
PCTK1	100
PDGFRA	100
PHKG2	100
PIK3C2B	100
PIK3CA(H1047L)	100
PIP5K1C	100
PKMYT1	100
PLK2	100
PRKD1	100
PRKR	100
RPS6KA4(Kin.Dom.2-C-terminal)	100
RPS6KA5(Kin.Dom.2-C-terminal)	100
SGK	100
SGK2	100

SGK3	100
SNARK	100
SNRK	100
SRMS	100
STK39	100
TAOK3	100
TNK2	100
TYK2(JH1domain-catalytic)	100
TYRO3	100
ULK2	100
VEGFR2	100
VPS34	100
YANK1	100
YES	100

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