

Supporting Information

Tetrahydroquinoline-Derived Macrocyclic Tool Box: The Discovery of Anti-angiogenesis Agents in Zebrafish Assay

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A) Abbreviations

aq	Aqueous
AcOH	Acetic acid
AllocCl	Allyl chloroformate
CDCl ₃	Deuterated chloroform
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DCM	Dichloromethane
DIEA	N, N-Diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
EtOAc	Ethyl acetate
eq	Molar equivalent(s)
ES	ElectroSpray
HCl	Hydrochloric acid
h	Hour
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
KHMDS	Potassium hexamethyldisilazide
KOH	Potassium hydroxide
K ₂ CO ₃	Potassium carbonate
LBH	Lithium borohydride
LRMS	Low Resolution Mass Spectrometry
LiOH.H ₂ O	Lithium hydroxide monohydrate
NH ₄ Cl	Ammonium chloride
Na ₂ SO ₄	Sodium sulphate
NaH	Sodium Hydride
NaBH ₄	Sodium borohydride
NMR	Nuclear magnetic resonance

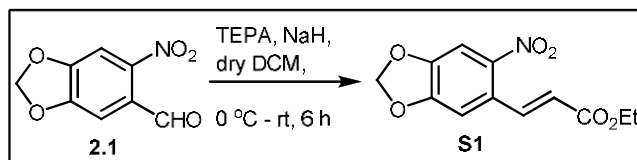
NaN ₃	Sodium azide
PBB	p-Bromophenyl
Ph	Phenyl
Py	Pyridine
p-TSA.H ₂ O	p-toulene sulphonic monohydrate
rt	Room temperature
R _f	Retardation factor
SO ₃ .py	Sulfur trioxide pyridine complex
TEPA	Triethyl phosphonoacetate
TBAI	Tetrabutylammonium iodide
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
Zn	Zinc

B) General Methods (Chemical synthesis):

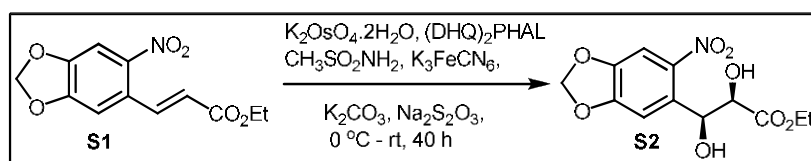
All reactions were carried out in flame-dried glassware under Nitrogen atmosphere. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel 60F₂₅₄ (Merck, 1.05554) and the spots were visualized with UV light at 254 nm or alternatively by staining with aqueous basic potassium permanganate or ceric ammonium molybdate. Flash column chromatography was performed using silica gel (Merck, 60A, 230-400 Mesh). Commercially available reagents were used as supplied and some of them were distilled before use. ¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded on Varian 400 MHz. NMR spectrometer at the frequency indicated. Where indicated, NMR peak assignments were made using COSY and NOESY experiments. All chemical shifts are quoted on the δ -scale and were referenced to residual solvent as an internal standard. Combinations of the following abbreviations are used to describe NMR spectra: s = singlet; bs = broad singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Mass spectra and LCMS were recorded using electron impact, chemical ionisation or electrospray ionisation techniques, mass spectrometer on Agilent 6430 Triple quadrupole. High-performance liquid chromatography was carried out on Agilent 1200 series. All reactions were performed in oven dried glassware. DMF, DCM and THF were dried immediately prior to use according to standard procedures. Acetone was distilled under inert atmosphere from K₂CO₃, Dimethylformamide, Dichloromethane was distilled under N₂ from CaH₂, and Tetrahydrofuran were distilled under N₂ over Na. All solvents were removed by evaporation under reduced pressure

C) Experimental Procedures

I. Synthesis of Chiral Scaffold (2.2)

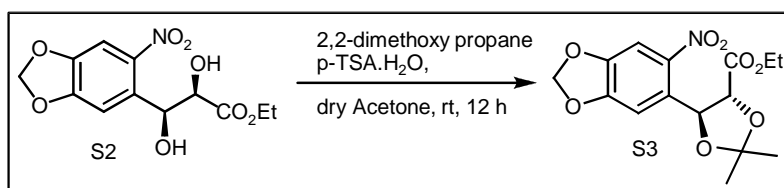


At 0 °C sodium hydride (1.84 g, 76.86 mmol) was added to dry THF (100 mL) followed by addition of triethylphosphonoacetate (7.62 mL, 38.4 mmol) carefully in nitrogen atmosphere and allowed to stir for 20 min. 6-nitropiperonal (**2.1**) (5g, 25.62 mmol) was added to the stirring solution. The reaction mixture was stirred until the starting material disappeared (TLC). The reaction was quenched with saturated NH_4Cl solution and the compound extracted twice with ethylacetate (2×100 mL) which was washed with water and brine. The organic phase was dried over anhydrous Na_2SO_4 . After solvent evaporation, the crude product was purified by flash chromatography on silica gel (3:1, hexane/ethyl acetate). The product **S1** was obtained as a white solid (2.37 g, 95%). Molecular Name: (E)-ethyl 3-(6-nitrobenzo[d][1,3]dioxol-5-yl)acrylate; Molecular Formula: $\text{C}_{12}\text{H}_{11}\text{NO}_6$; R_f (solvent system): 0.5 (7:3, hexane/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ ppm: 8.09 (d, $J = 15.74$ Hz, 1H), 7.53 (s, 1H), 6.98 (s, 1H), 6.24 (d, $J = 15.73$ Hz, 1H), 6.15 (s, 2H), 4.27 (q, $J = 7.13$ Hz, 3H), 1.33 (t, $J = 7.13$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3): 165.8, 152.0, 148.9, 143.0, 140.2, 127.2, 122.2, 107.3, 105.6, 103.4, 60.8, 14.2; LRMS: (ES+) $m/z = 265.9$ (M+1).

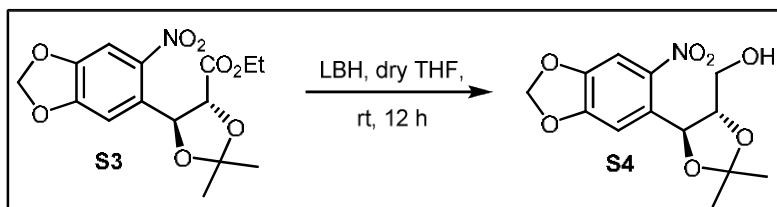


To a solution of the unsaturated carboxyl ester derivative **S1** (14.0 g, 52.8 mmol) in tert-butylalcohol (300 mL) was added water (300 mL). The mixture was cooled to 0 °C followed by the addition of methane sulfonamide (5.01 g, 52.7 mmol) and AD-mix- α (74 g). The reaction mixture was brought to room temperature and stirred for an additional 40 h. Sodium thiosulfate (14.5 g, 91.7 mmol) was added, and the mixture was stirred again for 30 min and then extracted with ethylacetate. The organic phase was washed with 2M KOH (80 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated. Purification by column

chromatography (40:1 to 20:1, dichloromethane/methanol) afforded the product **S2** (13.85 g, 88%) as a white solid. Molecular Name: (2R,3S)-ethyl 2,3-dihydroxy-3-(6-nitrobenzo[d][1,3]dioxol-5-yl)propanoate; Molecular Formula: C₁₂H₁₃NO₈; R_f (solvent system): 0.24(1:1,hexane/ethyl acetate); ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.55 (s, 1H), 7.28 (s, 1H), 6.14 (s, 1H), 6.11 (s, 1H), 5.74 (dd, *J* = 6.44, 1.73 Hz, 1H), 4.48 (dd, *J* = 5.90, 1.98 Hz, 1H), 4.35-4.30 (m, 2H), 3.29 (d, *J* = 5.99 Hz, 1H), 2.97 (d, *J* = 6.51 Hz, 1H), 1.34 (d, *J* = 7.14 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 172.5, 152.0, 147.0, 141.1, 135.1, 108.8, 104.6, 102.7, 73.6, 69.8, 61.6, 14.0; LRMS: (ES+) *m/z* = 300.1 (M+1).

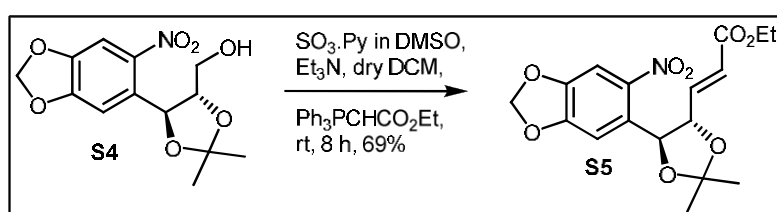


To a solution of the carboxylester **S2** (2.6 g, 8.69 mmol) in DCM (52 mL) at room temperature was added 2,2-dimethoxypropane (52 mL, 44.04 g, 422.89 mmol) and p-toluene sulfonic acid monohydrate (260 mg, 1.37 mmol). The reaction mixture was stirred for 12 h. Following dilution with CH₂Cl₂ and saturated NH₄Cl, the organic layer was collected. It was then washed with water and dried over anhydrous Na₂SO₄. Purification by flash chromatography over silica gel (5:1, hexane/ethyl acetate) afforded the product **S3** as a colorless oil in 95% yield. Molecular Name: (4R,5S)-ethyl 2,2-dimethyl-5-(6-nitrobenzo[d][1,3]dioxol-5-yl)-1,3-dioxolane-4-carboxylate; Molecular Formula: C₁₅H₁₇NO₈; R_f (solvent system): 0.26 (5:1 hexane/ethylacetate); ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.52 (s, 1H), 7.29 (s, 1H), 6.15 (d, *J* = 1.87 Hz, 2H), 5.90 (d, *J* = 7.25 Hz, 1H), 4.30-4.15 (m, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 1.26 (t, *J* = 7.14 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 169.6, 152.5, 147.7, 142.2, 130.9, 112.0, 106.8, 105.4, 103.2, 81.7, 76.2, 61.7, 27.0, 26.0, 13.9; LRMS:MS (ES+) *m/z* = 340.1 (M +1).

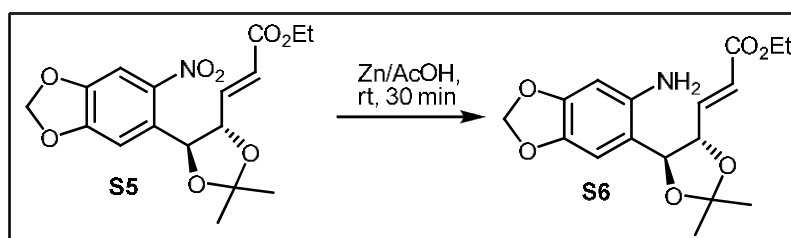


To a solution of the carboxyl ester **S3** (8.6 g, 26.36 mmol) in THF(250 mL) was added lithium borohydride (2.0 M solution in THF, 30 mL, 60 mmol) slowly at room temperature. The reaction mixture was stirred at room temperature for 12 h and cooled to 0 °C and then

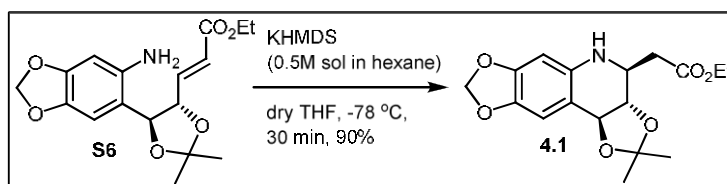
quenched with saturated NH_4Cl . After solvent evaporation, the residue was dissolved in dichloromethane, washed with water and brine and then dried over Na_2SO_4 . Purification by flash chromatography over silica gel (2:1, hexane/ethyl acetate) afforded the product **S4** (7.3 g, 85%) as a colorless oil; Molecular Name: ((4S,5S)-2,2-dimethyl-5-(6-nitrobenzo[d][1,3]dioxol-5-yl)-1,3-dioxolan-4-yl)methanol; Molecular Formula: $\text{C}_{13}\text{H}_{15}\text{NO}_7$; R_f (solvent system): 0.26 (2:1, hexane/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ ppm: 7.42 (s, 1H), 7.23 (s, 1H), 6.13 (d, $J = 1.21$ Hz, 2H), 5.48 (d, $J = 7.93$ Hz, 1H), 3.95-3.84 (m, 3H), 1.60 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 152.3, 147.6, 143.3, 130.5, 109.6, 107.6, 105.1, 103.1, 84.4, 74.3, 61.9, 27.1, 27.1; LRMS:MS (ES+) $m/z = 298.1$ (M + 1).



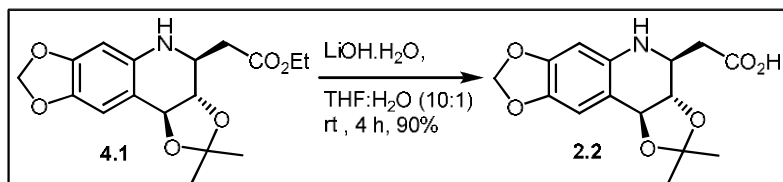
To a solution of **S4** (100 mg, 0.336 mmol) in 5.5 mL DCM:DMSO (10:1) was added triethylamine (0.28 mL, 2 mmol) at room temperature followed by the addition of sulfur trioxide pyridine complex (213 mg, 1.344 mmol) and Carbethoxymethylene triphenyl phosphorane (351 mg, 1 mmol). The reaction mixture was stirred for an additional 12 h at room temperature. The reaction was quenched with 5% HCl, extracted with DCM, dried over Na_2SO_4 , and concentrated. Purification by column chromatography over silica gel (7:1, hexane/ethyl acetate) afforded the trans product **S5** (86 mg, 70%) as a yellow oil; Molecular Name: (E)-ethyl 3-((4S,5S)-2,2-dimethyl-5-(6-nitrobenzo[d][1,3]dioxol-5-yl)-1,3-dioxolan-4-yl)acrylate; Molecular Formula: $\text{C}_{17}\text{H}_{19}\text{NO}_8$; R_f (solvent system): 0.29 (5:1, hexane/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ ppm: 7.44 (s, 1H), 7.24 (s, 1H), 7.01 (dd, $J = 15.58$, 5.97 Hz, 1H), 6.13 (s, 2H), 6.02 (d, $J = 15.59$ Hz, 1H), 5.50 (d, $J = 7.66$ Hz, 1H), 4.32 (t, $J = 6.79$ Hz, 1H), 4.20 (q, $J = 7.13$ Hz, 2H), 1.61 (s, 3H), 1.52 (s, 3H), 1.27 (d, $J = 7.14$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 165.6, 152.1, 147.7, 142.9, 142.6, 129.5, 122.9, 110.3, 107.1, 105.2, 103.1, 83.0, 60.4, 29.6, 26.9, 14.1; LRMS:MS (ES+) $m/z = 366.0$ (M + 1).



To a solution of **S5** (3.48 g, 9.53 mmol) in ethanol (95 mL) was added zinc powder (6.23 g, 95.30 mmol) in one portion at room temperature. This was then followed by dropwise addition of acetic acid (5.45 mL, 95.20 mmol). The reaction mixture was stirred for 15 min, filtered, and concentrated. Purification by flash chromatography over silica gel (5:1, hexane/ethyl acetate) afforded the product **S6** in quantitative yield as a yellow oil; Molecular Name: (E)-ethyl 3-((4S,5S)-5-(6-aminobenzo[d][1,3]dioxol-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate; Molecular Formula: $C_{17}H_{21}NO_6$; R_f (solvent system): 0.48 (4:1, hexane/ethyl acetate); 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.87 (dd, $J = 15.53, 4.77$ Hz, 1H), 6.58 (s, 1H), 6.25 (s, 1H), 6.09 (d, $J = 15.55$ Hz, 1H), 5.86 (s, 2H), 4.79-4.73 (m, 1H), 4.64 (d, $J = 8.65$ Hz, 1H), 4.19 (dd, $J = 13.88, 6.85$ Hz, 2H), 3.98 (s, 2H), 1.57 (s, 3H), 1.50 (s, 3H), 1.28 (t, $J = 7.04$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 165.9, 148.6, 143.5, 141.0, 140.2, 122.8, 110.3, 109.6, 108.7, 100.9, 99.0, 82.3, 77.8, 60.6, 27.2, 26.4, 14.2; LRMS:MS (ES+) $m/z = 336.1$ (M + 1).

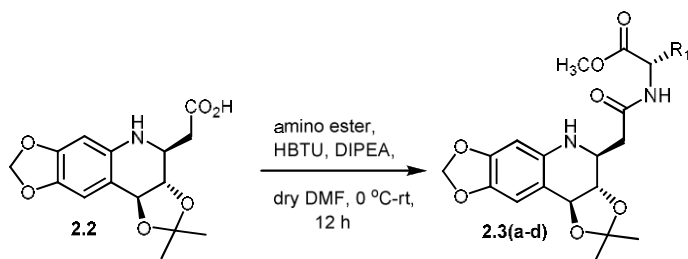


To a solution of **S6** (120 mg, 0.3578 mmol) in anhydrous THF (50 mL) was added KHMDS (0.5 M solution in hexane, 0.7 mL, 0.3578 mmol) dropwise at $-78\text{ }^\circ\text{C}$. After the mixture being stirred for an additional 30 min at $-78\text{ }^\circ\text{C}$, the reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate (2×50 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated. Purification by flash chromatography on silica gel (5:1 hexane/ethylacetate) afforded the product **4.1** as a white solid (57%); Molecular Name: ethyl 2-((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetate; Molecular Formula: $C_{17}H_{21}NO_6$; R_f (solvent system): 0.55 (4:1 hexane/ethyl acetate); 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.66 (s, 1H), 6.12 (s, 1H), 5.81 (d, $J = 3.31$ Hz, 2H), 4.64 (d, $J = 8.82$ Hz, 1H), 4.36 (s, 1H), 4.19 (d, $J = 6.67$ Hz, 2H), 3.96 (d, $J = 10.13$ Hz, 1H), 3.53 (t, $J = 9.30$ Hz, 1H), 2.89 (d, $J = 16.19$ Hz, 1H), 2.47-2.38 (m, 1H), 1.50 (d, $J = 12.56$ Hz, 6H), 1.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.0, 147.4, 139.5, 136.9, 113.2, 112.0, 104.3, 100.5, 96.1, 79.4, 60.9, 52.0, 38.9, 29.7, 27.1, 27.0, 14.2; LRMS:MS (ES+) $m/z = 336.1$ (M + 1).



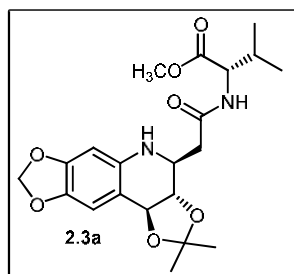
To a solution of **4.1** (500 mg, 1.49 mmol) in THF (50 mL) : H₂O (5 mL) was added LiOH.H₂O (312.6 mg, 7.45 mmol) at room temperature and allowed to stir until starting material disappeared on TLC. The reaction mixture was acidified with 5% HCl and the compound extracted twice with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered, and concentrated afforded the product **2.2** as a white solid (412 mg, 90%); Molecular Name: ethyl 2-((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetate Molecular Formula: C₁₅H₁₇NO₆; R_f (solvent system): 0.05 (1:1hexane/ethyl acetate); ¹H NMR (400 MHz, CDCl₃) δ ppm: 6.67 (s, 1H), 6.15 (s, 1H), 5.82 (d, *J* = 5.08 Hz, 2H), 4.65 (d, *J* = 8.88 Hz, 1H), 4.05-3.97 (m, 1H), 3.56 (t, *J* = 9.47 Hz, 1H), 3.02-2.95 (m, 1H), 2.52 (dd, *J* = 16.67, 10.15 Hz, 1H), 1.53 (s, 3H), 1.50 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ ppm: 177.1, 147.4, 139.7, 136.6, 113.3, 112.3, 104.3, 100.5, 96.4, 79.2, 51.8, 38.8, 27.0, 26.9; LRMS:MS (ES+) *m/z* = 307.9 (M +1).

II. Synthesis of 12-membered macrocycles [2.5(a-d)]



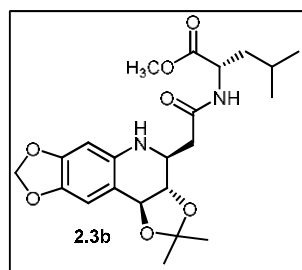
To a solution of **2.2** (1 eq) in dry DMF, was added amino ester (1.5 eq), HBTU (2 eq), and DIPEA (3 eq) at 0 °C . The reaction mixture was stirred for 12 h. The reaction was quenched with saturated NaHCO₃ solution, extracted twice with ethyl acetate and washed with brine. The organic phase was dried over anhydrous Na₂SO₄. After solvent evaporation, the crude product was purified by flash chromatography on silica gel (4:1, hexane/ethyl acetate) afforded the product **2.3(a-d)** as a white solid.

(S)-methyl 2-(2-((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetra hydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamido)-3-methylbutanoate (2.3a);



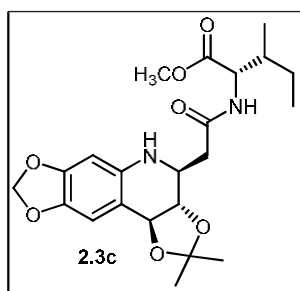
Molecular Formula: $C_{21}H_{28}N_2O_7$; R_f (solvent system): 0.35 (7:3, hexane/ethylacetate); Yield: 60%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.63 (s, 1H), 6.38-6.27 (m, 1H), 6.11 (s, 1H), 5.79 (dd, $J = 2.44, 1.48$ Hz, 2H), 4.72 (s, 1H), 4.63 (d, $J = 8.89$ Hz, 1H), 4.55 (dd, $J = 8.70, 4.93$ Hz, 1H), 3.93 (d, $J = 2.19$ Hz, 1H), 3.74 (s, 3H), 3.53 (t, $J = 9.42$ Hz, 1H), 2.80 (dd, $J = 14.90, 2.56$ Hz, 1H), 2.43-2.33 (m, 1H), 2.21-2.11 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 0.93 (dd, $J = 14.19, 6.87$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.3, 171.0, 147.4, 139.2, 137.0, 113.2, 111.7, 104.2, 104.2, 100.4, 96.1, 96.0, 79.7, 57.1, 52.5, 40.2, 31.1, 27.1, 26.9, 19.0, 17.8; LRMS: (ES+) $m/z = 421.2$ (M+1).

(S)-methyl 2-(2-(((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamido)-4-methylpentanoate (2.3b);



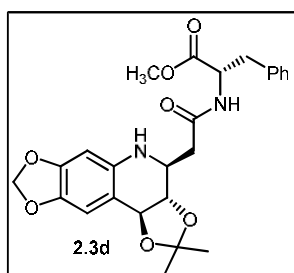
Molecular Formula: $C_{22}H_{30}N_2O_7$; R_f (solvent system): 0.35 (7:3, hexane/ethylacetate); Yield: 70%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.65 (s, 1H), 6.30 (d, $J = 7.79$ Hz, 1H), 6.13 (s, 1H), 5.81 (d, $J = 2.72$ Hz, 2H), 4.74 (s, 1H), 4.65 (d, $J = 8.91$ Hz, 1H), 4.61 (dd, $J = 8.53, 4.94$ Hz, 1H), 3.95 (dt, $J = 9.82, 2.25$ Hz, 1H), 3.75 (s, 3H), 3.55 (t, $J = 9.43$ Hz, 1H), 2.80 (dd, $J = 14.92, 2.53$ Hz, 1H), 2.39 (dd, $J = 14.91, 9.80$ Hz, 1H), 1.90 (tdd, $J = 9.49, 6.95, 4.91$ Hz, 1H), 1.53 (s, 3H), 1.49 (s, 3H), 1.48-1.39 (m, 1H), 1.20-1.12 (m, 1H), 0.92 (dd, $J = 11.05, 4.16$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.4, 170.9, 147.4, 139.2, 137.0, 113.2, 111.7, 104.2, 100.4, 96.1, 79.7, 52.5, 52.4, 52.4, 50.7, 41.4, 40.1, 27.1, 26.9, 24.9, 22.7, 21.9; LRMS: (ES+) $m/z = 435.3$ (M+1).

(2S,3S)-methyl 2-(2-(((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamido)-3-methylpentanoate (2.3c);

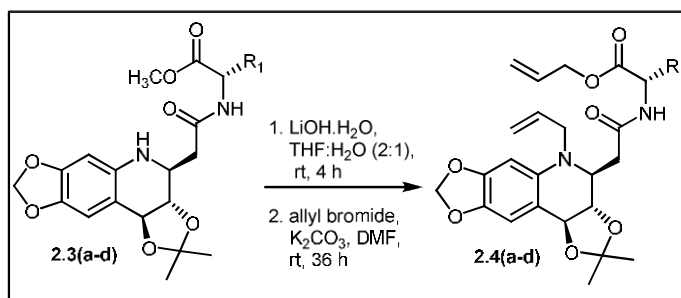


Molecular Formula: $C_{22}H_{30}N_2O_7$; R_f (solvent system): 0.35 (7:3, hexane/ethylacetate); Yield: 70%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.13 (s, 1H), 6.65 (s, 1H), 6.21 (s, 1H), 5.80 (d, J = 2.81 Hz, 2H), 4.74 (s, 1H), 4.67-4.58 (m, 2H), 3.96 (t, J = 9.88 Hz, 1H), 3.75 (s, 3H), 3.54 (t, J = 9.42 Hz, 1H), 2.79 (dd, J = 14.90, 2.48 Hz, 1H), 2.37 (dd, J = 14.90, 9.87 Hz, 1H), 1.71-1.61 (m, 2H), 1.56 (m, 4H), 1.49 (s, 3H), 0.95 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.3, 170.8, 147.4, 139.2, 137.0, 113.2, 111.7, 104.2, 100.4, 96.1, 79.7, 56.4, 52.5, 52.2, 40.2, 37.8, 27.1, 26.9, 25.2, 15.5, 11.5; LRMS: (ES+) m/z = 435.3 (M+1).

(S)-methyl 2-(2-((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetra hydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamido)-3-phenylpropanoate (2.3d);

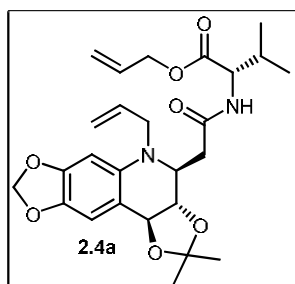


Molecular Formula: $C_{28}H_{28}N_2O_7$; R_f (solvent system): 0.35 (7:3, hexane/ethylacetate); Yield: 58%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.32-7.22 (m, 3H), 7.12-7.06 (m, 2H), 6.64 (s, 1H), 6.19 (d, J = 8.14 Hz, 1H), 6.09 (s, 1H), 5.80 (d, J = 2.39 Hz, 2H), 4.89 (dd, J = 13.73, 6.11 Hz, 1H), 4.61 (d, J = 8.67 Hz, 2H), 3.91 (dt, J = 9.91, 1.89 Hz, 1H), 3.74 (s, 3H), 3.50 (t, J = 9.44 Hz, 1H), 3.18 (dd, J = 13.94, 5.65 Hz, 1H), 3.07 (dd, J = 13.88, 6.35 Hz, 1H), 2.73 (dd, J = 14.92, 2.35 Hz, 1H), 2.29 (dd, J = 14.92, 10.02 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.8, 170.6, 147.4, 139.3, 137.0, 135.6, 129.1, 128.7, 127.3, 113.2, 111.7, 104.3, 100.4, 96.1, 79.6, 53.1, 52.4, 40.2, 37.8, 27.0, 26.9; LRMS: (ES+) m/z = 469.4 (M+1).



1. To a solution of **2.3(a-d)** (1 eq) in THF: H₂O (2:1) was added LiOH.H₂O (5 eq) at room temperature and allowed to stir until starting material disappeared on TLC. The reaction mixture was then acidified with 5% HCl and the compound extracted twice with ethylacetate. The organic phase was dried over Na₂SO₄, filtered, and concentrated afforded the carboxylic acid product as light yellow oil which is subjected to allylation without further purification.
2. To a solution of the above carboxylic acid product (1 eq) in dry DMF was added allyl bromide (5 eq), K₂CO₃ (5 eq), at room temperature. The reaction mixture was allowed to stir for 30 h. Water was added to the reaction mixture, extracted twice with ethyl acetate and washed with brine. The organic phase was dried over anhydrous Na₂SO₄. After solvent evaporation, the crude product was purified by flash chromatography on silica gel (4:1, hexane/ethyl acetate) afforded the bisallyl product **2.4(a-d)** as a light yellow oil.

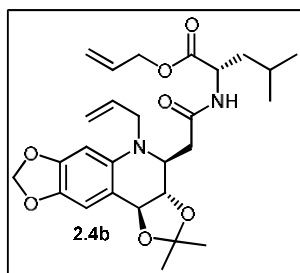
(S)-allyl 2-(2-((3aS,4S,10bS)-5-allyl-2,2-dimethyl-3a,4,5,10b-tetra hydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamido)-3-methylbutanoate (2.4a):



Molecular Formula: C₂₆H₃₄N₂O₇; R_f (solvent system): 0.4 (7:3, hexane/ethyl acetate); Yield: 80%; ¹H NMR (400 MHz, CDCl₃) δ ppm: 6.70-6.63 (m, 2H), 6.39 (s, 1H), 5.91-5.77 (m, 4H), 5.34-5.17 (m, 4H), 4.60-4.49 (m, 4H), 4.03 (m, 1H), 3.88-3.73 (m, 2H), 3.68 (t, *J* = 9.49 Hz, 1H), 2.66 (m, 2H), 2.16 (m, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 0.92 (dd, *J* = 11.98, 6.88 Hz, 6H);

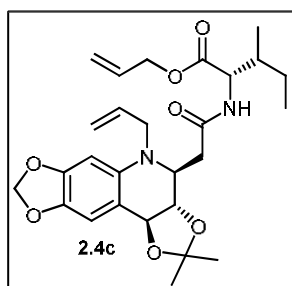
^{13}C NMR (100 MHz, CDCl_3) δ ppm: 171.5, 170.1, 147.3, 140.3, 138.7, 134.7, 131.6, 118.9, 117.6, 117.5, 113.1, 103.3, 100.7, 99.1, 80.7, 76.3, 65.7, 57.5, 57.1, 54.6, 39.7, 31.1, 27.1, 27.0, 19.0, 17.8; LRMS: (ES+) m/z = 487.4 (M+1).

(S)-allyl 2-(2-((3aS,4S,10bS)-5-allyl-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamido)-4-methylpentanoate (2.4b):



Molecular Formula: $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_7$; R_f (solvent system): 0.4 (7:3, hexane/ethyl acetate); Yield: 50%; ^1H NMR (400 MHz, CDCl_3) δ ppm: 6.67 (s, 1H), 6.57 (d, J = 7.87 Hz, 1H), 6.38 (s, 1H), 5.89-5.76 (m, 4H), 5.24 (m, 5H), 4.61-4.54 (m, 3H), 4.49 (d, J = 9.07 Hz, 1H), 4.00 (dd, J = 16.75, 4.67 Hz, 1H), 3.85-3.71 (m, 2H), 3.67 (t, J = 9.50 Hz, 1H), 2.62 (dq, J = 15.37, 4.68 Hz, 2H), 1.64-1.55 (m, 2H), 1.52 (s, 3H), 1.46 (s, 3H), 0.93-0.90 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 172.5, 170.8, 169.9, 147.4, 147.3, 139.3, 138.6, 137.0, 134.6, 131.6, 131.5, 119.0, 118.7, 117.8, 117.6, 113.2, 113.1, 111.7, 104.3, 104.3, 103.3, 103.3, 100.7, 100.5, 99.2, 99.2, 96.1, 96.1, 80.6, 79.7, 76.4, 66.0, 65.7, 57.4, 54.7, 52.6, 50.9, 50.8, 41.6, 41.5, 40.2, 39.5, 27.1, 27.0, 27.0, 25.0, 24.9, 22.8, 22.8, 22.0, 21.9; LRMS: (ES+) m/z = 501.5 (M+1).

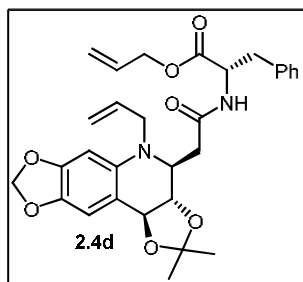
(2S,3S)-allyl 2-(2-((3aS,4S,10bS)-5-allyl-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamido)-3-methylpentanoate (2.4c):



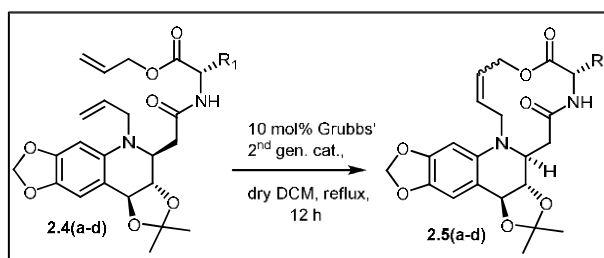
Molecular Formula: $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_7$; R_f (solvent system): 0.4 (7:3, hexane/ethyl acetate); Yield: 50%; ^1H NMR (400 MHz, CDCl_3) δ ppm: 6.70-6.64 (m, 2H), 6.39 (s, 1H), 5.87-5.77 (m, 4H), 5.34-5.20 (m, 4H), 4.65-4.56 (m, 4H), 4.53-4.48 (m, 1H), 4.02 (m, 1H), 3.85-3.78 (m,

1H), 3.68 (m, 1H), 2.65 (dd, $J = 4.71, 1.73$ Hz, 2H), 1.87 (m, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.16 (m, 2H), 0.93-0.88 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 171.4, 169.9, 147.3, 140.4, 138.7, 134.7, 131.6, 118.9, 117.6, 113.1, 103.3, 100.7, 99.2, 80.7, 76.4, 65.7, 57.5, 56.5, 54.6, 39.7, 37.8, 27.1, 27.0, 25.3, 15.5, 11.6; LRMS: (ES+) $m/z = 501.5$ (M+1).

(S)-allyl2-(2-((3aS,4S,10bS)-5-allyl-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamido)-3-phenylpropanoate (2.4d):

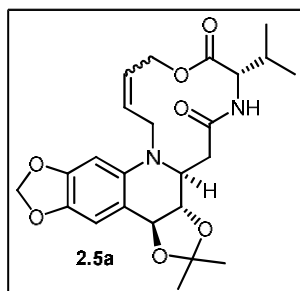


Molecular Formula: $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_7$; R_f (solvent system): 0.45 (7:3, hexane/ethyl acetate); Yield: 70%; ^1H NMR (400 MHz, CDCl_3) δ ppm: 7.31-7.23 (m, 3H), 7.14-7.08 (m, 2H), 6.71-6.63 (m, 2H), 6.17 (s, 1H), 5.84 (dd, $J = 8.61, 1.27$ Hz, 2H), 5.81-5.64 (m, 2H), 5.30-5.11 (m, 4H), 4.92 (td, $J = 7.69, 5.91$ Hz, 1H), 4.62-4.42 (m, 3H), 3.87 (dd, $J = 16.65, 4.81$ Hz, 1H), 3.76 (td, $J = 9.42, 4.56$ Hz, 1H), 3.63 (td, $J = 15.13, 8.04$ Hz, 2H), 3.09 (t, $J = 8.06$ Hz, 2H), 2.59 (dq, $J = 15.32, 4.57$ Hz, 2H), 1.44-1.38 (m, 3H), 1.49 (d, $J = 6.53$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 170.9, 169.6, 147.2, 140.4, 138.3, 135.9, 134.2, 131.3, 129.3, 129.1, 128.5, 128.4, 127.0, 118.9, 117.9, 117.6, 112.9, 103.1, 100.6, 99.4, 79.9, 76.2, 65.8, 57.1, 54.4, 52.9, 38.8, 37.7, 26.8; LRMS: (ES+) $m/z = 535.6$ (M+1).



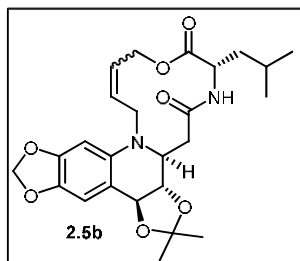
Bis allyl compound **2.4(a-d)** (1 eq) was taken in dry dichloromethane under nitrogen atmosphere and Grubbs' 2nd generation catalyst (0.1 eq) was added and reaction mixture was heated to 40 °C for 12 h. The reaction mixture was concentrated and the crude product was purified by flash chromatography on silica gel (4:1, hexane/ethyl acetate) afforded the product **2.5(a-d)**.

(3aS,3bS,7S,19bS,E/Z)-7-isopropyl-2,2-dimethyl-3b,4,6,7,13,19b-hexahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,4,8]oxadiazacyclododeca[8,7-a]quinoline-5,8(3aH,10H)-dione (2.5a):



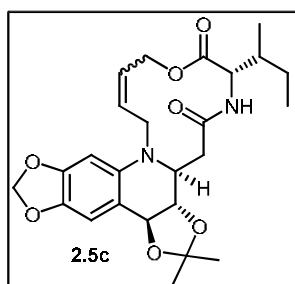
Molecular Formula: $C_{24}H_{30}N_2O_7$; R_f (solvent system): 0.3 (7:3, hexane/ethyl acetate); Yield: 23%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.66 (s, 1H), 6.58 (s, 1H), 5.99-5.92 (m, 1H), 5.88 (d, $J = 11.66$ Hz, 2H), 5.82-5.73 (m, 1H), 5.51-5.40 (m, 1H), 4.71-4.61 (m, 1H), 4.37 (d, $J = 10.39$ Hz, 3H), 4.26-4.14 (m, 1H), 3.93-3.85 (m, 1H), 3.67 (s, 1H), 3.39 (s, 1H), 2.80 (d, $J = 13.13$ Hz, 1H), 2.39-2.22 (m, 3H), 1.57 (s, 3H), 1.49 (s, 3H), 1.03 (dd, $J = 12.83, 6.87$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.3, 170.8, 147.7, 139.6, 135.9, 125.4, 114.2, 107.8, 101.0, 99.8, 61.9, 59.1, 46.8, 43.2, 37.0, 29.7, 28.9, 22.7, 19.4, 18.4; LRMS: (ES+) $m/z = 459.5$ (M+1).

(3aS,3bS,7S,19bS,E/Z)-7-isobutyl-2,2-dimethyl-3b,4,6,7,13,19b-hexahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,4,8]oxadiazacyclododeca[8,7-a]quinoline-5,8(3aH,10H)-dione (2.5b):



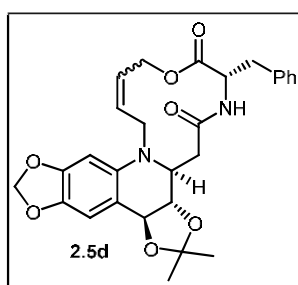
Molecular Formula: $C_{25}H_{32}N_2O_7$; R_f (solvent system): 0.3 (7:3, hexane/ethyl acetate); Yield: 22%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.66 (s, 1H), 6.58 (s, 1H), 5.88 (m, 3H), 5.51-5.42 (m, 1H), 5.81-5.74 (m, 1H), 4.65-4.60 (m, 1H), 4.58-4.51 (m, 1H), 4.38 (m, 2H), 4.30-4.21 (m, 1H), 3.94-3.87 (m, 1H), 3.68 (t, $J = 9.6$ Hz, 1H), 3.40 (t, $J = 9.6$ Hz, 1H), 2.76 (d, $J = 12.90$ Hz, 1H), 2.34 (m, 1H), 2.07-1.99 (m, 1H), 1.75 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.28 (m, 1H), 0.97 (dd, $J = 11.69, 6.04$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.6, 171.8, 147.5, 141.5, 138.1, 133.4, 124.0, 120.4, 112.8, 102.6, 100.9, 81.8, 60.5, 57.7, 51.9, 44.1, 39.4, 33.8, 31.9, 29.7, 27.1, 24.9, 23.0, 21.4, 14.1; LRMS: (ES+) $m/z = 472.5$ (M+1).

(3aS,3bS,7S,19bS,E/Z)-7-sec-butyl-2,2-dimethyl-3b,4,6,7,13,19b-hexahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,4,8]oxadiazacyclododeca[8,7-a]quinoline-5,8(3aH,10H)-dione (2.5c):



Molecular Formula: $C_{25}H_{32}N_2O_7$; R_f (solvent system): 0.3 (7:3, hexane/ethyl acetate); Yield: 28%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.66 (s, 1H), 6.59 (s, 1H), 5.94-5.86 (m, 3H), 5.79 (m, 1H), 5.47 (m, 1H), 4.71-4.63 (m, 1H), 4.47 (m, 1H), 4.40-4.31 (m, 2H), 4.20 (m, 1H), 3.90 (m, 1H), 3.66 (t, $J = 9.65$ Hz, 1H), 3.39 (t, $J = 9.60$ Hz, 1H), 2.79 (d, $J = 12.97$ Hz, 1H), 2.34 (m, 1H), 2.04-1.96 (m, 1H), 1.57 (s, 3H), 1.55-1.48 (m, 5H), 1.02 (d, $J = 6.86$ Hz, 3H), 0.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.8, 171.0, 147.5, 141.6, 138.1, 133.4, 124.1, 120.5, 112.8, 102.6, 100.9, 81.9, 76.1, 60.3, 58.1, 57.7, 51.2, 44.3, 35.6, 29.7, 27.1, 25.4, 16.0, 11.5; LRMS: (ES+) $m/z = 472.5$ (M+1).

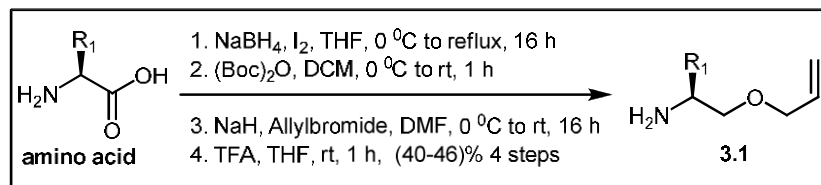
(3aS,3bS,7S,19bS,E/Z)-7-benzyl-2,2-dimethyl-3b,4,6,7,13,19b-hexahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,4,8]oxadiazacyclododeca [8,7-a]quinoline-5,8(3aH,10H)-dione (2.5d):



Molecular Formula: $C_{28}H_{30}N_2O_7$; R_f (solvent system): 0.3 (7:3, hexane/ethyl acetate); Yield: 29%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.55 (s, 1H), 6.65 (s, 1H), 7.36-7.19 (m, 6H), 5.98 (d, $J = 8.03$ Hz, 1H), 5.87 (dd, $J = 13.28, 1.16$ Hz, 2H), 5.72 (d, $J = 5.17$ Hz, 1H), 5.44 (d, $J = 2.26$ Hz, 1H), 4.80 (d, $J = 4.57$ Hz, 1H), 4.66-4.57 (m, 1H), 4.50 (dd, $J = 13.59, 6.65$ Hz, 1H), 4.35 (d, $J = 9.15$ Hz, 1H), 4.26 (dd, $J = 16.53, 11.06$ Hz, 1H), 3.90 (dd, $J = 16.23, 1.58$ Hz, 1H), 3.63 (t, $J = 9.69$ Hz, 1H), 3.40-3.24 (m, 2H), 3.10 (dd, $J = 14.49, 9.16$ Hz, 1H), 2.70 (d, $J = 13.14$ Hz, 1H), 2.25 (dd, $J = 13.23, 9.53$ Hz, 1H), 1.55 (s, 3H), 1.47 (d, $J = 5.76$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.4, 170.9, 147.5, 141.4, 138.0, 136.2, 132.9,

128.9, 128.8, 127.2, 123.9, 120.2, 112.8, 102.7, 102.2, 100.8, 81.6, 61.0, 57.6, 54.1, 50.8, 43.8, 36.2, 29.7, 27.1, 27.0; LRMS: (ES+) $m/z = 507.5$ (M+1).

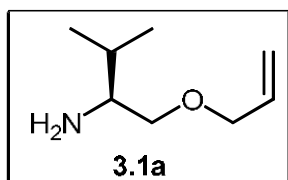
III. Synthesis of amino acid buildingblock [3.1(a-d)]



1. To a stirred solution of amino acid (18.18 mmol) and NaBH_4 (1.65 g, 43.6 mmol) in 50 mL THF, I_2 (4.59 g, 18.18 mmol) in 50 mL THF was added slowly at 0°C for 30 min, reflux for 16 h, cool the reaction to 0°C and quenched with methanol cautiously, solvents were removed under reduced pressure, 150 mL 20% KOH solution was added, stirred for another 6 h. After completion of reaction (monitored by TLC), 50 mL brine solution was added and extracted with ethyl acetate (3×200 mL). Combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude.
2. To the above crude in 60 mL DCM, $(\text{Boc})_2\text{O}$ (26.45 mmol) was added slowly at 0°C , stirred at rt for 1 h. After completion of reaction (monitored by TLC), 50 mL saturated NaHCO_3 solution was added and extracted with ethyl acetate (2×150 mL). Combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude.
3. To the above crude in 100 mL dry DMF, NaH (41.66 mmol) was added portionwise at 0°C , followed by allylbromide (41.66 mmol), stirred at rt for 16 h. After completion of reaction (monitored by TLC), 100 mL saturated ammonium chloride solution was added cautiously and extracted with ethyl acetate (2×100 mL). Combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude, which was purified by flash chromatography giving the pure compound.
4. To the above pure compound in 10 mL dry THF, 10 mL TFA was added at 0°C , stirred at rt for 2 h. After completion of reaction (monitored by TLC), 100 mL saturated NaHCO_3 solution was added cautiously and extracted with ethyl acetate (2×100 mL). Purification of compound by acid-base neutralisation technique, then

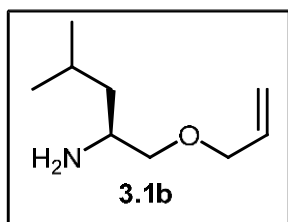
organic layer was dried over anhydrous sodium sulfate, filtered and concentrated afforded the amino alcohol buildingblock (**3.1**) .

(S)-1-(allyloxy)-3-methylbutan-2-amine (3.1a):



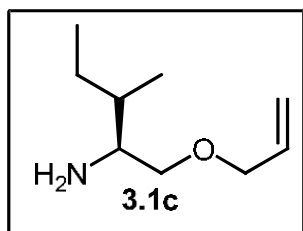
^1H NMR (400 MHz, CDCl_3) ppm: 5.87 (m, 1H), 5.21 (d, $J = 10.42$ Hz, 1H), 5.28 (d, $J = 17.76$ Hz, 1H), 4.02 (d, $J = 5.75$ Hz, 2H), 3.65 (dd, $J = 10.17, 3.51$ Hz, 1H), 3.52 (t, $J = 9.19$ Hz, 1H), 3.14-3.06 (m, 1H), 2.03 (m, 1H), 1.06 (d, $J = 6.81$ Hz, 3H), 0.99 (d, $J = 6.82$ Hz, 3H); ^{13}C NMR (100MHz, CDCl_3) ppm: 133.8, 117.9, 72.2, 67.4, 57.1, 28.3, 18.8, 18.2; LRMS: (ES+) $m/z = 144.2$ (M+1).

(S)-1-(allyloxy)-4-methylpentan-2-amine (3.1b):



^1H NMR (400 MHz, CDCl_3) ppm: 5.87 (m, 1H), 5.31-5.17 (m, 2H), 4.01 (d, $J = 5.77$ Hz, 2H), 3.60 (dd, $J = 10.01, 3.09$ Hz, 1H), 3.51-3.35 (m, 2H), 1.68 (m, 1H), 1.53 (m, 2H), 0.92 (dd, $J = 6.26, 3.81$ Hz, 6H); ^{13}C NMR (100MHz, CDCl_3) ppm: 133.7, 117.9, 72.2, 68.7, 50.0, 38.1, 21.7, 24.2, 22.5; LRMS: (ES+) $m/z = 158.1$ (M+1).

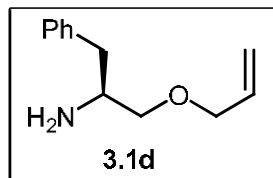
(2S,3S)-1-(allyloxy)-3-methylpentan-2-amine (3.1c):



^1H NMR (400 MHz, CDCl_3) ppm: 5.28 Hz, 1H), 5.86 (ddd, $J = 16.31, 10.91$), 5.27 (dd, $J = 17.23, 1.29$ Hz, 1H), 5.21 (d, $J = 10.37$ Hz, 1H), 4.01 (d, $J = 5.66$ Hz, 2H), 3.62 (dd, $J = 10.21, 3.64$ Hz, 1H), 3.56-3.49 (m, 1H), 3.27-3.20 (m, 1H), 1.88-1.76 (m, 1H), 1.58-1.50 (m,

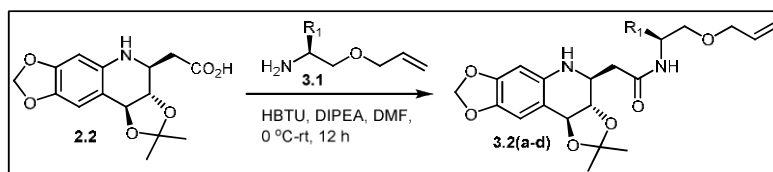
1H), 1.31-1.19 (m, 1H), 0.98-0.89 (m, 6H); ^{13}C NMR (100MHz, CDCl_3) ppm ^{13}C NMR (100MHz, CDCl_3) ppm: 133.7, 118.0, 72.2, 66.9, 55.5, 34.8, 25.6, 14.1, 10.9; LRMS: (ES+) m/z = 158.1 (M+1).

(S)-1-(allyloxy)-3-phenylpropan-2-amine (3.1d):



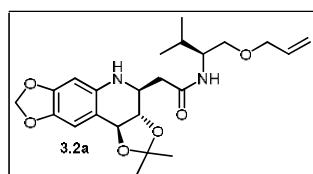
^1H NMR (400 MHz, CDCl_3) ppm: 7.25 (m, 5H), 5.56 Hz, 1H), 5.92 (ddd, J = 22.66, 10.78, 5.32-5.23 (m, 1H), 5.17 (d, J = 10.38 Hz, 1H), 3.99 (d, J = 5.45 Hz, 2H), 3.47-3.40 (m, 1H), 3.32-3.19 (m, 2H), 2.79 (dd, J = 13.34, 4.87 Hz, 1H), 2.55 (dd, J = 13.33, 7.83 Hz, 1H); ^{13}C NMR (100MHz, CDCl_3) ppm: 138.8, 134.7, 129.2, 40.7, 52.4, 72.1, 74.9, 116.9, 126.2, 128.4.; LRMS: (ES+) m/z = 192.1 (M+1).

IV. Synthesis of 12-membered macrocycles [3.4(a-d)]



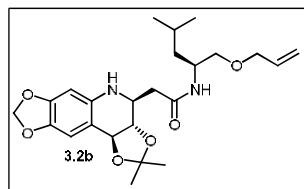
To a solution of Carboxylic acid **2.2** (1 eq) in dry DMF, were added primary amine **3.1** (1.5 eq), HBTU (2 eq), and DIPEA (3 eq) at 0 °C . The reaction mixture was stirred for 12 h. The reaction was quenched with saturated NaHCO_3 solution , extracted twice with ethyl acetate and washed with brine. The organic phase was dried over anhydrous Na_2SO_4 . After solvent evaporation, the crude product was purified by flash chromatography on silica gel (4:1, hexane/ethylacetate) afforded the product **3.2(a-d)**.

N-((S)-1-(allyloxy)-3-methylbutan-2-yl)-2-((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamide (3.2a);



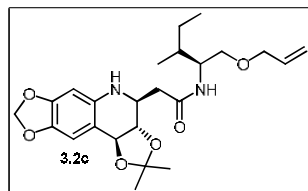
Molecular Formula: $C_{23}H_{32}N_2O_6$; R_f (solvent system): 0.25 (7:3, hexane/ethyl acetate); Yield: 70%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.66 (s, 1H), 6.14 (s, 1H), 5.95-5.83 (m, 2H), 5.81 (s, 1H), 5.80 (s, 1H), 5.22 (m, 2H), 4.65 (d, $J = 8.85$ Hz, 1H), 4.03-3.90 (m, 3H), 3.89-3.81 (m, 1H), 3.55 (m, 2H), 3.40 (dd, $J = 9.70, 3.80$ Hz, 1H), 2.77-2.69 (m, 1H), 2.36 (dd, $J = 14.82, 10.04$ Hz, 1H), 1.91 (m, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 0.95 (t, $J = 7.46$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 170.57, 147.42, 139.18, 137.11, 134.39, 117.27, 113.15, 111.63, 104.22, 100.41, 96.05, 79.82, 72.14, 69.77, 54.21, 52.66, 40.39, 29.37, 27.08, 26.96, 19.49, 19.07; LRMS: (ES+) $m/z = 433.2$ (M+1).

N-((S)-1-(allyloxy)-4-methylpentan-2-yl)-2-((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamide (3.2b);



Molecular Formula: $C_{24}H_{34}N_2O_6$; R_f (solvent system): 0.5 (1:1, hexane/ethyl acetate); Yield: 50%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.65 (s, 1H), 6.14 (s, 1H), 5.94-5.78 (m, 4H), 5.22 (m, 2H), 4.86 (s, 1H), 4.64 (d, $J = 8.84$ Hz, 1H), 4.17 (m, 1H), 4.03-3.90 (m, 3H), 3.53 (t, $J = 9.42$ Hz, 1H), 3.43 (d, $J = 3.49$ Hz, 2H), 2.69 (dd, $J = 14.74, 1.85$ Hz, 1H), 2.32 (dd, $J = 14.76, 10.02$ Hz, 1H), 1.60 (m, 1H), 1.53 (s, 3H), 1.51 (s, 3H), 1.47-1.35 (m, 2H), 0.93 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 170.32, 147.41, 139.15, 137.12, 134.42, 117.24, 113.14, 111.62, 104.21, 100.40, 96.02, 79.78, 72.18, 71.77, 52.69, 47.28, 40.88, 40.38, 27.07, 26.96, 24.96, 22.87, 22.37; LRMS: (ES+) $m/z = 446.2$ (M+1).

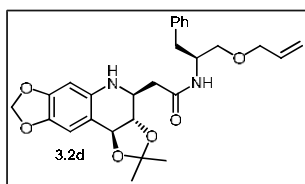
N-((2S,3R)-1-(allyloxy)-3-methylpentan-2-yl)-2-((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamide (3.2c);



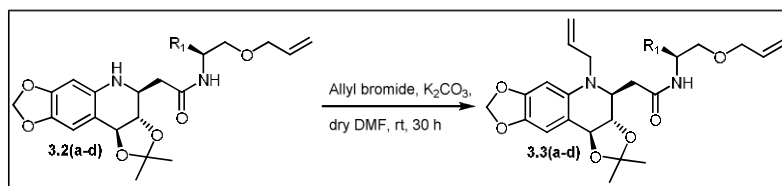
Molecular Formula: $C_{24}H_{34}N_2O_6$; R_f (solvent system): 0.5 (1:1, hexane/ethyl acetate); Yield: 58%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.66 (s, 1H), 6.14 (s, 1H), 5.95-5.83 (m, 2H), 5.81 (d, $J = 2.90$ Hz, 2H), 5.30-5.16 (m, 2H), 4.65 (d, $J = 8.91$ Hz, 1H), 4.02-3.87 (m, 4H), 3.60-

3.51 (m, 2H), 3.41 (dd, $J = 9.76, 3.63$ Hz, 1H), 2.73 (dd, $J = 14.83, 2.38$ Hz, 1H), 2.36 (dd, $J = 14.84, 9.98$ Hz, 1H), 1.72-1.62 (m, 1H), 1.54 (s, 3H), 1.50 (s, 3H), 1.22-1.07 (m, 2H), 0.91 (m, 6H); ^{13}C NMR (400 MHz, CDCl_3) δ ppm: 170.51, 147.43, 139.19, 137.12, 134.39, 117.31, 113.16, 111.64, 104.22, 100.41, 96.05, 79.81, 72.16, 69.59, 53.05, 52.68, 40.42, 35.84, 27.08, 26.96, 25.68, 15.49, 11.36; LRMS: (ES+) $m/z = 447.2$ (M+1).

N-((S)-1-(allyloxy)-3-phenylpropan-2-yl)-2-((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)acetamide (3.2d);

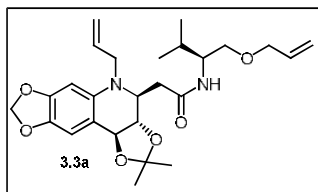


Molecular Formula: $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_6$; R_f (solvent system): 0.5 (1:1, hexane/ethylacetate); Yield: 70%; ^1H NMR (400 MHz, CDCl_3) δ ppm: 7.35-7.16 (m, 6H), 6.65 (s, 1H), 6.10 (s, 1H), 6.02-5.83 (m, 2H), 5.80 (d, $J = 3.01$ Hz, 2H), 5.24 (ddd, $J = 13.80, 11.40, 1.24$ Hz, 2H), 4.74-4.57 (m, 2H), 4.32 (ddd, $J = 11.70, 7.70, 4.25$ Hz, 1H), 4.03-3.88 (m, 3H), 3.50 (t, $J = 9.43$ Hz, 1H), 3.37 (d, $J = 3.53$ Hz, 2H), 2.27 (dd, $J = 14.82, 10.15$ Hz, 1H), 1.52 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) δ ppm: 170.28, 147.41, 139.17, 137.79, 137.07, 134.30, 129.30, 128.50, 126.56, 117.42, 113.14, 111.63, 104.23, 100.42, 96.03, 79.71, 72.19, 69.74, 52.60, 50.21, 40.38, 37.49, 27.08, 26.96; LRMS: (ES+) $m/z = 480$ (M+1).



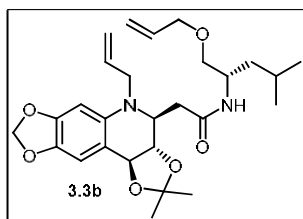
To a solution of the coupling compound **3.2(a-d)** (1 eq) in dry DMF was added allyl bromide (5 eq), K_2CO_3 (5 eq), at room temperature. The reaction mixture was allowed to stir for 30 h. Water was added to the reaction mixture, extracted twice with ethyl acetate and later washed with brine. The organic phase was dried over anhydrous Na_2SO_4 . After solvent evaporation, the crude product was purified by flash chromatography on silica gel (4:1, hexane/ethyl acetate) afforded the product **3.3(a-d)**.

2-((3aS,4S,10bS)-5-allyl-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)-N-((S)-1-(allyloxy)-3-methylbutan-2-yl)acetamide (3.3a);



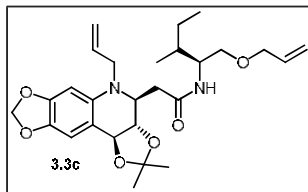
Molecular Formula: $C_{26}H_{36}N_2O_6$; R_f (solvent system): 0.26 (7:3, hexane/ethyl acetate); Yield: 80%; 1H NMR (400 MHz, $CDCl_3$, δ ppm: 6.69 (s, 1H), 6.40 (s, 1H), 6.30 (d, 1H), 5.89-5.74 (m, 4H), 5.20 (m, Hz, 4H), 4.50 (d, $J = 9.08$ Hz, 1H), 4.03 (dd, $J = 16.76, 4.67$ Hz, 1H), 3.90-3.73 (m, 5H), 3.64 (t, $J = 9.52$ Hz, 1H), 3.41 (dd, $J = 9.61, 4.19$ Hz, 1H), 3.31 (dd, $J = 9.63, 4.15$ Hz, 1H), 2.67-2.54 (m, 2H), 1.88 (m, 1H), 1.53 (s, 3H), 1.49 (s, 3H), 0.92 (t, $J = 7.28$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm: 169.67, 147.27, 140.34, 138.66, 134.61, 134.58, 117.69, 117.53, 116.95, 112.93, 103.31, 100.66, 99.14, 80.48, 72.00, 69.90, 57.60, 54.57, 53.91, 39.59, 29.20, 27.05, 27.02, 19.50, 18.79; LRMS: (ES+) $m/z = 473.2$ (M+1).

2-((3aS,4S,10bS)-5-allyl-2,2-dimethyl-3a,4,5,10b-tetrahydrobis [1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)-N-((S)-1-(allyloxy)-4-methylpentan-2-yl)acetamide (3.3b);



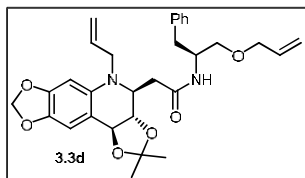
Molecular Formula: $C_{27}H_{38}N_2O_6$; R_f (solvent system): 0.5 (1:1, hexane/ethyl acetate); Yield: 80%; 1H NMR (400 MHz, $CDCl_3$, δ ppm: 6.68 (s, 1H), 6.65 (s, 1H), 6.39 (s, 1H), 6.14 (s, 2H), 5.91-5.78 (m, 10H), 5.31-5.12 (m, 8H), 4.86 (s, 1H), 4.65 (d, $J = 8.87$ Hz, 1H), 4.50 (d, $J = 9.08$ Hz, 1H), 4.15 (ddd, $J = 9.06, 7.39, 3.32$ Hz, 3H), 4.05-3.72 (m, 11H), 3.62 (t, $J = 9.51$ Hz, 2H), 3.53 (t, $J = 9.43$ Hz, 1H), 3.43 (d, $J = 3.55$ Hz, 2H), 3.33 (d, $J = 3.76$ Hz, 3H), 2.69 (dd, $J = 14.76, 2.04$ Hz, 1H), 2.62-2.50 (m, 3H), 2.32 (dd, $J = 14.74, 10.05$ Hz, 1H), 1.59 (dd, $J = 13.64, 6.96$ Hz, 3H), 1.53 (s, 7H), 1.49 (s, 4H), 1.47 (s, 4H), 1.38 (ddd, $J = 12.69, 9.59, 5.88$ Hz, 5H), 0.95-0.90 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$, δ ppm: 170.32, 169.42, 147.42, 147.27, 140.29, 139.16, 138.71, 137.12, 134.76, 134.61, 134.42, 117.64, 117.39, 117.24, 116.94, 113.15, 112.93, 111.63, 104.21, 103.28, 100.66, 100.41, 99.04, 96.02, 80.60, 79.79, 72.19, 72.08, 72.02, 71.78, 57.61, 54.52, 52.69, 47.29, 47.14, 41.00, 40.88, 40.39, 39.80, 29.67, 27.07, 27.04, 26.96, 24.96, 24.84, 23.08, 22.87, 22.37, 22.20; LRMS: (ES+) $m/z = 446.2$ (M+1).

2-((3aS,4S,10bS)-5-allyl-2,2-dimethyl-3a,4,5,10b-tetrahydro bis [1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)-N-((2S,3R)-1-(allyloxy)-3-methylpentan-2-yl)acetamide (3.3c);

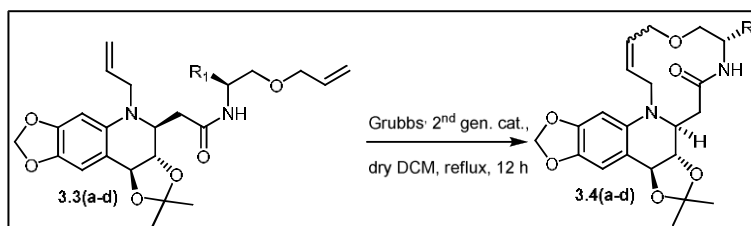


Molecular Formula: $C_{27}H_{38}N_2O_6$; R_f (solvent system): 0.5 (1:1, hexane/ethyl acetate); Yield: 60%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.69 (s, 1H), 6.39 (s, 1H), 6.32 (dd, $J = 11.21$, 7.31 Hz, 1H), 5.88-5.74 (m, 5H), 5.28-5.10 (m, 4H), 4.50 (d, $J = 9.12$ Hz, 1H), 4.03 (dd, $J = 16.70$, 4.67 Hz, 1H), 3.91 (qd, $J = 13.00$, 4.41, 4.10 Hz, 1H), 3.87-3.73 (m, 4H), 3.65 (t, $J = 9.52$ Hz, 1H), 3.43 (dd, $J = 9.63$, 4.12 Hz, 1H), 3.33 (dd, $J = 9.67$, 3.75 Hz, 1H), 2.67-2.54 (m, 2H), 1.63 (ddd, $J = 9.85$, 7.29, 3.47 Hz, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.19-1.05 (m, 2H), 0.88 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 169.58, 147.28, 140.33, 138.70, 134.67, 134.60, 117.68, 117.49, 116.99, 112.94, 103.32, 100.67, 99.12, 80.48, 72.04, 69.73, 57.61, 54.55, 52.86, 39.61, 35.79, 27.07, 27.04, 25.50, 15.51, 11.37; LRMS: (ES+) $m/z = 487.2$ (M+1).

2-((3aS,4S,10bS)-5-allyl-2,2-dimethyl-3a,4,5,10b-tetra hydrobis [1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)-N-((S)-1-(allyloxy)-3-phenylpropan-2-yl)acetamide (3.3d);

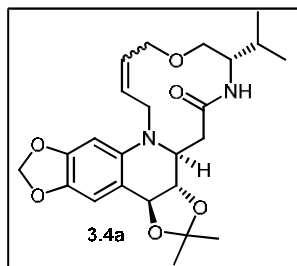


Molecular Formula: $C_{30}H_{36}N_2O_6$; R_f (solvent system): 0.5 (1:1, hexane/ethyl acetate); Yield: 80%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.25 (m, 6H), 6.66 (s, 1H), 6.43-6.34 (m, 1H), 6.23 (s, 1H), 5.82 (dt, $J = 10.38$, 1.97 Hz, 4H), 5.31-5.12 (m, 4H), 4.46 (d, $J = 9.11$ Hz, 1H), 4.37-4.27 (m, 1H), 3.98-3.89 (m, 1H), 3.89-3.83 (m, 2H), 3.83-3.75 (m, 1H), 3.70-3.61 (m, 1H), 3.58 (d, $J = 9.47$ Hz, 1H), 3.22 (t, $J = 3.95$ Hz, 2H), 2.86 (dd, $J = 6.99$, 2.52 Hz, 2H), 2.54 (dd, $J = 16.82$, 4.65 Hz, 2H), 1.44 (s, 3H), 1.51 (d, $J = 3.40$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 169.48, 147.27, 140.45, 138.53, 137.95, 134.49, 129.43, 129.30, 128.49, 128.42, 126.44, 117.93, 117.58, 117.09, 112.93, 103.28, 100.69, 99.32, 80.31, 72.03, 69.74, 57.48, 54.60, 49.79, 39.44, 37.25, 27.06, 27.03; LRMS: (ES+) $m/z = 521.2$ (M+1).



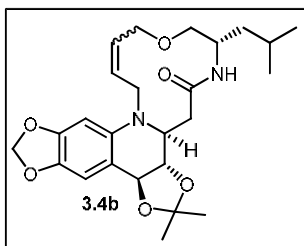
Bis allyl compound **3.3(a-d)** (1eq) was taken in dry dichloromethane under nitrogen atmosphere and Grubbs' 2nd generation catalyst (10 mol%) was added and reaction mixture was heated to 40 ° C for 12 h. The reaction mixture was concentrated and the crude product was purified by flash chromatography on silica gel (4:1, hexane/ethylacetate) afforded the product **3.4(a-d)**.

(3aS,3bS,7S,19bS,E/Z)-7-isopropyl-2,2-dimethyl-3b,4,6,7,8,10,13,19b-octahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,4,8] oxadiazia cyclododeca[8,7-a]quinolin-5(3aH)-one (3.4a);



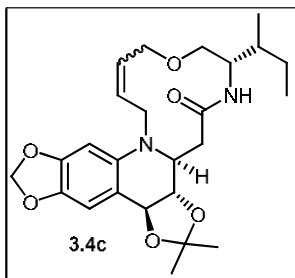
Molecular Formula: C₂₄H₃₂N₂O₆; R_f (solvent system): 0.3 (1:1, hexane/ethyl acetate); Yield: 80%; ¹H NMR (400 MHz, CDCl₃) δ ppm: 6.69 (s, 1H), 6.23 (s, 1H), 6.08-5.96 (m, 1H), 5.94-5.79 (m, 3H), 5.40 (d, *J* = 8.90 Hz, 1H), 4.71 (t, *J* = 9.75 Hz, 1H), 4.50 (d, *J* = 9.37 Hz, 1H), 4.10-3.99 (m, 1H), 3.95-3.75 (m, 4H), 3.68 (m, *J* = 10.04, 1H), 3.58 (dd, *J* = 11.59, 3.17 Hz, 1H), 3.39 (m, 1H), 2.74 (dd, *J* = 16.03, 2.77 Hz, 1H), 2.45 (dd, *J* = 16.10, 3.63 Hz, 1H), 1.78 (m, 1H), 1.55 (d, *J* = 2.56 Hz, 6H), 0.91 (dd, *J* = 14.46, 6.68 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) δ ppm: 169.51, 147.26, 140.77, 139.70, 133.81, 127.45, 115.97, 112.57, 103.57, 100.56, 97.00, 70.41, 66.84, 60.98, 29.67, 29.64, 28.99, 27.10, 27.05, 19.80, 19.66; LRMS: (ES+) *m/z* = 445; LRMS: (ES+) *m/z* = 444.3 (M+1).

(3aS,3bS,7S,19bS,E/Z)-7-isobutyl-2,2-dimethyl-3b,4,6,7,8,10,13,19b-octahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,4,8]oxadiazia cyclododeca[8,7-a]quinolin-5(3aH)-one (3.4b);



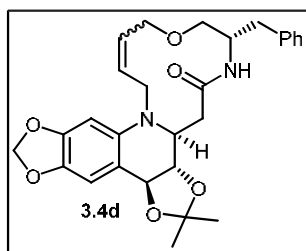
Molecular Formula: $C_{25}H_{34}N_2O_6$; R_f (solvent system): 0.4 (1:1, hexane/ethyl acetate); Yield: 66%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.24 (s, 1H), 6.69 (s, 1H), 6.05-5.97 (m, 1H), 5.83 (d, $J = 8.77$ Hz, 3H), 5.34-5.27 (m, 1H), 4.68-4.59 (m, 1H), 4.49 (d, $J = 9.16$ Hz, 1H), 4.02 (d, $J = 9.41$ Hz, 1H), 3.95 (s, 1H), 3.84 (s, 2H), 3.75-3.56 (m, 4H), 2.71-2.63 (m, 1H), 2.50-2.42 (m, 1H), 1.63-1.54 (m, 7H), 0.93 (d, $J = 6.42$ Hz, 2H), 0.89-0.85 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 169.56, 147.24, 140.78, 139.73, 134.27, 126.86, 116.10, 112.57, 103.48, 100.56, 97.15, 70.34, 68.65, 60.79, 56.33, 48.75, 40.04, 37.54, 29.67, 27.09, 27.06, 26.95, 24.71, 22.97, 22.13; LRMS: (ES+) $m/z = 459.3$ (M+1).

(3aS,3bS,7S,19bS,E/Z)-7-sec-butyl-2,2-dimethyl-3b,4,6,7,8,10,13,19b-octahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,4,8]oxadiazacyclododeca[8,7-a]quinolin-5(3aH)-one(3.4c);



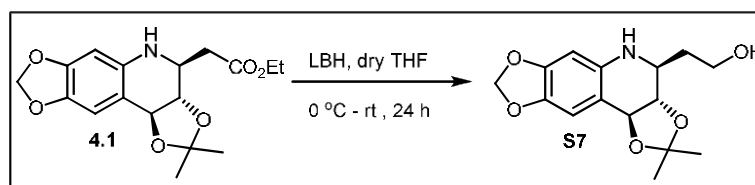
Molecular Formula: $C_{25}H_{34}N_2O_6$; R_f (solvent system): 0.48 (1:1, hexane/ethyl acetate); Yield: 50%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.64 (s, 1H), 6.47 (s, 1H), 5.95 (d, $J = 5.70$ Hz, 1H), 5.86 (s, 1H), 5.82 (s, 1H), 5.74 (d, $J = 6.89$ Hz, 1H), 4.66-4.59 (m, 1H), 4.49 (d, $J = 9.14$ Hz, 1H), 4.01 (t, $J = 9.96$ Hz, 1H), 3.89 (ddd, $J = 22.76, 12.95, 6.61$ Hz, 3H), 3.54 (d, $J = 5.40$ Hz, 1H), 3.46 (t, $J = 9.54$ Hz, 1H), 3.01 (s, 1H), 2.88 (d, $J = 14.60$ Hz, 1H), 2.47 (s, 1H), 2.30 (dd, $J = 14.63, 10.06$ Hz, 1H), 1.85 (dd, $J = 6.08, 4.28$ Hz, 1H), 1.72-1.67 (m, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.17 (m, 2H), 0.92 (dd, $J = 6.96, 2.05$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 172.76, 147.61, 146.40, 139.99, 138.05, 116.88, 112.76, 107.48, 103.33, 100.68, 98.95, 80.26, 70.24, 58.17, 54.18, 50.01, 43.33, 36.43, 29.67, 29.64, 27.12, 27.06, 25.89, 20.42, 14.99, 11.44; LRMS: (ES+) $m/z = 459.0$ (M+1).

(3aS,3bS,7S,19bS,E/Z)-7-benzyl-2,2-dimethyl-3b,4,6,7,8,10,13,19b-octahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,4,8] oxadiazacyclododeca[8,7-a]quinolin-5(3aH)-one (3.4d);



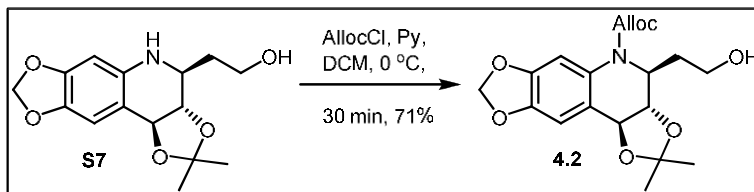
Molecular Formula: $C_{28}H_{32}N_2O_6$; R_f (solvent system): 0.48 (1:1, hexane/ethyl acetate); Yield: 50%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.33-7.18 (m, 6H), 6.47 (s, 1H), 6.65 (s, 1H), 5.89 (t, $J = 4.83$ Hz, 2H), 5.86 (d, $J = 1.33$ Hz, 1H), 5.82 (d, $J = 1.33$ Hz, 1H), 4.66 (td, $J = 8.92, 6.72$ Hz, 1H), 4.48 (d, $J = 8.50$ Hz, 1H), 4.22 (ddd, $J = 11.58, 7.51, 4.09$ Hz, 1H), 3.97 (t, $J = 9.75$ Hz, 1H), 3.75 (dq, $J = 11.19, 6.66$ Hz, 2H), 3.54 (ddd, $J = 15.38, 10.89, 5.98$ Hz, 1H), 3.44 (t, $J = 9.53$ Hz, 1H), 3.04 (dd, $J = 13.70, 5.38$ Hz, 1H), 2.96-2.79 (m, 4H), 2.57-2.47 (m, 1H), 2.30 (dd, $J = 14.89, 10.15$ Hz, 1H), 1.81 (dt, $J = 12.49, 12.21, 6.29$ Hz, 2H), 1.56 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ ppm: 172.55, 147.61, 145.94, 140.10, 138.09, 137.07, 129.29, 128.57, 126.72, 117.01, 112.82, 108.71, 103.33, 100.70, 99.04, 80.17, 70.67, 57.93, 51.25, 50.51, 43.13, 37.57, 27.10, 27.06, 20.33; LRMS: (ES+) $m/z = 492.9$ (M+1).

V. Synthesis of 14-membered macrocycles [4.5(a-d)] & [4.6(a-b)]

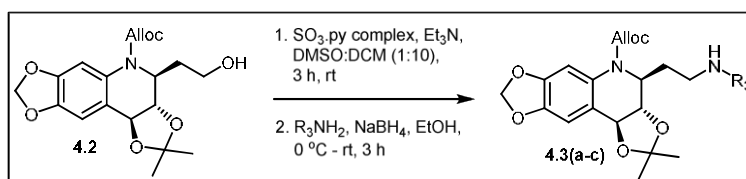


To a solution of **4.1** (500 mg, 1.49 mmol) in anhydrous THF (50 mL) was added LBH (81.13 mg, 3.72 mmol) at 0 °C. After stirring the mixture for an additional 24 h at room temperature, the reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 , filtered, and concentrated. Purification by flash chromatography on silica gel (4:1 hexane/ethylacetate) afforded the product **S7** as a white solid (402.3 mg, 92%); Molecular Name: 2-((3aS,4S,10bS)-2,2-dimethyl-3a,4,5,10b-tetrahydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinolin-4-yl)ethanol; Molecular Formula: $C_{17}H_{21}NO_5$; R_f (solvent system): 0.34 (hexane/ethylacetate 1:1); 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.68 (s, 1H), 6.10 (s, 1H), 5.81 (d, $J = 4.53$ Hz, 2H), 4.64 (d, $J = 8.61$ Hz, 1H), 3.87

(dd, $J = 6.59, 3.74$ Hz, 3H), 3.71 (td, $J = 10.54, 6.33$ Hz, 1H), 3.58 (t, $J = 9.33$ Hz, 1H), 2.61 (s, 1H), 1.99-1.91 (m, 1H), 1.83 (ddd, $J = 14.11, 10.45, 6.97$ Hz, 1H), 1.55 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 147.4, 139.2, 137.1, 113.3, 111.6, 104.3, 100.5, 95.5, 80.2, 77.3, 60.7, 55.4, 37.7, 27.1, 27.0; LRMS:MS(ES+) $m/z = 294.1$ ($M + 1$).



To a solution of **S7** (92 mg, 0.243 mmol) anhydrous dichloromethane (15 mL) at 0 °C was added pyridine (25 μL) and allylchloroformate (33 μL). After stirring for 20 min at 0 °C, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane, and the combined organic layer was dried with anhydrous sodium sulfate, filtered, and then concentrated in vacuo. The residue was purified by flash chromatography over silica gel with 4:1 hexane and ethyl acetate giving 84 mg(71%) of the product **4.2** as a yellow oil; Molecular Name: (3aS,4S,10bS)-allyl 4-(2-hydroxyethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate; Molecular Formula: $\text{C}_{19}\text{H}_{23}\text{NO}_7$; R_f (solvent system): 0.51(hexane/ethyl acetate,1:1); ^1H NMR (400 MHz, CDCl_3) δ ppm: 6.84 (d, $J = 22.30$ Hz, 2H), 5.96 (t, $J = 10.37$ Hz, 3H), 5.33-5.20 (m, 2H), 4.74-4.55 (m, 2H), 4.40 (dd, $J = 17.56, 8.18$ Hz, 2H), 3.74 (s, 2H), 3.26 (t, $J = 8.78$ Hz, 1H), 1.88 (d, $J = 0.95$ Hz, 2H), 1.63 (s, 1H), 1.55 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 146.2, 145.6, 132.1, 127.1, 125.2, 118.1, 114.0, 108.3, 101.8, 101.3, 84.4, 76.0, 66.9, 58.8, 54.7, 38.1, 29.6, 27.0, 26.9; LRMS:MS(ES+) $m/z = 378.1$ ($M + 1$).

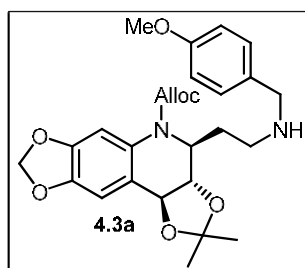


1. To a solution of the **4.2** (1 eq) in DCM:DMSO (1:10) at 0 °C under nitrogen was added triethylamine (6 eq) and sulfur trioxide pyridine complex (6 eq). After stirring at room temperature for 3 h, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with dichloromethane. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and then concentrated

in vacuo afforded aldehyde, which was subjected to reductive amination without further purification.

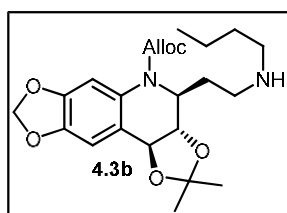
- To a solution of aldehyde in the ethanol was added primary amine (R_3NH_2) (1 eq) at room temperature and stirred for 3 h. Sodium boro hydride was added at 0 °C and stirred for 10min; the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted thrice with ethyl acetate. The combined organic layer was dried with anhydrous sodium sulfate, filtered, and then concentrated in vacuo. Purification of the residue by flash chromatography over silica gel with 1:1 hexane and ethyl acetate afforded secondary amine **4.3(a-c)**.

(3aS,4S,10bS)-allyl 4-(2-(4-methoxybenzylamino)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (4.3a);



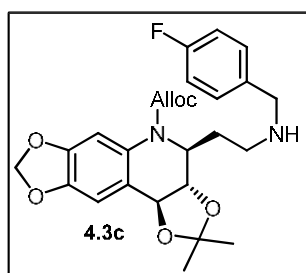
Molecular Formula: $C_{27}H_{32}N_2O_7$; R_f (solvent system): 0.2 (hexane/ ethyl acetate, 1:1); Yield: 55%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.21 (d, J = 8.38 Hz, 2H), 6.84 (dd, J = 22.78, 14.29 Hz, 4H), 5.96 (d, J = 8.37 Hz, 3H), 5.22 (d, J = 10.53 Hz, 2H), 4.67 (d, J = 5.32 Hz, 2H), 4.37 (d, J = 9.08 Hz, 1H), 4.35-4.26 (m, 1H), 3.79 (s, 3H), 3.71 (s, 2H), 3.25 (t, J = 8.79 Hz, 1H), 2.72 (t, J = 7.03 Hz, 2H), 2.14-2.04 (m, 1H), 1.83-1.72 (m, 2H), 1.54 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 158.6, 154.5, 146.2, 145.4, 132.3, 132.1, 129.3, 113.8, 113.7, 108.1, 101.8, 101.3, 76.1, 66.8, 55.4, 55.2, 53.1, 52.4, 44.8, 34.8, 31.9, 29.7, 29.6, 27.1, 27.0, 22.7, 14.1; LRMS:MS(ES+) m/z = 497.0 ($M+1$).

(3aS,4S,10bS)-allyl 4-(2-(butylamino)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (4.3b);

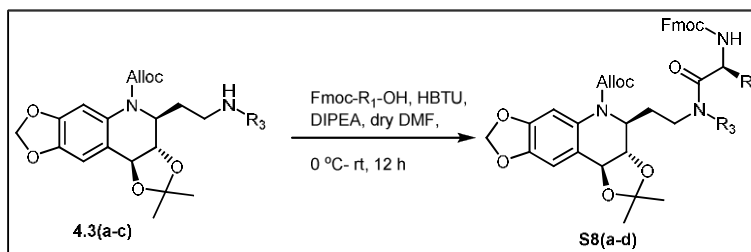


Molecular Formula: $C_{27}H_{32}N_2O_7$; R_f (solvent system): 0.2 (hexane/ ethyl acetate, 1:1); Yield: 50%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 6.80 (s, 1H), 6.65 (s, 1H), 5.95 (m, 3H), 5.86-5.77 (m, 1H), 5.65-5.58 (m, 1H), 5.37-5.31 (m, 1H), 5.26-5.22 (m, 1H), 4.65 (m, 2H), 4.39-4.35 (m, 1H), 3.24 (m, 1H), 2.71-2.68 (m, 1H), 2.57 (m, 4H), 1.62 (s, 3H), 1.55 (s, 3H), 1.34 (m, 4H), 0.91 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 154.5, 146.2, 145.4, 135.0, 132.3, 126.8, 117.7, 113.8, 109.3, 108.1, 101.3, 76.1, 66.7, 55.4, 50.9, 49.5, 49.1, 45.6, 32.2, 29.7, 27.0, 20.4, 14.0; LRMS:MS(ES+) m/z = 433.1 (M + 1).

(3aS,4S,10bS)-allyl 4-(2-(4-fluorobenzylamino)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (4.3c);



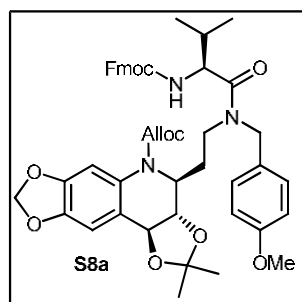
Molecular Formula: $C_{26}H_{29}FN_2O_6$; R_f (solvent system): 0.2 (hexane/ ethyl acetate, 1:1); Yield: 55%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.26 (t, J = 6.53 Hz, 2H), 6.98 (t, J = 8.53 Hz, 3H), 6.79 (s, 1H), 5.93 (dd, J = 15.60, 6.12 Hz, 3H), 5.38-5.18 (m, 2H), 4.74-4.55 (m, 2H), 4.34 (dd, J = 29.42, 6.84 Hz, 2H), 3.80-3.67 (m, 2H), 3.24 (s, 1H), 2.72 (t, J = 6.76 Hz, 2H), 2.15-2.01 (m, 1H), 1.79 (dd, J = 22.79, 15.49 Hz, 2H), 1.53 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 163.1, 160.6, 154.5, 146.2, 145.4, 135.9, 135.9, 132.3, 129.7, 129.6, 125.0, 118.0, 114.9, 113.8, 108.1, 101.8, 101.3, 84.0, 76.1, 66.8, 55.3, 53.0, 44.9, 34.9, 29.7, 27.0, 27.0, 22.7; LRMS:MS(ES+) m/z = 485.4 (M + 1).



To a solution of **4.3(a-b)** (1 eq) in anhydrous DMF at 0 °C was added Fmoc- R_1 -OH (1.2 eq), HBTU (1.5 eq) and DIPEA (3 eq) and allowed stirred for 12 h. The reaction mixture was quenched with sodium bicarbonate solution, concentrated, and extracted thrice with ethyl acetate. Combined organic layer was washed with brine, dried over anhydrous sodium

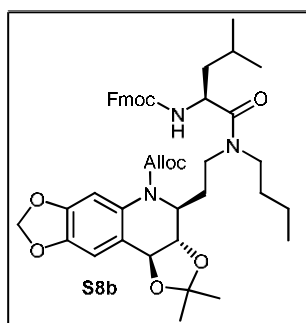
sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (1:4 ethyl acetate/hexanes) to give the compound **S8(a-d)** as a light yellow oil.

(3aS,4S,10bS)-allyl 4-(2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-N-(4-methoxybenzyl)-3-methylbutanamido)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (S8a);



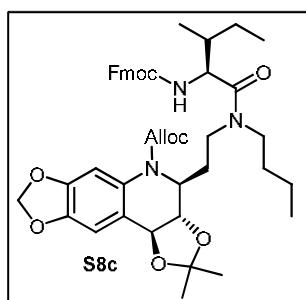
Molecular Formula: $C_{47}H_{51}N_3O_{10}$; R_f (solvent system): 0.4 (hexane/ethyl acetate, 7:3); Yield: 70%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.76 (d, $J = 7.53$ Hz, 2H), 7.65-7.58 (m, 2H), 7.39 (s, 2H), 7.35-7.27 (m, 2H), 7.14 (s, 2H), 6.83 (s, 2H), 6.77 (s, 1H), 5.93 (d, $J = 1.43$ Hz, 2H), 5.91-5.84 (m, 1H), 5.65-5.57 (m, 1H), 5.33-5.15 (m, 2H), 4.71-4.49 (m, 4H), 4.45-4.29 (m, 3H), 4.27-4.14 (m, 2H), 3.78 (s, 3H), 3.44-3.34 (m, 1H), 3.25-3.09 (m, 1H), 2.80 (s, 2H), 2.09-1.95 (m, 2H), 1.61 (m, 1H), 1.52 (d, $J = 2.80$ Hz, 3H), 1.46 (d, $J = 6.15$ Hz, 3H), 0.94-0.88 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 171.9, 171.9, 159.3, 159.0, 156.4, 156.2, 154.4, 146.3, 146.2, 145.5, 145.5, 144.0, 144.0, 143.9, 143.9, 141.3, 132.2, 129.6, 129.5, 129.1, 128.5, 128.1, 127.7, 127.6, 127.4, 127.1, 127.0, 125.2, 125.2, 125.1, 124.9, 124.8, 119.9, 114.3, 114.3, 114.2, 114.0, 113.9, 108.1, 101.8, 101.7, 101.3, 83.9, 67.0, 67.0, 66.8, 55.9, 55.2, 55.1, 54.8, 47.2, 38.6, 31.9, 31.8, 31.7, 29.7, 29.6, 29.3, 27.0, 27.0, 26.9, 22.7, 19.9, 19.6, 17.4, 17.2, 14.1; LRMS:MS(ES+) $m/z = 818.6$ (M + 1).

(3aS,4S,10bS)-allyl 4-(2-(((9H-fluoren-9-yl)methoxy) carbonylamino)-N-butyl-4-methylpentanamido)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (S8b);



Molecular Formula: $C_{44}H_{53}N_3O_9$; R_f (solvent system): 0.4 (hexane/ethyl acetate, 7:3); Yield: 65%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.75 (m, 2H), 7.60 (m, 2H), 7.38 (m, 3H), 7.31 (m, 3H), 5.95 (m, 3H), 5.60-5.50 (m, 1H), 5.39-5.28 (m, 1H), 5.26-5.18 (m, 1H), 4.64 (m, 2H), 4.57-4.47 (m, 1H), 4.34-4.27 (m, 1H), 4.24-4.20 (m, 1H), 4.45-4.38 (m, 1H), 3.98-3.79 (m, 2H), 3.31-3.06 (m, 2H), 1.62-1.54 (m, 6H), 1.49 (m, 4H), 0.93 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 172.2, 156.1, 154.5, 147.3, 146.3, 143.8, 141.3, 137.6, 132.5, 132.2, 127.7, 127.0, 125.2, 119.9, 114.0, 113.0, 112.0, 109.6, 104.2, 101.8, 101.3, 100.4, 96.2, 80.3, 76.1, 67.0, 55.2, 52.6, 49.3, 49.2, 47.2, 43.1, 31.3, 29.7, 27.0, 24.6, 23.5, 22.7, 21.6, 20.0, 13.7; LRMS:MS(ES+) m/z = 767.6 (M + 1).

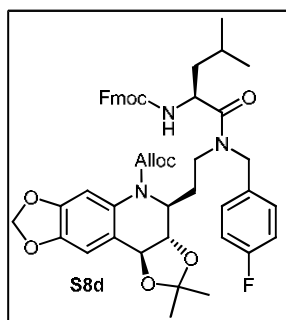
(3aS,4S,10bS)-allyl-4-(2-((2S,3R)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-N-butyl-3-methylpentanamido)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (S8c);



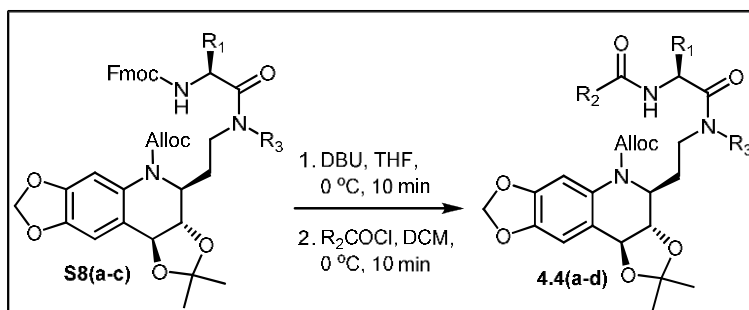
Molecular Formula: $C_{44}H_{53}N_3O_9$; R_f (solvent system): 0.4 (hexane/ethyl acetate, 7:3); Yield: 65%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.77-7.73 (m, 2H), 7.63-7.58 (m, 2H), 7.38 (m, 3H), 7.30 (m, 3H), 5.96 (m, 3H), 5.59-5.46 (m, 1H), 5.26-5.15 (m, 1H), 4.68-4.59 (m, 2H), 4.53-4.37 (m, 3H), 4.33-4.17 (m, 3H), 4.17-4.06 (m, 1H), 3.72-3.02 (m, 4H), 1.67 (m, 6H), 1.60-1.50 (m, 6H), 1.36-1.30 (m, 2H), 0.95-0.86 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.9, 156.3, 156.1, 143.8, 141.3, 132.5, 127.7, 127.0, 125.2, 119.9, 117.7, 109.6, 101.8, 101.5, 101.3, 76.1, 66.9, 66.0, 65.7, 55.1, 54.9, 54.9, 48.9, 47.2, 38.5, 38.3, 29.7, 29.4,

29.3, 27.1, 27.0, 26.7, 20.4, 20.1, 19.9, 16.0, 15.9, 15.8, 13.7, 11.3; LRMS:MS (ES+) m/z = 767.5 (M + 1).

(3a*S*,4*S*,10b*S*)-allyl 4-(2-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-*N*-(4-fluorobenzyl)-4-methylpentanamido)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-*c*:4',5'-*g*]quinoline-5(10b*H*)-carboxylate (S8d);



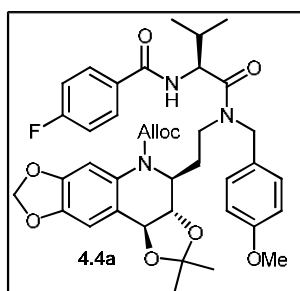
Molecular Formula: $C_{47}H_{50}FN_3O_9$; R_f (solvent system): 0.4 (hexane/ethyl acetate, 7:3); Yield: 68%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.76 (d, J = 7.18 Hz, 1H), 7.39 (t, J = 6.88 Hz, 2H), 7.35-7.08 (m, 5H), 7.08-6.90 (m, 3H), 6.77 (d, J = 2.35 Hz, 1H), 7.59 (t, J = 6.62 Hz, 2H), 5.92 (t, J = 18.91 Hz, 3H), 5.57-5.42 (m, 1H), 5.22 (dd, J = 21.20, 14.22 Hz, 2H), 5.03-4.80 (m, 1H), 4.76-4.52 (m, 4H), 4.44-4.28 (m, 3H), 4.21 (d, J = 7.78 Hz, 2H), 3.44-3.27 (m, 1H), 3.27-3.10 (m, 1H), 2.13-1.96 (m, 1H), 1.72-1.59 (m, 4H), 1.53 (d, J = 7.91 Hz, 3H), 1.45 (d, J = 8.69 Hz, 3H), 0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.0, 163.4, 161.0, 156.1, 156.1, 154.4, 146.3, 146.2, 145.6, 143.9, 143.8, 141.3, 132.1, 129.8, 128.5, 127.6, 127.0, 125.1, 120.9, 119.9, 115.7, 115.4, 114.3, 114.0, 112.4, 108.1, 101.8, 101.7, 101.3, 84.0, 70.3, 66.9, 54.8, 47.2, 43.0, 34.1, 31.9, 29.7, 27.0, 27.0, 27.0, 24.6, 23.5, 22.7, 21.5, 14.1; LRMS:MS (ES+) m/z = 820.9 (M + 1).



To a solution of **S8(a-c)** (1 eq) in little amount of dry THF at 0 °C was added DBU (2 eq), then stirred for 10min. Dry DCM was added to the reaction mixture followed by acid chloride (R_2COCl) carefully at 0 °C. The reaction mixture was allowed to stir for 10 min. Saturated

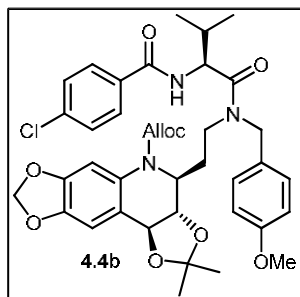
sodium bicarbonate solution was added to the reaction mixture and compound extracted thrice with ethylacetate. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification of the residue by flash chromatography over silica gel with 4:1 hexane and ethyl acetate afforded product **4.4(a-d)** as a light yellow oil.

(3aS,4S,10bS)-allyl-4-(2-((S)-2-(4-fluorobenzamido)-N-(4-methoxybenzyl)-3-methylbutanamido)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (4.4a);

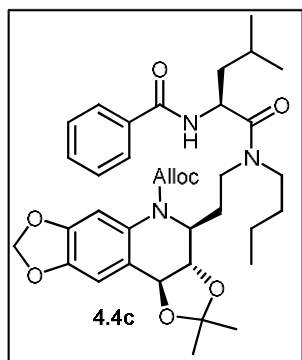


Molecular Formula: $C_{39}H_{44}FN_3O_9$; R_f (solvent system): 0.4 (hexane/ethyl acetate, 7:3); Yield: 55%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.86 (m, 2H), 7.20-7.04 (m, 5H), 6.92-6.75 (m, 3H), 6.00-5.83 (m, 3H), 5.26 (d, $J = 27.80$ Hz, 2H), 5.14-5.01 (m, 1H), 4.64 (d, $J = 22.78$ Hz, 3H), 4.41-4.11 (m, 2H), 3.79 (d, $J = 7.41$ Hz, 3H), 3.39 (s, 1H), 3.25-3.12 (m, 1H), 2.06 (s, 2H), 1.50 (dd, $J = 21.33, 14.38$ Hz, 6H), 0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.8, 159.3, 156.2, 154.4, 146.2, 145.5, 143.9, 143.9, 141.3, 132.2, 129.5, 129.1, 128.5, 127.6, 127.6, 127.0, 127.0, 125.2, 119.9, 114.2, 114.2, 114.0, 113.9, 108.1, 101.7, 101.7, 101.3, 83.9, 76.0, 76.0, 67.0, 66.8, 55.8, 55.2, 55.2, 54.7, 47.2, 37.1, 36.6, 31.9, 29.7, 29.6, 29.3, 28.0, 27.0, 24.7, 22.7, 19.9, 17.3, 17.1, 14.1; LRMS:MS(ES+) $m/z = 718.6$ (M + 1).

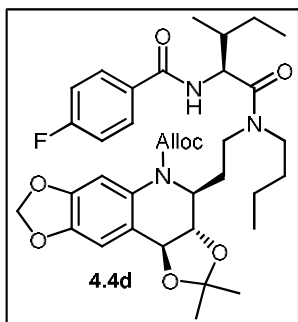
(3aS,4S,10bS)-allyl-4-(2-((S)-2-(4-chlorobenzamido)-N-(4-methoxybenzyl)-3-methylbutanamido)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (4.4b);



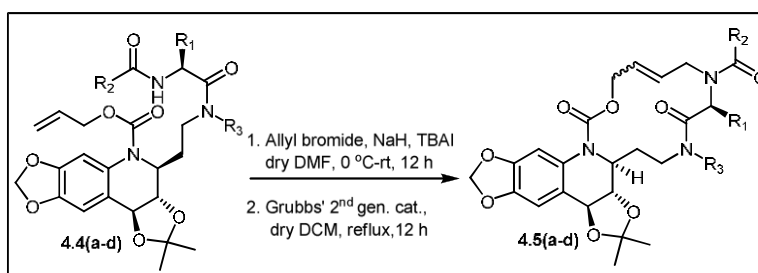
(3aS,4S,10bS)-allyl-4-(2-((S)-2-benzamido-N-butyl-4-methylpentanamido)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (4.4c);



(3aS,4S,10bS)-allyl-4-(2-((2S,3R)-2-benzamido-N-butyl-3-methylpentanamido)ethyl)-2,2-dimethyl-3a,4-dihydrobis[1,3]dioxolo[4,5-c:4',5'-g]quinoline-5(10bH)-carboxylate (4.4d):

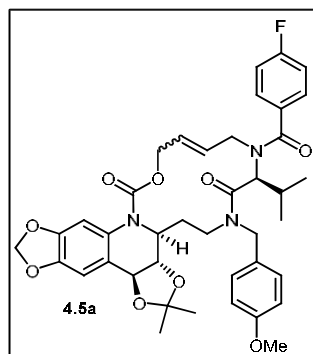


Molecular Formula: $C_{36}H_{46}FN_3O_8$; R_f (solvent system): 0.4 (hexane/ethyl acetate, 7:3); Yield: 58%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 8.17-8.05 (m, 1H), 8.03-7.80 (m, 2H), 7.10 (m, 3H), 5.93 (m, 3H), 5.63-5.39 (m, 1H), 5.37-5.11 (m, 2H), 5.06-4.93 (m, 1H), 4.64 (s, 2H), 4.45-4.07 (m, 2H), 4.05-3.83 (m, 1H), 3.68-3.32 (m, 2H), 3.31-3.07 (m, 1H), 1.98-1.77 (m, 1H), 1.74-1.44 (m, 8H), 1.38 (m, 2H), 1.27 (m, 5H), 0.93 (m, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 172.3, 168.4, 166.0, 164.6, 163.5, 154.5, 132.6, 132.5, 129.7, 128.7, 127.0, 121.0, 119.7, 115.6, 115.3, 114.0, 109.6, 101.5, 76.0, 66.8, 65.7, 53.5, 49.2, 47.6, 38.2, 31.9, 31.4, 29.7, 29.4, 26.9, 26.7, 20.1, 19.9, 15.9, 13.8, 13.7, 11.1; LRMS:MS(ES⁺) m/z = 668.5 ($M+1$).



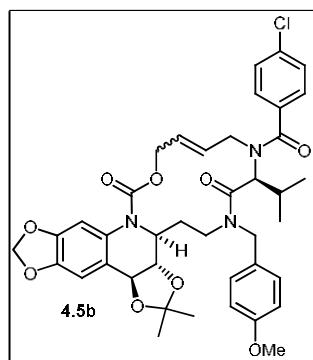
1. To a solution of **4.4(a-d)** (1 eq) in dry DMF added sodium hydride (3 eq) at 0 °C then added allylbromide (5 eq), tetra butyl ammonium iodide (0.5 eq) and stirred for 12 h at room temperature. The reaction mixture was quenched with saturated ammonium chloride and the compound extracted thrice with ethylacetate. The combined organic phase was washed with water, brine and dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification of the residue by flash chromatography over silica gel with 4:1 hexane and ethylacetate afforded allyl product as a light yellow oil.
2. To a solution of above allyl product (1 eq) in dry DCM added Grubbs' 2nd generation catalyst (0.1 eq) under nitrogen atmosphere. The reaction mixture was stirred for 12 h reflux and concentrated which was subjected to flash chromatography over silica gel with 4:1 hexane and ethylacetate afforded cyclised product **4.5(a-d)** as a light yellow oil.

(3aS,3bS,8R,21bS,E/Z)-9-(4-fluorobenzoyl)-8-isopropyl-6-(4-methoxybenzyl)-2,2-dimethyl-3b,4,5,6,9,10,13,21b-octahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,3,7,10]oxatriaza cyclotetradeca[3,4-a] quinoline-7,15(3aH,8H)-dione (4.5a);



Molecular Formula: $C_{40}H_{44}FN_3O_9$; R_f (solvent system): 0.3 (hexane/ethyl acetate, 7:3); Yield: 90%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.39 (dd, $J = 8.41, 5.39$ Hz, 2H), 7.17 (d, $J = 8.47$ Hz, 2H), 7.13-7.04 (m, 3H), 6.91-6.77 (m, 3H), 5.94 (d, $J = 3.44$ Hz, 3H), 5.29 (d, $J = 10.57$ Hz, 1H), 5.24-5.11 (m, 2H), 4.78-4.69 (m, 1H), 4.68-4.60 (m, 1H), 4.53 (d, $J = 8.89$ Hz, 1H), 4.41-4.31 (m, 2H), 4.13-3.98 (m, 2H), 3.89-3.83 (m, 1H), 3.80 (s, 3H), 3.18 (s, 1H), 3.03-2.93 (m, 1H), 2.92-2.81 (m, 1H), 2.61-2.50 (m, 1H), 2.08-1.98 (m, 1H), 1.60 (s, 3H), 1.37 (s, 3H), 0.88 (dd, $J = 8.15, 4.10$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.5, 171.1, 164.4, 161.9, 158.9, 153.3, 146.4, 145.4, 139.2, 132.5, 132.5, 129.5, 128.8, 128.7, 127.6, 127.5, 127.2, 124.3, 115.4, 115.2, 114.0, 114.0, 107.9, 101.7, 101.3, 84.2, 76.1, 63.9, 57.9, 55.7, 55.3, 50.5, 45.9, 43.4, 33.8, 31.9, 29.7, 29.6, 29.3, 27.2, 27.1, 22.7, 20.0, 17.7, 14.1; LRMS:MS(ES+) $m/z = 730.5$ (M + 1).

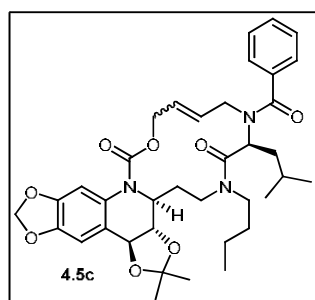
(3aS,3bS,8R,21bS,E/Z)-9-(4-chlorobenzoyl)-8-isopropyl-6-(4-methoxybenzyl)-2,2-dimethyl-3b,4,5,6,9,10,13,21b-octahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,3,7,10]oxatriaza cyclotetradeca[3,4-a] quinoline-7,15(3aH,8H)-dione (4.5b);



Molecular Formula: $C_{40}H_{44}ClN_3O_9$; R_f (solvent system): 0.3 (hexane/ethyl acetate, 7:3); Yield: 83%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.39 (d, $J = 8.06$ Hz, 2H), 7.33 (d, $J = 8.09$ Hz, 2H), 7.17 (d, $J = 8.17$ Hz, 2H), 6.88 (d, $J = 8.21$ Hz, 2H), 7.05 (s, 1H), 6.79 (s, 1H),

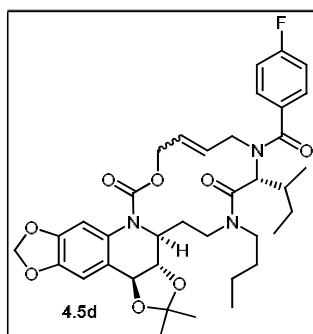
5.91-5.82 (m, 1H), 5.94 (d, $J = 3.44$ Hz, 2H), 5.32-5.10 (m, 3H), 4.79-4.70 (m, 1H), 4.67 (s, 1H), 4.54 (d, $J = 8.93$ Hz, 1H), 4.38 (d, $J = 12.35$ Hz, 2H), 4.14-3.98 (m, 2H), 3.81 (s, 4H), 3.19 (s, 1H), 3.04-2.93 (m, 1H), 2.93-2.80 (m, 1H), 2.62-2.50 (m, 1H), 2.09-1.98 (m, 1H), 1.37 (s, 3H), 1.60 (s, 3H), 0.89 (dd, $J = 12.51, 6.44$ Hz, 6H); ^{13}C NMR (400 MHz, CDCl_3) δ ppm: 171.362, 171.1, 158.9, 153.3, 146.4, 145.4, 135.5, 134.8, 129.5, 128.5, 128.0, 127.6, 124.3, 114.0, 114.0, 107.9, 101.7, 101.7, 101.3, 84.2, 64.0, 57.8, 57.8, 55.7, 50.5, 45.8, 43.4, 34.2, 31.9, 29.7, 27.2, 22.7, 20.0, 17.7, 14.1; LRMS:MS(ES+) $m/z = 747.1$ ($M + 1$).

(3aS,3bS,8R,21bS,E/Z)-9-benzoyl-6-butyl-8-isobutyl-2,2-dimethyl-3b,4,5,6,9,10,13,21b-octahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,3,7,10]oxatriazacyclotetradeca[3,4-a]quinoline-7,15(3aH,8H)-dione (4.5c);

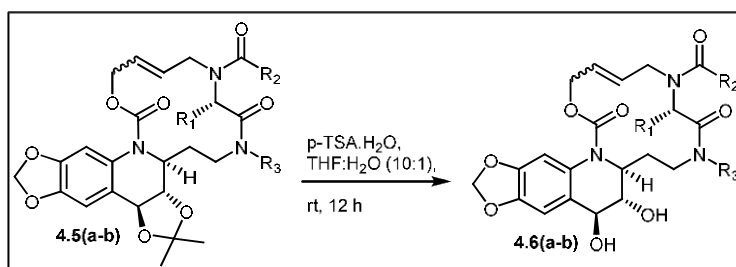


Molecular Formula: $\text{C}_{37}\text{H}_{47}\text{N}_3\text{O}_8$; R_f (solvent system): 0.3 (hexane/ethyl acetate, 7:3); Yield: 53%; ^1H NMR (400 MHz, CDCl_3) δ ppm: 7.42 (m, 5H), 7.17-7.12 (m, 1H), 6.65 (s, 1H), 5.98 (s, 3H), 5.89-5.83 (m, 1H), 5.60-5.46 (m, 2H), 5.28-5.11 (m, 3H), 4.92-4.82 (m, 1H), 4.79-4.61 (m, 2H), 4.41-4.34 (m, 1H), 4.33-4.25 (m, 1H), 3.82-3.65 (m, 3H), 3.49-3.38 (m, 1H), 3.05-2.96 (m, 1H), 2.59-2.47 (m, 1H), 1.88-1.75 (m, 1H), 1.52 (s, 3H), 1.49 (s, 3H), 1.45 (m, 4H), 1.02-0.93 (m, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm: 171.7, 168.8, 154.8, 147.6, 136.4, 134.4, 133.0, 132.4, 129.4, 128.5, 126.3, 126.0, 119.2, 112.3, 111.7, 110.0, 109.4, 102.0, 85.0, 80.2, 64.1, 55.3, 53.4, 49.9, 46.0, 45.2, 43.7, 39.0, 30.5, 29.7, 29.6, 27.2, 27.0, 24.8, 22.9, 22.9, 19.7, 13.9; LRMS:MS(ES+) $m/z = 662.5$ ($M + 1$).

(3aS,3bS,8R,21bS,E/Z)-8-sec-butyl-6-butyl-9-(4-fluorobenzoyl)-2,2-dimethyl-3b,4,5,6,9,10,13,21b-octahydrobis[1,3]dioxolo[4,5-c:4',5'-g][1,3,7,10]oxatriaza cyclotetradeca[3,4-a]quinoline-7,15(3aH,8H)-dione (4.5d);

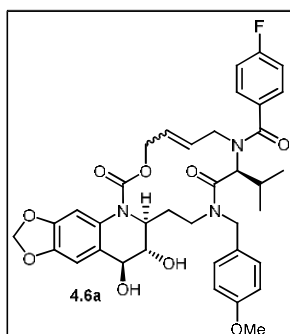


Molecular Formula: $C_{37}H_{46}FN_3O_8$; R_f (solvent system): 0.3 (hexane/ethyl acetate, 7:3); Yield: 46%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.12 (m, 4H), 6.62 (s, 2H), 5.98 (s, 3H), 5.87 (m, 1H), 5.53-5.47 (m, 1H), 5.37-5.30 (m, 1H), 5.17 (m, 3H), 4.87-4.79 (m, 1H), 4.78-4.70 (m, 1H), 4.66-4.60 (m, 1H), 4.41-4.36 (m, 1H), 4.30-4.23 (m, 1H), 3.80-3.70 (m, 2H), 3.57-3.49 (m, 1H), 3.06-2.98 (m, 1H), 2.61-2.52 (m, 1H), 2.35-2.27 (m, 1H), 2.07-1.99 (m, 1H), 1.65-1.61 (m, 1H), 1.50 (m, 6H), 1.41-1.35 (m, 4H), 1.00-0.88 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.4, 168.6, 164.3, 161.8, 154.8, 147.5, 146.8, 134.3, 132.7, 128.2, 128.2, 126.5, 119.2, 115.5, 112.3, 109.4, 102.0, 85.0, 80.2, 64.2, 56.4, 55.3, 45.9, 44.1, 33.6, 31.9, 30.9, 29.7, 29.3, 27.2, 23.8, 22.7, 19.8, 15.9, 14.1, 13.9, 11.0; LRMS:MS(ES⁺) m/z = 680.6 (M + 1).



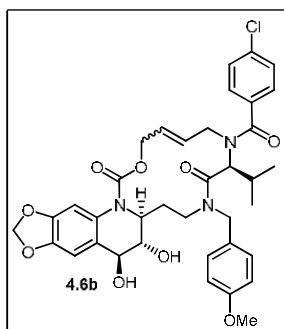
To a solution of **4.5(a-b)** in THF:H₂O (10:1) added p-toluene sulfonic acid monohydrate (5 eq) allowed to stir for 12 h at room temperature. Saturated sodium bicarbonate was added to the reaction mixture and compound extracted twice with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. Purification of the residue by flash chromatography over silica gel with 1:1 hexane and ethyl acetate afforded product **5.1(a-b)** as a light yellow oil.

(8S,12aS,13S,14S,E/Z)-7-(4-fluorobenzoyl)-13,14-dihydroxy-8-isopropyl-10-(4-methoxybenzyl)-7,8,10,11,12,12a,13,14-octahydro-[1,3]dioxolo[4,5-g][1,3,7,10]oxatriazacyclo tetradeca[3,4-a]quinoline-1,9(3H,6H)-dione (4.6a);



Molecular Formula: $C_{37}H_{40}FN_3O_9$; R_f (solvent system): 0.2 (hexane/ethyl acetate, 1:1); Yield: 74%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.36 (dd, $J = 8.46, 5.33$ Hz, 2H), 7.15-7.06 (m, 4H), 7.00 (s, 1H), 6.86 (d, $J = 8.60$ Hz, 2H), 6.77 (s, 1H), 5.96-5.91 (m, 2H), 5.88-5.78 (m, 1H), 5.19 (d, $J = 10.59$ Hz, 1H), 5.10 (d, $J = 16.81$ Hz, 2H), 4.87 (s, 2H), 4.28 (dd, $J = 10.59, 5.98$ Hz, 3H), 4.14-3.95 (m, 2H), 3.87-3.80 (m, 1H), 3.78 (s, 3H), 3.22-3.16 (m, 1H), 3.00-2.90 (m, 1H), 2.63-2.45 (m, 2H), 2.04 (s, 1H), 1.40 (s, 2H), 0.87 (dd, $J = 13.62, 11.03$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 171.6, 171.4, 164.4, 161.9, 158.9, 153.2, 146.6, 145.6, 132.5, 132.5, 129.6, 128.8, 128.1, 127.4, 126.8, 126.2, 124.9, 115.5, 115.3, 114.2, 106.4, 102.9, 101.4, 78.7, 71.2, 63.7, 58.1, 57.4, 55.3, 50.5, 46.0, 43.8, 33.6, 31.9, 29.7, 29.7, 29.6, 29.4, 27.3, 22.7, 20.0, 17.8, 14.1; LRMS:MS(ES+) $m/z = 690.6$ (M + 1).

(8S,12aS,13S,14S,E/Z)-7-(4-chlorobenzoyl)-13,14-dihydroxy-8-isopropyl-10-(4-methoxybenzyl)-7,8,10,11,12,12a,13,14-octahydro-[1,3]dioxolo[4,5-g][1,3,7,10]oxatriazacyclopentadeca[3,4-a]quinoline-1,9(3H,6H)-dione (4.6b);



Molecular Formula: $C_{37}H_{40}ClN_3O_9$; R_f (solvent system): 0.2 (hexane/ethyl acetate, 1:1); Yield: 70%; 1H NMR (400 MHz, $CDCl_3$) δ ppm: 7.38 (d, $J = 8.33$ Hz, 2H), 7.30 (d, $J = 8.34$ Hz, 2H), 7.13 (d, $J = 8.54$ Hz, 2H), 7.02 (s, 1H), 6.87 (d, $J = 8.54$ Hz, 2H), 6.79 (s, 1H), 5.94 (d, $J = 7.28$ Hz, 2H), 5.88-5.77 (m, 1H), 5.15 (dd, $J = 34.77, 13.72$ Hz, 3H), 4.87 (s, 2H), 4.37-4.24 (m, 3H), 4.14-4.05 (m, 1H), 4.03-3.95 (m, 1H), 3.79 (s, 4H), 3.22 (d, $J = 3.32$ Hz, 1H), 3.02-2.93 (m, 1H), 2.65-2.49 (m, 2H), 2.09-2.00 (m, 1H), 1.42 (d, $J = 7.15$ Hz, 2H), 0.86 (dd, $J = 13.82, 9.47$ Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm: 171.2, 158.8, 153.0, 146.6, 145.5, 135.4, 134.8, 129.6, 128.4, 127.9, 127.3, 126.7, 126.0, 114.1, 106.4, 102.8,

102.8, 101.3, 78.7, 71.2, 63.6, 57.3, 55.2, 45.9, 31.9, 29.7, 29.6, 27.3, 22.7, 20.0, 17.7, 14.1;
LRMS:MS(ES+) $m/z = 707.0$ (M +1).

VI. Zebrafish Screen

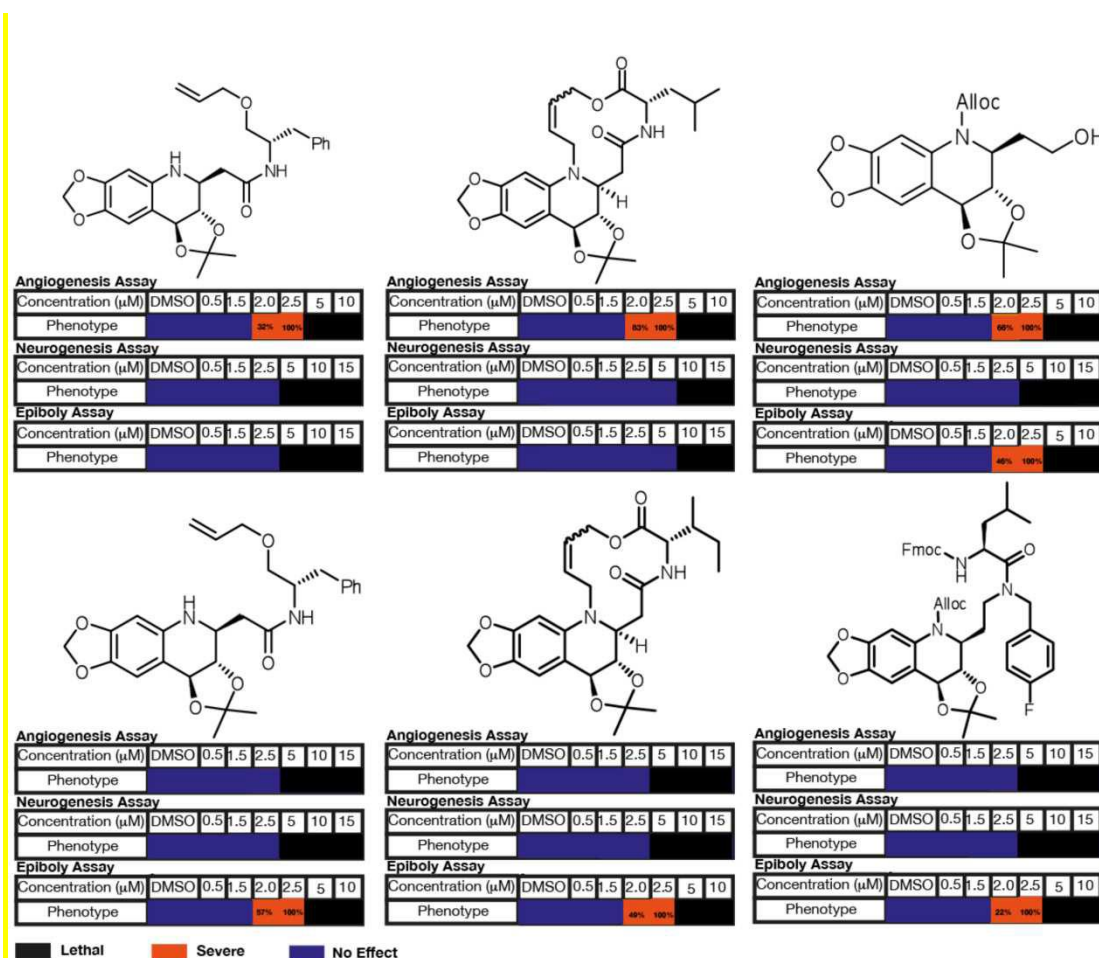
Zebrafish husbandry

Animals were maintained separately under 14/10-hour light/dark cycle and embryos were obtained by natural mating and staged according to Kimmel et. al (1). Zebrafish embryos of stages older than 24 hpf were treated with 0.03% PTU (N-Phenylthiourea) when needed to inhibit pigment formation. Transgenic line Tg (fli:EGFP) was used to assess effects on angiogenesis, Islet1:GFP was used to assess trunk neurogenesis and axonal growth and AB wild type strain was used for studying epiboly effects of the compounds.

Zebrafish embryo collection and Small molecule Screening

Zebrafish embryos for small molecule screening experiments were collected via pair wise matings, cleaned and incubated in PTU treated E3 water at 28.3 °C. One to four cell stage embryos were then distributed into 96 well clear bottom plate (Corning). The compound exposure was done in 96 well plate (Corning) and three embryos were taken in each well contain 200µl of (0.5 to 15µM) compound in PTU treated egg water. The 96 well plates were incubated at 28.3 °C and the embryos were allowed to grow for 10 hpf to assess the effect on epiboly or up to 36 hpf to assess the effect on angiogenesis and trunk neurons. Phenotypes were scored using a Zeiss Axiovert 200 inverted microscope equipped with a cooled CCD camera. Photographs were processed and assembled using Photoshop software.

We exposed a total of 30 embryos per compound producing defects in angiogenesis and early embryo developmental defects. We then quantified the number of embryos exhibiting severe defects in each treatment. Embryos at 2.5 µM completely exhibited the severe phenotype, this percentage dropped drastically when the concentration was slightly lowered.



Additional Materials and Methods:

The compounds producing phenotype (Angiogenesis and Early Developmental Defect) in zebrafish were taken for further analyses. A total of 10 embryos per well (n= 3X10 embryos (30 embryos) for each compound) in a 6 well plate were exposed to either 1.5, 2.0 or 2.5 M of the hit compound and the number of embryos producing the effect were visually quantified and represented in percentage. Compounds at 1.5 M concentration did not produce any effect (100% no effect), however at 2.0 M some of the embryos did exhibit severe effect of the compound.

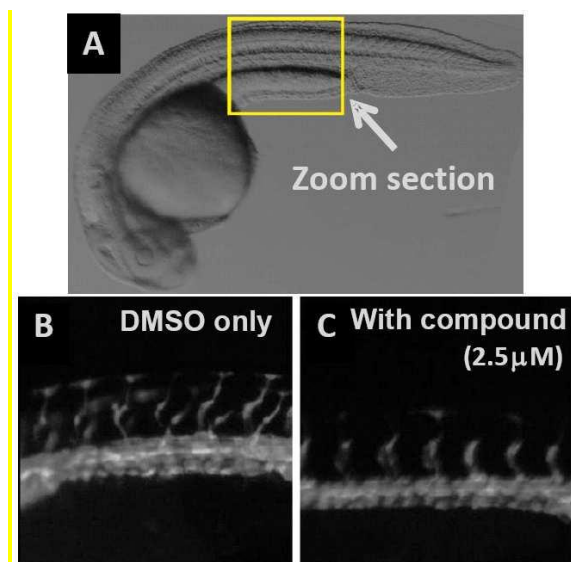
Phenotypic evaluation and classification was done manually looking at the embryos after compound exposure. Three embryos were taken per concentration of each compound.

Transgenic Fli and Islet GFP (Lawson, N.D., Weinstein, B.M., 2002. In vivo imaging of embryonic vascular development using transgenic zebrafish. *Dev. Biol.* 248, 307–318.

FOR FLI:EGFP. Higashijima S (2008) Transgenic zebrafish expressing fluorescent proteins in central nervous system neurons. *Dev Growth Differ* 50:407-413.

FOR ISLET GFP. Uemura O, *et al.* (2005) Comparative functional genomics revealed

conservation and diversification of three enhancers of the *isl1* gene for motor and sensory neuron-specific expression. *Dev Biol* 278:587-606 (FOR ISLET GFP) was used for evaluating the effect on blood vessels and neurons.



(note – the figures are shown with compound **2.5b**)

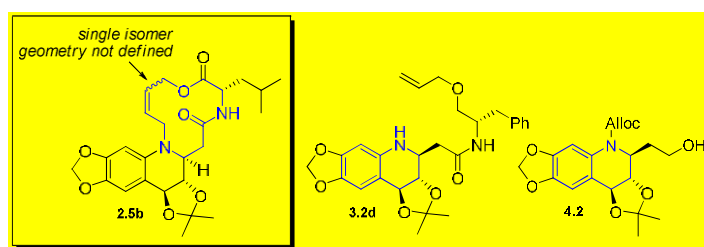
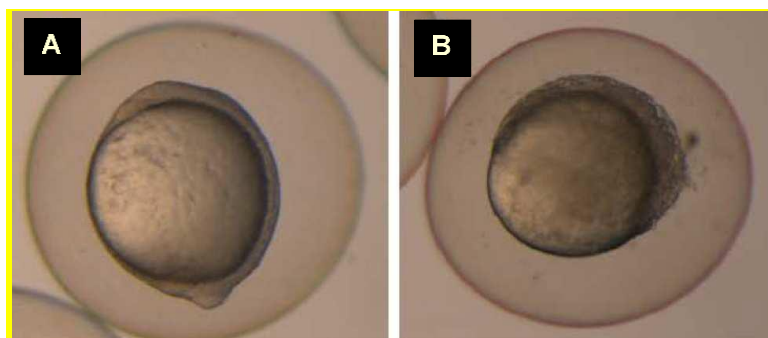


Figure 1: Zebrafish screen for angiogenesis: (A) zoom section of wild-type or vehicle treated embryo, and (B and C) zoom sections after treatment with compound **2.5b**. One macrocyclic derivative (**2.5b**) and two tetrahydroquinoline-based compounds (**3.2d** and **4.2**) showed complete inhibition at 2.5 M.



(note: the figures are shown with compound **2.5c**)

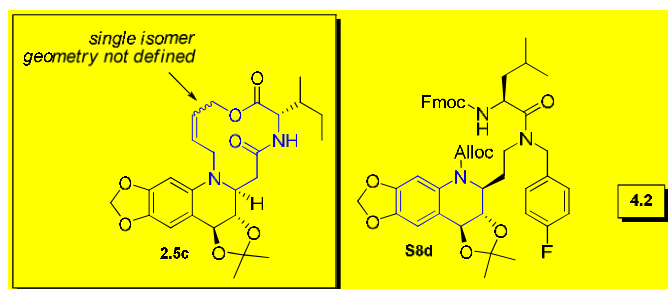


Figure 2: Zebrafish screen for an early embryo development: **(A)** DMSO exposed embryos at 10 hpf of development, **(B)** small molecule **2.5c** exposed embryos causing a delay in epiboly. One macrocyclic derivative (**2.5c**), and two tetrahydroquinoline-based compounds (**S8d** and **4.2**) exhibited the complete inhibition of an early embryo development at 2.5 μ M.

1. Kimmel CB, Ballard WW, Kimmel SR, Ullmann B, Schilling TF. Stages of embryonic development of the zebrafish. Dev Dyn. 1995;203(3):253-310.