Supplemental Table S1 and Chemical Methods
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Supplemental Table S1. Physical properties of Dimeric Quinacrine Inhibitors

COMPOUND	MW	PKA	CLOGP	TPSA	NROTB	LINKER ATOMS
DQ 221	600.54	7.996	10.3455	70.48	10	7
DQ 330	614.571	9.02	10.3715	79.27	12	9
DQ 331	628.598	9.07	10.9955	70.48	12	9
DQ 340	628.598	9.43	10.265	79.27	13	10
DQ 341	642.625	9.383	10.8445	70.48	13	10
DQ 440	642.625	9.74	10.1575	79.27	14	11
DQ 441	656.652	9.693	10.6935	70.48	14	11
DQ 550	670.679	10.009	11.2155	79.27	16	13
DQ 551	684.706	9.963	11.7515	70.48	16	13
DQ 660	698.733	10.229	12.2735	79.27	18	15
DQ 661	712.76	10.182	12.8095	70.48	18	15
DQ 770	726.787	10.241	13.3315	79.27	20	17
DQ 771	740.814	10.195	13.8675	70.48	20	17
DQ 880	754.841	10.293	14.3895	79.27	22	19
DQ 881	768.868	10.246	14.9255	70.48	22	19
DQ 11110	839.003	10.302	17.5635	79.27	28	25
DQ 11111	853.03	10.256	18.0995	70.48	28	25

** Calculated with ChemBio Draw Ultra 2015

General Chemical Methods
Solvents used for extraction and purification were HPLC grade from Fisher Scientific. Unless otherwise indicated, all reactions were run under an inert atmosphere of argon. Anhydrous tetrahydrofuran, ethyl ether and toluene were obtained via passage through an activated alumina column. Commercial reagents were used as received. VWR pre-coated silica gel plates (250 μm, 60 F254) were used for analytical TLC. Spots were visualized using 254 nm ultraviolet light with either potassium permanganate or ninhydrin stains as visualizing agents. Chromatographic purifications were performed on Sorbent Technologies silica gel (particle size 32-63 microns). ^{1}H and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively in $CDCl_3$ on a Bruker AM-500 or DRX-500 spectrometer. Chemical shifts are reported relative to internal chloroform (δ = 7.26 for ^{1}H, δ = 77.00 for ^{13}C). Infrared spectra were recorded on a NaCl plate using a Perkin-Elmer 1600 series Fourier transform spectrometer. High-resolution mass spectra were obtained by Dr. Rakesh Kohli at the University of Pennsylvania Mass Spectrometry Service Center on an Autospec high resolution double-focusing electrospray ionization/chemical ionization spectrometer with either DEC 11/73 or OPUS software data system. Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Fluorescence spectroscopy:
Small molecule fluorescent properties were observed on a Tecan M1000 fluorescent plate reader. UV-Vis spectroscopy was collected in triplicate and 420 nm was found to be the average most red shifted absorption across the library of dimeric quinacrines. Emission spectra were collected for each compound at 1 uM solutions, which was confirmed to be in the linear range of fluorescence. Solutions of pH 7.4 and 1 N HCl, were used to interrogate the protonation states of the heterocycles. Emission data was processed with a five point floating average to reduce instrument noise. The data was then normalized to the fluorescence maximum of the library, DQ 661.

4-Bromo-7-chloroquinoline: [1]

At 0 ˚C under an atmosphere of argon, phosphorus tribromide (5.8 mL, 0.079 moles, 1.10 equiv.) was added slowly to a solution of 7-chloro-4-hydroxyquinoline (13.02 g, 0.073 moles, 1.00 equiv.) in anhydrous DMF (150 mL, 0.5 M soln.). The reaction was allowed to warm to room temperature and followed by TLC. Complete consumption of starting material was observed after 90 minutes stirring. The reaction mixture was poured onto ice and the pH was rendered alkaline using solid sodium bicarbonate. This resulted in a white precipitate. The mixture was then filtered and the resulting solid was dried under vacuum affording an off-white solid (17.30 g, 99 %). The material was recrystallized from ethyl acetate to give white needles (12.20 g, 70 %). R_f = 0.70 (hex:EtoAc; 1:1); Mp = 99 – 101 ˚C, EtoAc, IR λ (neat/cm^{-1}) 3853, 3745, 2924, 1836, 1739, 1697, 1647, 1547, 840; m/z (ES) 241.98 (MH^+, 100%), 243.97 (MH^+, 100%); δ_H (500 MHz, $CDCl_3$) 7.61 (1H, dd, *J* = 9.0, 2.0 Hz, ArH), 7.70 (1H, d, *J* = 4.5 Hz, ArH), 8.11-8.15 (2H, m, ArH), 8.68 (1H, d, *J* = 5.0 Hz, ArH) ppm.

2-Chloro-4-methoxyaniline: [2]

A solution of (2-Chloro-4-methoxyphenyl)carbamic acid *tert*-butyl ester (1.99 g, 7.71 mmol, 1.00 equiv.) in DCM (16 mL, 0.5 M) was treated with TFA (6 mL, 77.06 mmol, 10.00 equiv.). The reaction was stirred vigorously at room temperature for 1 hour. TLC analysis revealed that the reaction had reached completion after 30 minutes. Following this the reaction was neutralized via the slow addition of a saturated aqueous solution of $NaHCO_3$ (100 mL). The resulting mixture was extracted with methylene chloride (3 × 25 mL). Combined methylene chloride extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the product as a colorless oil (1.07 g, 88% yield). NMR analysis showed that the material obtained from this work-up was highly pure (≥ 95%) and did not require further purification. R_f = 0.45 (hex:EtOAc; 4:1); IR λ (neat/cm^{-1}) 3389, 2951, 2386, 1601, 1502, 1033; HRMS (ES) calcd for C_7H_9ClNO 158.0373, found 158.036; δ_H (500 MHz, $CDCl_3$) 3.73 (5H, s(br), CH_3, NH), 6,67 – 6.73 (2H, m, ArH), 6.85 (1H, d, *J* = 2.5 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 55.9, 114.3, 114.7, 116.8, 119.9, 136.7, 152.7 ppm.

8-Chloro-6-methoxyquinoline: [2]

A 2-necked rbf was charged with 2-chloro-4-methoxyaniline (1.24 g, 7.89 mmol 1.00 equiv.), methane sulfonic acid (4.1 mL, 63.10 mmol, 8.00 equiv.), nitrobenzene (0.5 mL, 4.97 mmol, 0.63 equiv.) and iron(III)sulfate hydrate (0.10 g, 0.24 mmol, 0.03 equiv.). To this stirred mixture was added glycerol (1.5 mL, 20.11 mmol, 2.55 equiv.) in three equal measures at 3 hour intervals, whilst maintaining the reaction at room temperature. Following the final addition, the reaction was heated to 125 ˚C and heating was maintained for 12 hours. Following this, the reaction mixture was cooled to room temperature and transferred to a conical flask with water (100 mL). The flask was cooled to 0 ˚C and the pH of the reaction mixture was adjusted to 14 using 2 M aqueous NaOH (50 mL). The resulting alkaline mixture was then extracted with diethyl ether (3 × 50 mL). The aqueous mixture was neutralized and further extracted with diethyl ether (50 mL). Combined organic extracts were washed with a saturated solution of ammonium chloride (100 mL), and brine (100 mL), then dried over Na_2SO_4. Filtration followed by solvent evaporation afforded a red oil (1.94 g). Purification via flash column chromatography (hex:EtOAc; 4:1) afforded the product as a white solid (1.01 g, 66% yield). R_f = 0.20 (hex:EtOAc; 4:1); δ_H (500 MHz, $CDCl_3$) 3.94 (3H, s, CH_3), 7.03 (1H, d, *J* = 2.5 Hz, ArH), 7.43 (1H, dd, *J* = 4.0, 8.5 Hz, ArH), 7.55 (1H, d, *J* = 2.5 Hz, ArH), 8.07 (1H, dd, *J* = 1.5, 8.5 Hz, ArH), 8.90(1H, dd, *J* = 1.5, 4.0 Hz, ArH) ppm.

4-Chloro-2-[(4-methoxyphenyl)amino]benzoic acid: [3]

A 2-necked round bottom flask was fitted with a reflux condenser, and charged with *p*-anisidine (5.36 g, 43.50 mmol, 1.00 equiv.), 2,4-dichlorobenzoic acid (12.47 g, 65.30 mmol, 1.50 equiv.), anhydrous potassium carbonate (12.44 g, 90.0 mmol, 2.07 equiv.) and copper powder (1.25 g, 19.6 mmol, 0.45 equiv.). The solid reagents were placed under an atmosphere of argon. Anhydrous DMF (150 mL) was added via cannulation. The resulting reaction was stirred at 130 ˚C for 12 hours. The reaction was cooled to room temperature and water (250 mL) was added. Copper salts precipitated out of solution and were

removed via filtration on celite. The pH of the filtrate was adjusted to 1, which resulted in the precipitation of a solid. This solid was collected via filtration, then dissolved in chloroform (100 mL) and washed with brine (3 × 100 mL). The chloroform solution was dried over Na_2SO_4, filtered and concentrated. The resulting residue was purified via trituration with DCM, yielding the product as light-yellow crystals (6.13 g, 51% yield). R_f = 0.45 (hex:EtOAc; 1:1); Mp = 192 – 193 ˚C, benzene (198 – 201 ˚C); IR λ (neat/cm^{-1}) 3434, 3019, 1653, 1513, 1215, 929; m/z (ES) 278.13 (MH^+, 100%, ^{35}Cl), 280.12 (MH^+, 50%, ^{37}Cl), 276.07 (MH^-, 100%, ^{35}Cl), 278.08 (MH^-, 50%, ^{37}Cl); δ_H (500 MHz, $CDCl_3$) 3.84 (3H, s, CH_3), 6.64 (1H, dd, *J* = 2.0, 8.5 Hz, ArH), 6.88 (1H, d, *J* = 2.0 Hz, ArH), 6.95 (2H, d, *J* = 9.0 Hz, ArH), 7.17 (2H, d, *J* = 9.0 Hz, ArH), 7.91 (1H, d, *J* = 8.5 Hz, ArH), 9.19 (1H, s(br), COOH) ppm.

6,9-Dichloro-2-methoxyacridine: [3]

To solid 4-chloro-2-[(4-methoxyphenyl)amino]benzoic acid (2.79 g, 10.07 mmol, 1.00 equiv.) was added $POCl_3$ (40 mL). The resulting reaction was stirred at 140 ˚C for 3 hours. The reaction was poured onto ice and ammonium hydroxide was added very slowly to bring the pH of the reaction mixture to 11. **NOTE**! Care was taken during this reaction quench not to let the internal temperature of the reaction mixture exceed 10 ˚C. The alkaline mixture was extracted with DCM (3 × 50 mL). Combined DCM extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered then concentrated to give the product as a greenish solid (2.13 g, 76 % yield, purity ≥ 95%). R_f = 0.53 (hex:EtOAc; 4:1); Mp = 160 – 161 ˚C, benzene (lit160 – 163 ˚C); IR λ (neat/cm^{-1}) 3684, 3619, 3019, 1710. 1261, 1213, 1029; m/z (ES) 278.06 (MH^+, 100%, ^{35}Cl × 2), 280.09 (MH^+, 50%, ^{35}Cl, ^{37}Cl), 282.09 (MH^+, 20%, ^{37}Cl × 2); δ_H (500 MHz, $CDCl_3$) 4.04 (3H, s, CH_3), 7.49 – 7.52 (2H, m, ArH).

(2-Chloro-4-hydroxyphenyl)carbamic acid *tert*-butyl ester:

To 4-amino-3-chlorophenol hydrochloride (2.54 g, 14.11 mmol, 1.00 equiv.) in THF and water (3:1; 70 mL, 0.2 M) was added di-*tert*-butyl dicarbonate (3.08 g, 14.11 mmol, 1.00 equiv.) and $NaHCO_3$ (11.76 g, 141.10 mmol, 10 equiv.). The resulting reaction was stirred at rt for 1 hr before a second equivalent of di-*tert*-butyl dicarbonate (3.08 g, 14.11 mmol, 1.00 equiv.) was added. The reaction was stirred for 1 further hr until complete consumption of 4-amino-3-chlorophenol hydrochloride was observed by TLC. The reaction mixture was portioned between water (50 mL) and DCM (50 mL). The layers were separated and the aqueous layer was further extracted with DCM (2 × 50 mL). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give a solid. The material obtained from the work-up was purified via flash column chromatography (hex:EtOAc; 6:1) to give the product as an off-white solid (2.54 g, 74 % yield). R_f = 0.15 (hex:EtOAc; 4:1); Mp = 113 – 115 ˚C; IR λ (neat/cm^{-1}) 3943, 3054, 2987, 1713, 1422, 1264, 896; HRMS (ES) calcd for $C_{11}H_{13}ClNO_3$ 242.0584, found 242.0574; δ_H (500 MHz, $CDCl_3$) 1.52 (9H, s, CH_3), 5.71 (1H, s(br), OH), 6.64 (1H, s(br), NH), 6.65 – 6.67 (1H, dd, *J* = 3.0, 9.0 Hz ArH), 6.83 (1H, d, *J* = 3.0 Hz, ArH), 7.73 (1H, d, *J* = 9.0 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 28.3, 81.0, 114.8, 116.2, 122.6, 124.2, 128.2, 151.9, 153.2 ppm.

(2-Chloro-4-methoxyphenyl)carbamic acid *tert*-butyl ester:

Under argon, a solution of (2-chloro-4-hydroxyphenyl)carbamic acid *tert*-butyl ester (2.52 g, 10.34 mmol, 1.00 equiv.) in anhydrous DMF (15 mL) was treated with anhydrous K_2CO_3 (2.86 g, 20.68 mmol, 2.00 equiv.). Methyl Iodide (1.3 mL, 20.68 mmol, 2.00 equiv.) was added and the reaction was stirred for 90 minutes. The reaction was poured onto water (50 mL) and neutralised via the addition of 1 M aqueous HCl (15 mL). The resulting mixture was extracted with diethyl ether (3 × 20 mL). Combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4 and filtered. Concentration under reduced pressure afforded a red oil (2.27 g, 88% crude yield). Purification via flash column chromatography (hex:EtOAc; 96:4) afforded the product as a colourless oil (2.01 g, 79% yield). R_f = 0.75 (hex:EtOAc; 4:1); IR λ (neat/cm^{-1}) 3427, 3006, 2982, 2937, 2838, 1724, 1581, 1520, 1369, 1210, 1158, 906; δ_H (500 MHz, $CDCl_3$) 1.52 (9H, s, CH_3), 3.77 (3H, s, CH_3), 6.73 (1H, s(br), NH), 6.81 (1H, dd, *J* = 3.0, 9.0 Hz, ArH), 6.90 (1H, d, *J* = 3.0 Hz, ArH), 7.97 (1H, d, *J* = 9.0 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 28.3, 55.7, 80.7, 113.3, 114.5, 121.6, 123.3, 128.5, 152.7, 155.5 ppm.

Linkers

***N*,*N*-Bis(3-cyanopropyl)-benzylamine**:[3]

To a stirred solution of benzylamine (2.2 mL, 20.12 mmol, 1.00 equiv.) in *n*-butanol (40 mL, 0.5 M) was sequentially added bromo-butyrnitrile (5.0 mL, 50.30 mmol, 2.50 equiv.), potassium iodide (1.17 g, 7.04 mmol, 0.35 equiv.) and potassium carbonate (8.34 g, 60.37 mmol, 3.00 equiv.). The resulting reaction was stirred at 115 ˚C for 24 hours. Following this, the reaction was cooled to room temperature and portioned between water (100 mL) and Et_2O (100 mL). The resulting biphasic mixture was separated and the aqueous layer was further extracted with Et_2O (70 mL, then 50 mL). Combined ethereal extracts were washed with brine (200 mL) and dried over Na_2SO_4. Filtration followed by solvent evaporation afforded 5.33 g of an orange oil (108% crude yield) which contained some small impurities. This oil was purified via flash column chromatography (eluent: hex:EtOAc; 4:1) to give the product as a colourless oil (3.45 g, 71% yield). R_f = 0.65 (hex:EtOAc; 4:1); δ_H (500 MHz, $CDCl_3$) 1.81 (4H, p, *J* = 7.0 Hz, CH_2), 2.37 (4H, t, *J* = 7.0 Hz, CH_2), 2.57 (4H, t, *J* = 7.0 Hz, CH_2), 3.55 (2H, s, CH_2), 7.27 – 7.29 (3H, m, ArH), 7.32 – 7.35 (2H, m, ArH) ppm.

***N*,*N*-Bis(4-aminobutyl)-benzylamine**: [3]

N,*N*-Bis(3-cyanopropyl)-benzylamine (3.42 g, 14.16 mmol, 1.00 equiv.) was fully dissolved in a solvent mixture of EtOH and THF (4:1, 140 mL, 0.1 M). To this stirred solution was sequentially added 5 M_{aq} NaOH (23 mL, 113.24 mmol, 8.00 equiv.) and Raney Nickel (7 mL, 0.5 mL per mmol). The reaction was placed under and atmosphere of hydrogen and stirred at room temperature for 10 hours. Following this, the reaction was filtered on celite, washing through with MeOH (100 mL). The resulting filtrate was concentrated under reduced pressure. This afforded a residue which was portioned between DCM (50 mL) and water (50 mL). The resulting layers were separated and the aqueous layer was further extracted with DCM (2 × 50 mL). Combined DCM extracts were washed with brine (150 mL) and dried over Na_2SO_4. Filtration followed by solvent evaporation afforded the product as a colourless oil (3.06 g, 87 % yield). δ_H (500 MHz, $CDCl_3$) 1.40 – 1.51 (8H, m, CH_2), 2.41 (4H, t, *J* = 7.0 Hz, CH_2), 2.65 (4H, t, *J* = 7.0 Hz, CH_2), 3.54 (2H, s, CH_2), 7.22 (1H, t, *J* = 7.0 Hz, ArH), 7.27 – 7.32 (4H, m, ArH) ppm.

Bis-(4-aminobutyl)-amine: [3]

A solution of *N*,*N*-Bis(4-aminobutyl)-benzylamine (3.06 g, 12.26 mmol, 1.00 equiv.) in fully degassed EtOH (120 mL, 0.1 M) was treated with Pd/C 10 wt% (1.31 g, 1.23 mmol, 0.1 equiv.). The reaction was placed under an atmosphere of hydrogen and stirred at room temperature for 4 hours. Following this, the reaction was filtered on celite, washing through with MeOH (100 mL). The filtrate was concentrated to give a pink coloured oil (1.82 g, 93% yield). δ_H (500 MHz, $CDCl_3$) 1.43 – 1.54 (8H, m, CH_2), 2.61 (4H, t, *J* = 7.0 Hz, CH_2), 2.69 (4H, t, *J* = 6.5 Hz, CH_2) ppm.

***N*,*N*-Bis(4-cyanobutyl)-benzylamine**:[3]

To a stirred solution of benzylamine (2.0 mL, 18.32 mmol, 1.00 equiv.) in *n*-butanol (60 mL, 0.3 M) was sequentially added 5-bromovalerionitrilenitrile (6.4 mL, 54.93 mmol, 3.00 equiv.), potassium iodide (1.06 g, 6.41 mmol, 0.35 equiv.) and potassium carbonate (7.59 g, 60.37 mmol, 3.00 equiv.). The resulting reaction was stirred at 115 ˚C for 2 hours. Following this, the reaction was cooled to room temperature and portioned between water (100 mL) and Et_2O (100 mL). The resulting biphasic mixture was separated and the aqueous layer was further extracted with Et_2O (70 mL, then 50 mL). Combined ethereal extracts were washed with brine (200 mL) and dried over Na_2SO_4. Filtration followed by solvent evaporation afforded 8.21 g of a turbid white gel (166% crude yield) which contained the product, starting material and a number of impurities. This gel was purified via flash column chromatography (eluent: hex:EtOAc; 4:1) to give the product as a colourless oil (2.04 g, 41% yield). R_f = 0.50 (hex:EtOAc; 4:1); δ_H (500 MHz, $CDCl_3$) 1.57 – 1.69 (8H, m, CH_2), 2.27 (4H, t, *J* = 7.0 Hz, CH_2), 2.43 (4H, t, *J* = 6.5 Hz, CH_2), 3.52 (2H, s, CH_2), 7.23 – 7.33 (5H, m, ArH) ppm.

***N*,*N*-Bis(5-aminopentyl)-benzylamine**: [3]

N,*N*-Bis(4-cyanobutyl)-benzylamine (2.04 g, 7.57 mmol, 1.00 equiv.) was fully dissolved in a solvent mixture of EtOH and THF (4:1, 150 mL, 0.05 M). To this stirred solution was sequentially added 5 M_{aq} NaOH (12.12 mL, 60.58 mmol, 8.00 equiv.) and Raney Nickel (15 mL, 2 mL per mmol). The reaction was placed under and atmosphere of hydrogen and stirred at room temperature for 6 hours. Following this, the reaction was filtered on celite, washing through with MeOH (100 mL). The resulting filtrate was concentrated under reduced pressure. This afforded a residue which was portioned between DCM (50 mL) and water (50 mL). The resulting layers were separated and the aqueous layer was further extracted with DCM (2 × 50 mL). Combined DCM extracts were washed with brine (150 mL) and dried over Na_2SO_4. Filtration followed by solvent evaporation afforded the product as a colourless oil (1.03 g, 49 % yield). δ_H (500 MHz, $CDCl_3$) 1.29 – 1.49 (12H, m, CH_2), 2.39 (4H, t, *J* = 7.0 Hz, CH_2), 2.65 (4H, t, *J* = 7.0 Hz, CH_2), 3.53 (2H, s, CH_2), 7.20 – 7.23 (1H, m, ArH), 7.27 – 7.31 (4H, m, ArH) ppm.

Bis-(4-aminopentyl)-amine: [3]
A solution of *N*,*N*-Bis(5-aminopentyl)-benzylamine (1.54 g, 5.54 mmol, 1.00 equiv.) in fully degassed EtOH (50 mL, 0.1 M) was treated with Pd/C 10 wt% (0.59 g, 0.55 mmol, 0.1 equiv.). The reaction was placed under an atmosphere of hydrogen and stirred at room temperature for 4 hours. Following this, the reaction was filtered on celite, washing through with MeOH (100 mL). The filtrate was concentrated to give a colourless oil (1.02 g, 98% yield). δ_H (500 MHz, $CDCl_3$) 1.31 – 1.53 (12H, m, CH_2), 2.59 (4H, t, *J* = 7.0 Hz, CH_2), 2.68 (4H, t, *J* = 7.0 Hz, CH_2) ppm.

1 –Bromo-7-Azidoheptane
1,7-Dibromoheptane (959 mg, 3.81 mmol) was weighed into a round bottom flask. The flask was placed under argon gas, and to this DMSO (4mL) was added via a syringe. Sodium azide (124 mg, 1.90 mmol) was added, and allowed to stir for five hours at room temperature. Upon completion, the reaction was diluted with water (40mL), and extracted with diethyl ether (3x25 mL). The organic layer was washed with brine, and dried over sodium sulfate. Concentration yielded a clear oil (1.00g), which was purified by column chromatography (30mm x 150mm, 10:1 Hexanes: Ethyl Acetate) to yield a clear oil (264mg, 63%). HRMS (ESI) (M+H) calc $C_7H_{15}BrN_3$ 220.0449, found 220.0420. IR λ (neat/cm^{-1}) 2932, 2857, 2095.^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.41 (t, *J* = 6.8 Hz, 1H), 3.26 (t, *J* = 6.9 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.64 – 1.57 (m, 1H), 1.50 – 1.30 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.41, 33.79, 32.64, 28.75, 28.30, 28.00, 26.55, 19.60.
1 –Bromo-8-Azidooctane
Synthesized by the general procedure used for 1-Bromo-7-Azidoheptane. Yield (1.07g, 60%) HRMS (ESI) (M-N_2) calc $C_8H_{15}BrN_1$ 206.0544, found 206.0624. IR λ (neat/cm^{-1}) 2931, 2857, 2095. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.41 (t, *J* = 9.8, 4.1 Hz, 2H), 3.26 (t, *J* = 8.1, 5.8 Hz, 2H), 1.86 (q, 2H), 1.60 (q, 2H), 1.48 – 1.42 (m, 2H), 1.40 – 1.31 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51. 51574, 34.071, 32.873, 29.097, 28.933, 28.744, 28.179, 26.748.
7-azido-N-(7-azidoheptyl)-N-benzylheptan-1-amine
1 –Bromo-7-Azidoheptane (1.577g, 7.168 mmol), potassium carbonate (1.348g, 9.77 mmol), and potassium iodide (108 mg, 0.652 mmol) were added to a round bottom flask. After placing the reaction under argon gas, n-butanol (14 ml) was added and heated to 115 ˚C. Benzylamine (356 ul, 3.26 mmol) was added via a syringe, and the reaction was stirred for (16 hours). The reaction was dissolved in diethyl ether (60 ml), filtered through celite, and concentrated to a yellow oil (1.61g). The crude material was purified by column chromatography (dry loaded onto 2g SiO_2, then eluted on a 40mm x 150 mm column with 5:1 Hexanes:Ethyl Acetate), yielding a yellow oil (435mg , 35%). HRMS (ESI) calc (M+H)$C_{21}H_{36}N_7$ 386.3032, found 386.3012. IR λ (neat/cm^{-1}) 2932, 2857, 2797, 2094^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.25(m, 5H), 3.58 (s, 2H), 3.28 (t, *J* = 7.0 Hz, 4H), 2.47 – 2.40 (m, 4H), 1.61 (q, *J* = 7.2 Hz, 4H), 1.55 – 1.47 (m, 4H), 1.43 – 1.27 (m, 12H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 140.05 , 128.86 , 128.77 , 128.12 , 128.09 , 126.71 , 58.68 , 53.73 , 51.47 , 51.46 , 29.05 , 28.81 , 27.24 , 27.23 , 26.92 , 26.72 , 26.70 .
8-azido-N-(8-azidoheptyl)-N-benzyloctan-1-amine
Synthesized by the general procedure used for 7-azido-N-(7-azidoheptyl)-N-benzylheptan-1-amine. Yield (310 mg, 39%). HRMS (ESI) calc (M+H) $C_{23}H_{40}N_7$ 414.3278, found 414.3301. IR λ (neat/cm^{-1}) 2932, 2857, 2797, 2094. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 – 7.22 (m, 7H), 3.56 (s, 2H), 3.28 (t, *J* = 6.8 Hz, 4H), 2.42 (t, *J* = 7.5 Hz, 4H), 1.62 (p, *J* = 7.1 Hz, 4H), 1.48 (s, 4H), 1.34 (d, *J* = 42.1 Hz, 18H). ^{13}C

NMR (126 MHz, $CDCl_3$) δ 167.57, 128.97, 128.22, 126.76, 124.74, 58.85, 54.00, 51.67, 29.57, 29.32, 29.01, 27.50, 27.21, 26.87.

N^1-7(-aminoheptyl)heptane-1,7-diamine

7-azido-N-(7-azidoheptyl)-N-benzylheptan-1-amine (435mg, 1.12 mmol) was added to a round bottom flask and dissolved in methanol. The reaction was degassed by bubbling argon gas through the mixture for ten minutes. To this palladium on carbon (356 mg of 10 weight %, 0.336 mmol) was added and the reaction sealed with a septum. Using a balloon and needle, hydrogen gas was bubbled through the reaction for fifteen minutes. Then placed under a balloon of hydrogen at one atmosphere for 6 hours. Upon completion, argon gas was bubbled through the reaction mixture for fifteen minutes, sonicated in methanol, and filtered through a pad of celite. Concentration of this reaction mixture gave a white solid (235 mg, 86%) with no further purification required. HRMS (ESI) calc $C_{14}H_{34}N_3$ (M+H)244.2753, found 244.2755. IR λ (neat/cm^{-1}) 2923, 2851. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.19 (m, 1H), 2.61 (h, *J* = 7.9, 6.8 Hz, 4H), 2.53 (q, *J* = 7.4, 6.1 Hz, 5H), 1.78 – 1.73 (m, 9H), 1.45 – 1.34 (m, 13H), 1.33 – 1.17 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.09, 49.90, 42.20, 33.76, 33.71, 30.06, 29.44, 27.42, 27.00, 26.87.

N^1-(8-aminooctyl)octane-1,8-diamine

The same general synthesis as N^1-7(-aminoheptyl)heptane-1,7-diamine was used. Yield (160 mg, 79%). HRMS (ESI) calc $C_{16}H_{38}N_3$ (M+H) 272.3066, found 272.3063. IR λ (neat/cm^{-1}) 2923, 2851. ^{1}H NMR (500 MHz, Chloroform-*d* with drops of Methanol-*d*) δ 2.69 – 2.61 (m, 4H), 2.55 (td, *J* = 7.5, 2.8 Hz, 5H), 1.65 (bs, 8H), 1.48 – 1.37 (m, 11H), 1.28 (d, *J* = 5.7 Hz, 19H). ^{13}C NMR (126 MHz, $CDCl_3$) δ50.28, 50.21, 42.30, 33.85, 30.19, 29.65, 29.54, 27.47, 26.94.

11-Aminoundecanol

To a flame dried round bottom flask, 11-aminoundecanoic acid (3.04g, 15 mmol) was added. The reaction vessel was evacuated and placed under a positive pressure of argon. THF was added to the vessel, and the reaction was cooled to 0 ˚C in an ice bath. Stirring at 0 ˚C, $LiAlH_4$ (2.281g, 60 mmol) was added slowly. Caution, vigorous bubbling will occur upon addition. Slowly add $LiAlH_4$ to avoid bubbling over. Once total $LiAlH_4$ was added, reaction was heated to reflux under a condenser for 20 hours. Upon completion, the reaction was cooled to 0 ˚C and the excess $LiAlH_4$ was quenched with slow addition of saturated aqueous sodium sulfate. Caution, quenching reaction is extremely exothermic, perform addition very slowly. The addition was stopped once the color of the $LiAlH_4$ was lost, a white precipitate formed, and bubbling upon further addition ceased. Reaction slurry was filtered through a pad of celite using ethyl acetate, and concentrated to yield a white solid (85%), 11-aminoundecanol. IR λ (neat/cm^{-1}) 3336, 2917, 2850. HRMS (ES) Calc $C_{11}H_{27}NO$ 188.2104 found (M+H) 188.2005. Mp = 87-89 ˚C ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.64 (t, *J* = 6.6 Hz, 2H), 2.67 (t, *J* = 7.0 Hz, 2H), 1.60 – 1.52 (m, 2H), 1.44 (dd, *J* = 14.1, 7.4 Hz, 3H), 1.36 – 1.22 (m, 16H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 62.893, 42.175, 33.759, 32.731, 29.475, 29,395, 29.307, 26.779, 25.643.

Benzyl (11-hydroxyundecyl)carbamate

To a reaction vessel 11-aminoundecanol (466mg, 2.49 mmol) was added, placed under a positive pressure of argon gas, and dissolved in tetrahydrofuran (8mL). Triethylamine (800 ul, 5.73) was added to the reaction mixture via a syringe, and the reaction was cooled to 0 ˚C. While stirring, benzyl chloroformate (400 ul, 2.74 mmol) was added slowly via a syringe. The reaction was allowed to stir 6 hours at 55 ˚C till completion. The reaction was filtered through celite and concentrated to a yellow-white solid 800 mg. The solid was purified on by column chromatography (SiO2, 30 mm x 150 mm, 3% MeOH: CH2Cl2). Collect 463 mg of product 58% yield. IR λ (neat/cm^{-1}) 3346, 2922, 2852, 1685, 1531, 1267, 1245. HRMS (ES) Calc $C_{19}H_{31}NO_3Na$ 321.2304, found (M+Na) 343.2198. Mp = 66-69 ˚C. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 5H), 5.08 (s, 2H), 4.88 – 4.78 (m, 1H), 3.62 (t, *J* = 6.7 Hz, 2H), 3.17 (q, *J* = 6.8 Hz, 2H), 1.64 (s, 1H), 1.55 (p, *J* = 6.8 Hz, 2H), 1.47 (q, *J* = 7.1 Hz, 2H), 1.36 – 1.20 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.54, 136.77, 128.61, 128.22, 128.18, 66.68, 63.09, 41.22, 32.90, 30.05, 29.66, 29.60, 29.57, 29.52, 29.45, 29.35, 26.83, 25.85.

benzyl (11-oxoundecyl)carbamate

To a flame dried round bottom flask, DCM (83 ml) was added followed by distilled oxalyl chloride (960 ul, 11.2 mmol). The reaction vessel was cooled to -78 ˚C, and stirred under a positive pressure of argon gas. Dimethyl sulfoxide (1.59 ml, 22.4 mmol) was added via a syringe, and allowed to stir 45 min until the reaction ceases bubbling. In a solution of dichloromethane (10 ml) Benzyl (11-hydroxyundecyl)carbamate (3.00g, 9.332 mmol) was added to the reaction mixture, and allowed to stir for 30 minutes. Triethylamine

(6.5 ml, 46.7 mmol) was added and the reaction was stirred 60 min warming to room temperature until the oxidation was complete. Upon completion, the reaction was washed 3 x 20 mL with a saturated NH4Cl solution, washed with brine, and the organic layer was dried over sodium sulfate. Concentration of the organic layer yielded a paste, which was dissolved in toluene and evaporated till a white solid (2.8g, 94 %) forms. IR λ (neat/cm^{-1}) 3325, 2922, 2851, 1688, 1634, 1556, 1469. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.71 (s, 1H), 7.29 (dd, *J* = 20.5, 4.4 Hz, 5H), 5.05 (s, 2H), 4.96 (t, *J* = 6.1 Hz, 1H), 3.14 (q, *J* = 6.7 Hz, 2H), 2.37 (td, *J* = 7.3, 1.8 Hz, 2H), 1.59 (q, *J* = 7.2 Hz, 2H), 1.45 (p, *J* = 7.2 Hz, 2H), 1.36 – 1.17 (m, 13H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.97, 202.94, 156.43, 136.73, 128.47, 128.38, 128.05, 128.01, 127.76, 66.46, 43.87, 41.08, 29.93, 29.48, 29.43, 29.31, 29.30, 29.28, 29.22, 29.12, 29.11, 26.71, 22.04.

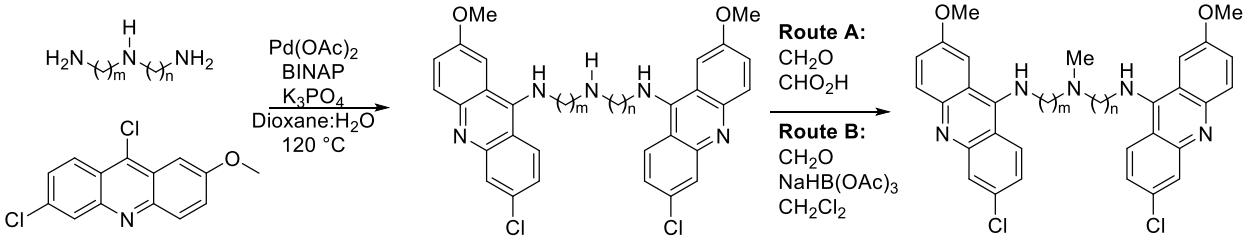
dibenzyl((benzylazanediyl)bis(undecane-11,1-diyl))dicarbamate

To a round bottom flask, benzyl (11-oxoundecyl)carbamate (2.8g, 8.77 mmol) was added and placed under a positive pressure of argon gas. DCM was added (80 ml), then benzyl amine (435 ul, 3.984 mmol) was added via a syringe. Once the reaction becomes homogenous, sodium triacetoxyborohydride was added (4.240g, 20 mmol). Upon completion, the reaction was diluted by half and excess sodium triacetoxyborohydride was quenched by reaction with an equal volume of 2N aqueous sodium hydroxide for 1 hour. The organic layer was separated, washed with brine, and dried over sodium sulfate. Product purified by column chromatography (SiO2, 45 mm x 150 mm, 3:1 Hexanes:THF). Yield a white solid (2.334g, 82%). IR λ (neat/cm^{-1}) 2923, 2852, 1685, 1531. HRMS (ES) Calc $C_{45}H_{67}N_3O_4Na$ 736.5032, found (M+Na) 736.5029. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.39 – 7.27 (m, 16H), 7.24 – 7.20 (m, 1H), 5.10 (s, 5H), 4.85 (s, 1H), 3.54 (s, 2H), 3.17 (t, *J* = 7.0 Hz, 4H), 2.39 (t, 4H), 1.52 – 1.41 (m, 10H), 1.34 – 1.19 (m, 35H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.46, 140.41, 136.80, 128.91, 128.59, 128.20, 128.15, 128.12, 126.65, 77.39, 66.62, 58.72, 53.92, 41.22, 41.09, 30.05, 29.73, 29.68, 29.66, 29.65, 29.40, 27.56, 27.56, 27.12, 26.86.

N1-(11-aminoundecyl)undecane-1,11-diamine

To a round bottom flask, dibenzyl ((benzylazanediyl)bis(undecane-11,1-diyl))dicarbamate (800mg, 1.12 mmol) was added, and dissolved in methanol (12.5 ml). The reaction was then degassed by bubbling argon gas through the solution for 10 minutes. Palladium on carbon (10% by weight, 367 mg, .336 mmol) was added to the reaction mixture, and while stirring, hydrogen gas was bubbled through the reaction mixture for 15 minutes. The reaction was then placed under a balloon of hydrogen, and stirred till the starting material was consumed. Upon completion the reaction was degassed by bubbling argon gas through the reaction for 15 minutes. Then, the reaction was sonicated and filtered through celite using methanol. The methanol was concentrated yielding N1-(11-aminoundecyl)undecane-1,11-diamine (360 mg, 91%), as a white solid. IR λ (neat/cm^{-1}) 2925, 2850, 2812. HRMS (ES) $C_{22}H_{50}N_3$ calc (M+H) 356.3926, found 356.4001. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 2.67 (t, *J* = 7.0 Hz, 4H), 2.58 (t, 3H), 1.45 – 1.39 (m, 1H), 1.35 – 1.22 (m, 34H).). ^{13}C NMR (126 MHz, $CDCl_3$ + CD_3OD Drops) δ 70.99, 60.277, 47.396, 43.852, 39.418, 29.573, 29.51, 29.466, 29.390, 29.193, 29.148, 227.552, 26.663, 26.533, 26.490, 25.991

Synthesis of dimeric inhibitors.



General procedure for Buchwald-Hartwig amination

To a resealable vial, triamine (1.0 Eq), Arylhalide (2.2 eq), $Pd(OAc)_2$ (0.05 eq), racemic BINAP (0.10 eq), and K_3PO_4 (3.0 eq) were added. The reaction vessel was sealed, evacuated and placed under an argon atmosphere. To the vial, a solution of 10:1 1,4-Dioxane:Water (degassed by freeze-pump-thaw method) was added(0.4M final reaction concentration), and the reaction was heated to 120°C. Upon completion, the reaction was allowed to cool to 23°C and filtered through celite using either $CHCl_3$ or CH_2Cl_2, and concentrated under reduced pressure. The compounds were then dissolved in a minimum amount of either ethyl acetate, or CH_2Cl_2. The HCl salt was formed by added 3.0 eq of HCl in diethyl ether. The precipitate was filtered and collected via vacuum filtration. The organic layer is washed 3 x with H_2O. The precipitate was dissolved in H_2O unless specified. The H_2O layer was then washed once with CH_2Cl_2.

Following the organic wash, the pH of the aqueous layer was adjusted to 12 by the addition of aqueous ammonium hydroxide. The aqueous layer was then extracted with 25% 2-propanol in $CHCl_3$, and dried over anhydrous sodium sulfate. The organic reaction was concentrated to a solid or film yielding the dimeric inhibitor. Further purification used when specified.

Lys 05 / DC221

Lys 05 was synthesized and isolated according to the general procedure above. The compound was isolated as a pure compound as an orange solid (2.74 g, 71 %). R_f = 0.70 ($CHCl_3$:MeOH:TEA; 85:10:5); Mp = 199 – 200 ˚C, EtoAc (Lit., [PNAS] 199 – 200 ˚C); IR λ (neat/cm^{-1}) 3622, 3012, 2947, 2831, 1697, 1516, 1458, 1219, 1026, 760; m/z (ES) 440.35 (MH^+, 100 %), 443.35 (MH^+, 65 %) 438.32 (MH^-, 100 %), 440.35 (MH^-, 50 %); δ_H (500 MHz, $CDCl_3$) 2.46 (1H, s, CH_3), 2.89 (4H, t, *J* = 6.0 Hz, CH_2), 3.40 (4H, quart., *J* = 5.0 Hz, CH_2), 5.45 (2H, s(br), NH), 6.38 (2H, d, *J* = 5.5 Hz, ArH), 6.99 (2H, dd, *J* = 9.0, 2.0 Hz, ArH), 7.41 (2H, d, *J* = 9.0 Hz, ArH), 7.94 (2H, d, *J* = 2.0 Hz, ArH), 8.53 (2H, d, *J* = 5.5 Hz, ArH) ppm.

DC340

DC340 was synthesized and isolated by the general procedure above. The product as a white solid (785 mg, 91% yield). R_f = 0.10 (EtOAc:MeOH:TEA; 80:15:5); δ_H (500 MHz, MeOD) 1.69 – 1.71 (2H, m, CH_2), 1.76 – 1.82 (2H, m, CH_2), 1.92 – 1.98 (2H, m, CH_2), 2.70 (2H, t, *J* = 7.0 Hz, CH_2), 2.78 (2H, t, *J* = 7.0 Hz, CH_2), 3.37 – 3.44 (4H, m, CH_2), 6.51 – 6.53 (2H, m, ArH), 7.36 – 7.39 (2H, m, ArH), 7.77 (2H, t, *J* = 2.0 Hz, ArH), 8.04 – 8.09 (2H, m, ArH), 8.34 (2H, t, *J* = 5.5 Hz, ArH) ppm. ; δ_C (125 MHz, DMSO) 152.267, 150.465, 149.412, 133.725, 127.825, 124.453, 124.313, 117.803, 98.910, 49.286, 48.924, 47.553, 41.426, 39.382, 27.926, 27.205, 26.035.

DM 340

To a vial was added 3-Chloro-2,8-bis(trifluoromethyl)quinoline (558.00 mg, 1.86 mmol, 2.40 equiv,), BINAP (72.00 mg, 0.12 mmol, 0.15 equiv.), $Pd(OAc)_2$ (14.00 mg, 0.06 mmol, 0.075 equiv.), finely ground K_3PO_4 (659.00 mg, 3.10 mmol, 4.00 equiv.) and spermidine (120.0 □L, 0.78 mmol, 1.00 equiv.). The reagents were placed under a blanket of Argon; then a mixture of degassed dioxane and water (3 mL, 10:1) was added. The reaction vial was sealed and heated to 120 ˚C for 12 hours. The reaction was then cooled to room temperature and filtered on a pad of celite; washing with chloroform (3 × 10 mL). Combined organic layers were acidified to pH 1 using 1M aqueous HCl solution (4.7 mL, 4.66 mmol, 6.00 equiv.) and diluted with water (20 mL). The resulting biphasic mixture was separated and the water layer was washed with chloroform (2 × 15 mL). The pH of the aqueous layer was adjusted to 11 using ammonium hydroxide. The now alkaline mixture was washed with chloroform (3 × 20 mL). These 3 chloroform extracts were combined, washed with brine, dried over Na_2SO_4 and concentrated which afforded the product as an off-white foam (243.00 mg, 50% yield). The purity of this material was calculated to be ≥ 95% which negated the need for further purification. R_f = 0.25 (CCl_3:MeOH:TEA; 85:10:5); Mp = 84 – 87 ˚C; IR λ (neat/cm^{-1}) 3406, 3020, 2976, 1523, 1215, 771; HRMS (ES) calcd for $C_{29}H_{26}F_{12}N_5$ 672.1997, found 672.2033; δ_H (500 MHz, DMSO) 1.55 – 1.60 (2H, m, CH_2), 1.70 – 1.75 (2H, m ,CH_2), 1.79 – 1.85 (2H, m, CH_2), 2.58 (2H, t, *J* = 7.0 Hz, CH_2), 2.65 (2H, t, *J* = 6.0 Hz, CH_2), 3.39 – 3.43 (4H, m, CH_2), 6.86 (2H, d, *J* = 7.5 Hz, ArH), 7.59 – 7.66 (2H, m, ArH), 8.03 (1H, s(br), NH), 8.08 (1H, d, *J* = 7.0 Hz, ArH), 8.12 (1H, d, *J* = 7.0 Hz, ArH), 8.26 (1H, s(br), NH), 8.53 (1H, d, *J* = 8.5 Hz, ArH), 8.61 (1H, d, *J* = 8.5 Hz, ArH)8 ppm; δ_C (125 MHz, DMSO) 25.9, 27.3, 28.0, 41.6, 42.8, 47.5, 49.4, 94.4, 119.7, 119.7, 120.9, 123.1, 124.8 (d), 126.6, 126.8, 127.2, 127.3, 129.3 (br), 144.17, 144.23, 152.7, 152.8 ppm.

DP340

To a vial was added 8-Chloro-6-methoxyquinoline (193.0 mg, 1.0 mmol, 2.20 equiv,), BINAP (45.00 mg, 0.072 mmol, 0.16 equiv.), $Pd_2(dba)_3$ (33.00 mg, 0.036 mmol, 0.08 equiv.), NaOtBu (130.0 mg, 1.37 mmol, 3.0 equiv) and spermidine (71.0 □L, 0.455 mmol, 1.00 equiv.). The reagents were placed under a blanket of Argon; then 1 mL of dioxane was added. The reaction vial was sealed and heated to 110 ˚C for 48 hours. The reaction was then cooled to room temperature and filtered on a pad of celite; washing with chloroform (3 × 10 mL). The filtrate was concentrated and dissolved with methanol and dichloromethane, and adsorbed onto 400 mg of SiO_2. These materials were separated via flash column chromatography (EtOAc:MeOH:TEA; 90:9:1) to afford the product as a red brown solid (173 mg, 83%); HRMS (ES) calcd for $C_{27}H_{34}N_5O_2$ 460.2713, found 460.2707; δ_H (500 MHz, $CDCl_3$) 1.69 – 1.75 (2H, m, CH_2), 1.90 – 1.98 (2H, m, CH_2), 2.17 – 2.22 (2H, m, CH_2), 2.93 (2H, t, *J* = 7.5 Hz, CH_2), 3.06 (2H, t, *J* = 7.5 Hz, CH_2), 3.19 (2H, t, *J* = 7.0 Hz, CH_2), 3.34 – 3.37 (2H, m, CH_2), 3.86 (3H, s, CH_3), 3.87 (3H, s, CH_3), 6.07 (2H, s(br), NH), 6.23 (1H, d, *J* = 2.5 Hz, ArH), 6.27 (1H, d, *J* = 2.5 Hz, ArH), 6.34 (2H, dd, *J* = 2.5, 8.0 Hz, ArH), 7.24

– 7.26 (2H, m, ArH), 7.86 – 7.89 (2H, m, ArH), 8.51 (2H, dd, *J* = 1.5, 4.0 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 26.2 (2C's), 29.6, 40.8, 42.7, 46.3, 47.9, 55.1 (2C's), 92.2, 92.6, 96.8, 97.1, 121.75, 121.81, 129.60, 129.61, 134.6, 135.17, 135.19, 144.3, 144.5, 145.3, 145.5, 159.2, 159.3 ppm.

DQ 221

DQ 221 was was prepared by the above general procedure. Required flash column chromatography (EtOAc:MeOH:TEA; 90:9:1) to afford the product as a red solid (240.00 mg, 33%). R_f = 0.15 (EtOAc:MeOH:TEA; 92:7:1); Mp = 163 – 164 ˚C; IR λ (neat/cm^{-1}) 3688, 3619, 3019, 1219, 929; HRMS (ES) calcd for $C_{33}H_{32}Cl_2N_5O_2$ 600.1933, found 600.1935 (matches double Cl pattern); δ_H (500 MHz, $CDCl_3$) 2.45 (3H, s, CH_3), 2.88 (4H, t, *J* = 6.0 Hz, CH_2), 3.73 (6H, s, CH_3), 3.85 (4H, t, *J* = 6.0 Hz, CH_2), 5.65 (2H, s(br), NH), 7.16 (2H, d, *J* = 9.0 Hz, ArH), 7.21 (2H, d, *J* = 2.5 Hz, ArH), 7.32 (2H, d, *J* = 8.5 Hz, ArH), 7.95 (2H, d, *J* = 9.0 Hz, ArH), 8.01 – 8.07 (4H, m, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 42.0, 47.4, 55.4, 57.9, 99.5, 115.5, 117.8, 124.3, 124.4, 127.5, 130.8, 135.1, 145.9, 147.8, 149.9, 156.1 ppm.

DQ 330

DQ 330 was prepared by the above general procedure. The workup was altered from the general procedure as follows. After formation of the HCl salt, and following the standard workup showed little product moved into the aqueous layer, therefore the collected precipitate (380mg) was recrystallized from methanol yielding (229 mg). The HCl salt solubilized in a solution of a 1:1 mixture of dichloromethane to basic methanol. The residue was dissolved in dichloromethane, washed with water (2x20 mL) then washed with brine and dried over Na_2SO_4. Concentration of the organic phase yielded an orange solid (172 mg, 56%). HRMS (ES) $C_{34}H_{34}Cl_2N_5O_2$ (calc) 614.2090, found 614.2088 IR λ (neat/cm^{-1}) 2925, 2853, 1631, 1562, 1466, 1238. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.01 – 7.96 (m, 2H), 7.92 (d, *J* = 9.3 Hz, 4H), 7.33 (dd, *J* = 9.4, 2.7 Hz, 2H), 7.21 (d, *J* = 2.7 Hz, 2H), 7.10 (dd, *J* = 9.2, 2.2 Hz, 2H), 6.01 (s, 2H), 3.83 – 3.75 (m, 10H), 3.49 (s, 1H), 2.82 (t, *J* = 6.3 Hz, 4H), 1.89 (p, *J* = 6.4 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.56, 149.93, 134.72, 124.37, 123.86, 123.72, 117.50, 115.26, 100.41, 55.52, 49.90, 30.87, 25.41.

DQ 340

DQ 340 was prepared by the above general procedure. The isolated product yielded a mixture of the dimeric product and the monomer (3:7, 369.00 mg). These materials were separated via flash column chromatography (EtOAc:MeOH:TEA; 84:16:1) to afford the product as a red solid (160.00 mg, 56%). R_f = 0.10 (EtOAc:MeOH:TEA; 84:15:1); Mp = 115 – 118 ˚C; IR λ (neat/cm^{-1}) 3435, 3019, 1635, 1216, 929; HRMS (ES) calcd for $C_{35}H_{36}Cl_2N_5O_2$ 628.2246, found 628.2247); δ_H (500 MHz, $CDCl_3$) 1.68 – 1.74 (2H, m, CH_2), 1.80 – 1.86 (2H, m, CH_2), 1.88 – 1.92 (2H, m, CH_2), 2.73 (2H, t, *J* = 7.0 Hz, CH_2), 2.89 (2H, t, *J* = 7.0 Hz, CH_2), 3.74 (2H, t, *J* = 7.0 Hz, ArH), 3.87 (3H, s, CH_3), 3.89 – 3.92 (5H, m, CH_3, and CH_2), 7.11 – 7.24 (3H, m, ArH), 7.31 – 7.39 (3H, m, ArH), 7.95 – 8.04 (6H, m, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 27.2, 29.5, 30.1, 49.0, 49.7, 50.5, 50.8, 55.6 (2C), 99.5, 101.3, 117.9, 118.4, 118.5, 120.6, 123.5, 123.6, 124.1, 124.4, 124.5, 124.8, 134.9, 135.2, 148.2, 149.7, 150.8, 155.4, 156.0 ppm.

DQ 440

DQ 440 was prepared by the above general procedure yielding the product as an orange foam (0.35 g, 39% yield). R_f = 0.25 (EtOAc:MeOH:TEA; 80:15:5); Mp = 58 – 62 ˚C; IR λ (neat/cm^{-1}) 3943, 3688, 3054, 2987, 2685, 1631, 1559, 1528, 14211264, 1032, 896; HRMS (ES) calcd for $C_{36}H_{38}N_5O_2Cl_2$ 642.2403, found 642.2402; δ_H (500 MHz, $CDCl_3$) 1.55 – 1.61 (4H, m, CH_2), 1.72 – 1.78 (4H, m, CH_2), 2.60 (4H, t, *J* = 7.0 Hz, CH_2), 3.68 – 3.71 (4H, m, CH_2), 3.92 (6H, s, CH_3), 7.23 (2H, d, *J* = 2.5 Hz, ArH), 7.26 (2H, dd, *J* = 2.0, 9.0 Hz, ArH), 7.40 (2H, dd, *J* = 2.5, 9.5 Hz, ArH), 7.98 – 8.00 (4H, m, ArH), 8.05 (2H, d, *J* = 1.5 Hz, ArH) ppm; δ_c (125 MHz, $CDCl_3$) 27.5, 29.5, 49.3, 50.6, 55.6, 67.1, 99.6, 115.9, 117.9, 124.1, 124.2, 124.4, 128.3, 131.6, 134.7, 146.9, 148.4, 149.8, 155.9 ppm.

DQ 550

DQ 550 was prepared by the above general procedure yielding the product as an orange solid (0.73 g, 83% yield). R_f = 0.15 (EtOAc:MeOH:TEA; 84:15:1); Mp = 52 – 54 ˚C; IR λ (neat/cm^{-1}) 3943, 3692, 3054, 2987, 2934, 2858, 2685, 1631, 1560, 1519, 1421, 1265, 896; HRMS (ES) calcd for $C_{38}H_{42}N_5O_2Cl_2$ 670.2716, found 670.2715 (matches double Cl pattern); δ_H (500 MHz, $CDCl_3$) 1.47 (8H, s(br), CH_2), 1.73 – 1.75 (4H, m, CH_2), 2.51 – 2.53 (4H, m, CH_2), 3.65 – 3.66 (4H, m, CH_2), 3.93 (6H, s, CH_3), 7.19 (2H, s(br), ArH), 7.25 (2H, s(br), ArH), 7.38 – 7.40 (2H, m, ArH), 7.96 – 7.98 (4H, m, ArH), 8.04 (2H, s(br), ArH)

ppm; δ_c (125 MHz, $CDCl_3$) 24.7, 29.7, 31.6, 49.7, 50.5, 55.5, 99.3, 115.8, 117.9, 124.0, 124.4 (2C), 128.1, 131.4, 134.8, 146.6, 148.3, 149.7, 156.0 ppm.

DQ 660

DQ 660 was prepared by the above general procedure. This compound, the precipitated HCl salt was recrystallized in methanol, and then solubilized in a solution of a 1:1 mixture of dichloromethane to basic methanol. The residue was dissolved in dichloromethane, washed with water (2x20 mL) then washed with brine and dried over Na_2SO_4. Evaporation yielded an orange solid (4.28g, 68%). R_f = 0.30 (EtOAc:MeOH:TEA; 80:15:5); Mp = 52 – 54 ˚C; IR λ (neat/cm^{-1}) 3943, 3692, 3054, 2987, 1560, 1421, 1265, 896; HRMS (ES) calcd. for $C_{40}H_{46}N_5O_2Cl_2$ 698.3029, found 698.3029 (matches double Cl pattern); δ_H (500 MHz, $CDCl_3$) 1.31 – 1.36 (4H, m, CH_2), 1.40 – 1.47 (8H, m, CH_2), 1.71 – 1.77 (4H, m, CH_2), 2.51 (4H, t, *J* = 7.0 Hz, CH_2), 3.69 (4H, t, *J* = 7.0 Hz, CH_2), 3.95 (6H, s, CH_3), 7.20 (2H, d, *J* = 2.5 Hz, ArH), 7.30 (2H, dd, *J* = 2.0, 9.5 Hz, ArH), 7.42 (2H, dd, *J* = 2.5, 9.5 Hz, ArH), 8.00 (2H, dd, *J* = 3.0. 9.5 Hz, ArH), 8.06 (2H, d, *J* = 2.0 Hz, ArH) ppm; δ_C (125 MHz, $CDCl_3$) 26.8, 27.1, 31.8, 49.9, 50.7, 55.6, 99.1, 115.9, 118.0, 124.0, 124.5, 124.6, 128.4, 131.6, 134.8, 146.3, 149.0, 149.7, 156.0 ppm.

DQ 770

DQ 770 was prepared by the above general procedure. Solid HCl salt was recrystallized from ethanol yielding 331 mg. This solid was converted to its free base form by dissolution in a one to one mixture of aqueous ammonium hydroxide and 25% 2-propanol/75% $CHCl_3$ yielding an orange foam (145 mg, 38%). IR λ (neat/cm^{-1}) 2927, 2853, 2358,23301558,1507. HRMS (ES) $C_{42}H_{50}Cl_2N_5O_2$ (calc) 725.3263, found 725.3339 matches double Cl pattern. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.07 (d, J = 2.1 Hz, 2H, ArH), 8.00 (dd, 4H, ArH), 7.42 (dd, J = 9.4, 2.7 Hz, 2H, ArH), 7.30 (dd, J = 9.2, 2.1 Hz, 2H, ArH), 7.20 (d, J = 2.7 Hz, 2H, ArH), 4.67 (t, J = 5.9 Hz, 2H, NH), 3.96 (s, 6H), 3.68 (q, 4H, CH_2), 2.54 (t, J = 8.1, 7.4 Hz, 4H, CH_2), 1.74 (p, J = 7.3 Hz, 4H, CH_2), 1.48 – 1.37 (m, 9H, CH_2), 1.36 – 1.25 (m, 12H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.04, 149.87, 148.43, 146.80, 134.85, 131.53, 128.27, 124.56, 124.53, 124.18, 117.96, 115.87, 99.30, 77.39, 55.64, 50.78, 50.14, 31.84, 30.11, 29.36, 27.37, 26.95.

DQ 880

DQ 880 was prepared by the above general procedure. The product required recrystallization from methanol, and flash column chromatography (Ethyl Acetate with 5% Triethylamine). Yielded an orange paste (125 mg, 33%). IR λ (neat/cm^{-1}) 3292, 2927, 2854, 2359, 2341, 1632, 1559, 1434, 1336, 924. HRMS (ES) (calc) $C_{44}H_{54}Cl_2N_5O_2$ 753.3576, found 753.3510. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 2.1 Hz, 2H, ArH), 8.04 – 7.97 (m, 4H, ArH), 7.42 (dd, *J* = 9.4, 2.7 Hz, 2H, ArH), 7.34 – 7.24 (m, 7H, ArH), 7.21 (d, *J* = 2.7 Hz, 2H, ArH), 4.68 (bs, 2H, N-H), 3.97 (d, *J* = 2.7 Hz, 6H, CH_3), 3.69 (t, 4H, CH_2), 2.55 (t, *J* = 7.2 Hz, 4H, CH_2), 1.78 – 1.71 (m, 4H, CH_2), 1.44 (t, *J* = 7.0 Hz, 10H, CH_2), 1.36 – 1.23 (m, 16H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.98, 149.72, 148.44, 146.88, 134.70, 131.64, 128.38, 124.51, 124.41, 123.98, 117.96, 115.91, 99.16, 55.52, 50.77, 50.15, 31.81, 29.54, 29.44, 29.26, 27.40, 27.28, 27.11.

DQ 11110

DQ 11110 was prepared by the above general procedure except for purification. The reaction, post celite filtration is adsorbed onto silica, and purified by flash chromatography (20 mm x 150 mm, 4% MeOH, 26% ethyl acetate, 1% Triethylamine, and 69% CH2Cl2) to yield an orange paste (95 mg, 30%). $C_{50}H_{65}Cl_2N_5O_2$ (calc) 838.4515, found (M+H) 838.4574. IR λ (neat/cm^{-1}) 3302, 2925, 2852, 2360, 2341,1631, 1561, 1518, 1465, 1434,1235. ^{1}H NMR (500 MHz, Chloroform-*d* and drops of CD_3OD) δ 8.08 (s, 2H), 8.06 – 7.98 (m, 3H), 7.43 (dd, *J* = 9.4, 2.8 Hz, 2H), 7.31 (dd, *J* = 9.4, 2.3 Hz, 2H), 7.25 (s, 2H), 4.92 (s, 2H), 3.99 (s, 6H), 3.73 (t, 4H), 2.66 (t, 4H), 1.78 (p, 4H, CH_2), 1.56 (p, 4H, CH_2), 1.44 (q, *J* = 7.8 Hz, 4H), 1.39 – 1.22 (m, 24H, CH_2).^{13}C NMR (126 MHz, $CDCl_3$) δ 155.98, 150.01, 148.02, 146.28, 144.57, 141.08, 134.96, 128.02, 124.52, 124.46, 124.15, 117.75, 99.34, 55.57, 50.80, 50.70, 49.84, 31.73, 29.43, 29.42, 29.37, 29.25, 27.29, 26.88.

General reductive alkylation procedure

Method 1: Reductive alkylation with sodium triacetoxyborohydride

Dimeric inhibitor is added to a flask and dissolved in CH_2Cl_2 , to give a final reaction concentration of 0.3M. Aqueous formaldehyde (2 equiv.) was added to the reaction and allowed to stir for 15 minutes. Once the reaction becomes homogenous, sodium triacetoxyborohydride was added (4 equiv.). Upon disappearance of the starting DQ compound as observed by TLC, approximately 16 hours, the reaction

was diluted by half with dichloromethane and the excess sodium triacetoxyborohydride was quenched by reaction with a volume of 2N aqueous sodium hydroxide, equal to the dichloromethane, for 1 hour at 23°C. To the dichloromethane solution was added 1 M_{aq} HCl solution. The mixture was stirred vigorously at room temperature for 1 hour, resulting in the formation of a water soluble salt of the desired product. Both layers were separated. The aqueous layer was further washed with $CHCl_3$ (2 × 15 mL) and combined chloroform washings were discarded at this point. Using $NH_4{\cdot}OH$, the pH of the aqueous layer was adjusted to 11, resulting in the liberation of the free base of the product. The product was extracted into a solvent mixture of $CHCl_3$ and *i*-propanol (4:1). These combined extracts were washed with brine and dried over Na_2SO_4. The combined organic layers were concentrated under reduced pressure to afford a pure product unless specified.

Method 2: Eschweiler-Clarke Methylation

The dimeric inhibitor was added to a flask under an atmosphere of argon and dissolved in 88% formic acid (to give a reaction concentration of 0.5M). Aqueous formaldehyde was added to the reaction (3 equiv.), and then heated to reflux at 105°C till consumption of the starting material is observed by TLC. Upon completion, between one and three hours, the reaction was poured over water, resulting in a twofold dilution. The pH of the aqueous layer was adjusted to pH 12 by addition of aqueous ammonium hydroxide. When a precipitate formed, it was dissolved in a solution of 50:50 Methanol:CH_2Cl_2. To this solution aqueous ammonium hydroxide was added. The solution was then concentrated under reduced pressure to near dryness, and dissolved in both CH_2Cl_2 and water. The organic layer was separated, and the aqueous layer was then extracted three times CH_2Cl_2. The combined organic layer was then dried over sodium sulfate, and concentrated under reduced pressure to yield the methylated inhibitor. The compound required no further purification unless specified.

DQ 331

DQ 331 was synthesized by general method 2. The product was isolated as an orange film (21mg, 86%). Mp = 62 – 65 ˚C. HRMS(ESI) $C_{35}H_{36}Cl_2N_5O_2$ calc 628.2246, found 628.2244. IR λ (neat/cm^{-1}) 3254, 295, 2926, 2359, 2341, 1633, 1236. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.99 (d, *J* = 2.1 Hz, 2H, ArH), 7.89 (dd, *J* = 19.6, 9.3 Hz, 4H, ArH), 7.32 (dd, *J* = 9.4, 2.7 Hz, 2H, ArH), 7.15 – 7.09 (m, 4H, ArH), 3.78 (s, 6H, CH_3), 3.76 (t, *J* = 6.4 Hz, 4H, CH_2), 2.56 (t, *J* = 6.3 Hz, 4H, CH_2), 2.35 (s, 3H, CH_3), 1.88 (p, *J* = 6.4 Hz, 4H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.71, 149.84, 148.64, 146.92, 134.78, 131.59, 128.38, 124.21, 124.13, 123.93, 117.51, 115.37, 100.20, 57.06, 55.61, 50.10, 42.91, 28.34.

DQ 341

DQ 341 was prepared by the general method 2. The product as a dark-red solid (34.0 mg, 94% yield). Mp = 61 – 66 ˚C; IR λ (neat/cm^{-1}) 3434, 1653, 1213, 929; HRMS (ES) calcd for $C_{36}H_{38}Cl_2N_5O_2$ 642.2403, found 642.2398 (matches double Cl pattern); δ_H (500 MHz, CD_2Cl_2) 1.61 – 1.67 (4H, m, CH_2), 1.84 (2H, pent, *J* = 5.5 Hz, CH_2), 2.32 (3H, s, CH_3), 2.44 (2H, t, *J* = 7.0 Hz, CH_2), 2.57 (2H, t, *J* = 7.0 Hz, CH_2), 3.67 (2H, t, *J* = 6.5 Hz, CH_2), 3.83 (3H, s, CH_3), 3.86 (3H, s, CH_3), 3.89 (2H, t, *J* = 4.5 Hz, CH_2), 7.07 – 7.14 (4H, m, ArH, NH), 7.24 (1H, d, *J* = 2.5 Hz, ArH), 7.30 – 7.34 (3H, m, ArH), 7.86 (2H, dd, *J* = 3.5, 9.5 Hz, ArH), 7.92 (3H, d, *J* = 9.5 Hz, ArH), 8.02 (1H, d, *J* = 9.5 Hz, ArH) ppm; δ_C (125 MHz, CD_2Cl_2) 25.1, 27.7, 30.4, 43.0, 51.0, 51.7, 56.0, 56.1, 57.8, 58.7, 99.7, 101.3, 115.0, 116.4, 117.2, 118.4, 123.5, 124.0, 124.7 (2C), 124.8, 125.6, 128.4, 128.7, 131.7, 132.0, 134.9 (2C), 148.8, 149.2 (2C), 150.0, 150.9, 155.8, 156.5

DQ 441

DQ 441 was synthesized by general method 1. Filtration followed by solvent evaporation afforded the product as a red solid (0.13 g, 83% yield). R_f = 0.55 (EtOAc:MeOH:TEA; 80:15:5); Mp = 60 – 62 ˚C; IR λ (neat/cm^{-1}) 3054, 2987, 1559, 1422, 1265, 896; HRMS (ES) calcd for $C_{37}H_{40}N_5O_2Cl_2$ 656.2559, found 656.2565; δ_H (500 MHz, $CDCl_3$) 1.52 – 1.58 (4H, m, CH_2), 1.67 – 1.83 (4H, m, CH_2), 2.15 (3H, s, CH_3), 2.30 (4H, t, *J* = 7.0 Hz, CH_2), 3.68 (4H, t, *J* = 6.5 Hz, CH_2), 3.91 (6H, s, CH_3), 5.06 (2H, s(br), NH), 7.22 (2H, d, *J* = 2.5 Hz, ArH), 7.24 (1H, d, *J* = 2.0 Hz, ArH), 7.26 (1H, s(br), ArH), 7.39 (2H, dd, *J* = 2.5, 9.5 Hz, ArH), 7.97 – 7.99 (4H, m, ArH), 8.04 (2H, d, *J* = 2.0 Hz, ArH) ppm; δ_c (125 MHz, $CDCl_3$) 24.6, 29.6, 42.2, 50.5, 55.6, 57.0, 99.6, 115.8, 117.9, 124.1, 124.2, 124.4, 128.3, 131.6, 134.7, 146.8, 148.4, 149.9, 155.9 ppm.

DQ 551

DQ 551 was synthesized by general method 1. The product was isolated as a red foam (0.30 g, 50% yield). Mp = 48 – 52 ˚C; IR λ (neat/cm^{-1}) 3944, 3692, 3054, 2987, 1631, 1560, 1422, 1262, 896; HRMS (ES) calcd for $C_{39}H_{44}N_5O_2Cl_2$ 684.2872, found 684.2897 (matches double Cl pattern); δ_H (500 MHz, CD_2Cl_3) 1.45 (8H, s(br), CH_2), 1.78 (4H, s(br), CH_2), 2.12 (3H, s, CH_3), 2.26 (4H, s(br), CH_2), 3.73 (4H, t, *J* = 6.5 Hz, CH_2), 3.98 (6H, s, CH_3), 7.31 – 7.34 (4H, m, ArH), 7.41 – 7.45 (2H, m, ArH), 7.96 – 7.98 (2H, m, ArH), 8.03 (2H, s, ArH), 8.10 (2H, d, *J* = 8.0 Hz, ArH) ppm; δ_c (125 MHz, CD_2Cl_3) 24.7, 26.9, 31.5, 41.8, 50.6, 55.5, 57.4, 99.3, 115.7, 117.8, 124.0, 124.3, 124.5, 128.0, 131.4, 134.4, 146.7, 148.4, 149.8, 155.9 ppm.

DQ 661

DQ 661 was synthesized by general method 2. The product was isolated as a brown orange solid/foam (2.98g, 91%). HRMS (ES) calcd for $C_{41}H_{48}N_5O_2Cl_2$ 712.3185, found 712.3164. IR λ (neat/cm^{-1}) 3293, 2934, 2854,1687, 1657, 1235, 925, 829 ^{1}H NMR (500 MHz, Chloroform-d) δ 8.08 (d, J = 2.1 Hz, 2H, ArH), 8.02 (t, J = 8.9 Hz, 4H, ArH), 7.43 (dd, J = 9.4, 2.7 Hz, 2H, ArH), 7.32 (dd, J = 9.3, 2.1 Hz, 1H, ArH), 7.23 (d, J = 2.7 Hz, 2H, ArH), 4.75 (s, 2H, NH), 3.97 (d, J = 2.9 Hz, 6H, CH_3), 3.70 (s, 4H, CH_2), 2.25 (t, J = 7.6 Hz, 4H, CH_2), 2.17 (s, 3H, CH_3), 1.75 (p, J = 7.5 Hz, 4H, CH_2), 1.43 (d, J = 7.6 Hz, 8H, CH_2), 1.32 (m, 4H, CH_2).^{13}C NMR (126 MHz, $CDCl_3$) δ 155.66, 149.78, 147.98, 146.18, 134.67, 130.80, 127.55, 124.36, 124.28, 123.95, 117.44, 115.25, 99.29, 57.59, 55.43, 50.31, 42.15, 31.50, 29.72, 27.20, 26.79.

DQ 771

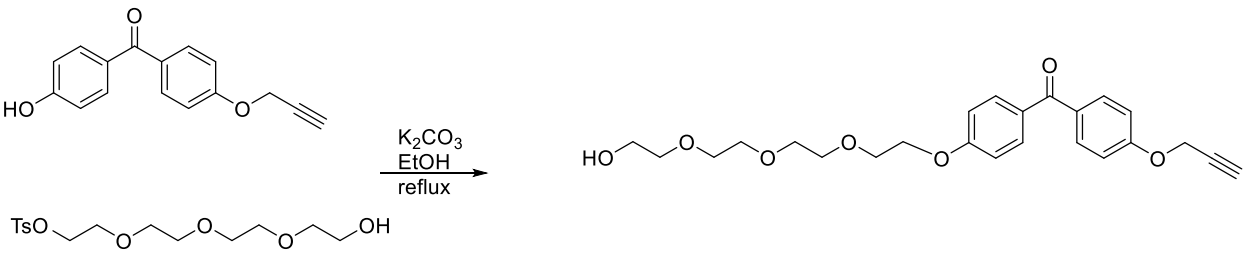
DQ 771 was synthesized by general method 2. The product was isolated as a black/orange solid film. (31mg, 74%). IR λ (neat/cm^{-1}) 3302, 2930, 2854, 2793, 2359, 2341, 1632, 1559, 1236. HRMS (ES) $C_{43}H_{52}Cl_2N_5O_2$ (calc) 739.3420, found 739.3522. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.05 (s, 2H, ArH), 8.02 – 7.95 (m, 4H, ArH), 7.40 (dd, J = 9.4, 2.7 Hz, 2H, ArH), 7.28 (dd, 2H, ArH), 7.22 – 7.18 (m, 2H, ArH), 4.76 (d, *J* = 20.5 Hz, 2H, NH), 3.95 (s, 6H, CH_3), 3.67 (t, J = 7.3 Hz, 4H, CH_2), 2.28 – 2.23 (m, 3H, CH_2), 2.16 (s, 1H, CH_3), 1.73 (p, J = 7.2 Hz, 5H, CH_2), 1.41 (p, J = 6.9 Hz, 9H, CH_2), 1.36 – 1.20 (m, 16H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.99, 149.77, 136.79, 146.18, 134.77, 131.49, 128.23, 124.50, 124.43, 124.01, 117.91, 99.22, 57.79, 55.53, 53.42, 50.72, 42.27, 31.75, 29.29, 27.44, 27.21, 26.90.

DQ 881

DQ 881 was synthesized by general method 2. The product was isolated as a red orange film (15 mg, 72%). IR λ (neat/cm^{-1}) 2930, 2854, 2359, 1632, 1559,1236. HRMS (ES) $C_{45}H_{56}Cl_2N_5O_2$ (calc) 767.3733, found 767.3719. 1H NMR (500 MHz, Chloroform-*d*) δ 8.06 (s, 2H, ArH), 8.03 – 7.97 (m, 4H, ArH), 7.42 (dd, *J* = 9.4, 2.9 Hz, 2H, ArH), 7.30 (dd, *J* = 9.2, 3.4, 2.1 Hz, 2H, ArH), 7.21 (d, *J* = 2.8 Hz, 2H, ArH), 4.72 (s, 2H, NH), 3.96 (d, *J* = 4.6 Hz, 6H, CH_3), 3.68 (t, *J* = 7.1 Hz, 4H, CH_2), 2.27 (dd, *J* = 8.9, 6.2 Hz, 4H, CH_2), 2.18 (d, *J* = 3.5 Hz, 3H, CH_3), 1.73 (p, *J* = 7.5 Hz, 4H, CH_2), 1.49 – 1.19 (m, 24H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.17, 149.93, 148.57, 146.99, 134.91, 131.77, 128.51, 124.71, 124.59, 124.15, 118.13, 116.08, 99.36, 58.06, 57.96, 55.71, 50.95, 42.49, 31.98, 29.66, 29.64, 29.50, 29.47, 28.91, 28.80, 27.63, 27.47, 27.44, 27.08, 27.05, 25.49, 17.30.

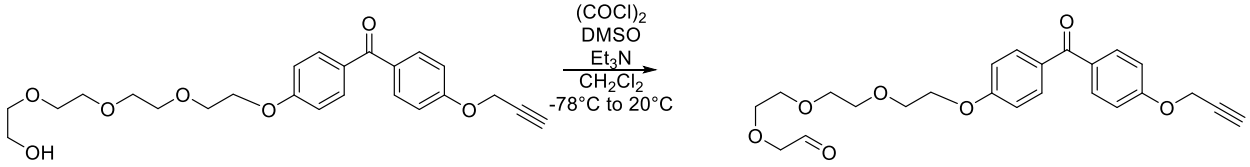
DQ 11111

DQ 11111 was synthesized by general method 2. The product was isolated as a red orange paste (53mg, 75%). IR λ (neat/cm^{-1}) 2925, 2852, 2793, 1631, 1465, 1236. HRMS (ES) $C_{51}H_{68}Cl_2N_5O_2$ (Calc) 852.4672, found (M+H) 852.4634. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 2.1 Hz, 2H, ArH), 7.98 (dd, *J* = 9.4, 2.3 Hz, 4H, ArH), 7.40 (dd, *J* = 9.4, 2.7 Hz, 2H, ArH), 7.30 – 7.26 (m, 4H, ArH), 7.18 (d, *J* = 2.7 Hz, 2H, ArH), 3.94 (s, 6H, CH_3), 3.66 (t, *J* = 7.2 Hz, 4H, CH_2), 2.31 – 2.24 (m, 4H, CH_2), 2.19 (s, 3H, CH_3), 1.72 (p, *J* = 7.3 Hz, 4H, CH_2), 1.46 – 1.36 (m, 8H, CH_2), 1.34 – 1.15 (m, 30H, CH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.09, 149.90, 148.54, 146.95, 134.85, 131.67, 128.41, 124.59, 124.56, 124.16, 118.03, 115.97, 99.31, 58.13, 55.65, 53.57, 50.90, 45.69, 42.52, 31.95, 29.76, 29.70, 29.64, 29.61, 29.47, 27.77, 27.52, 27.06.



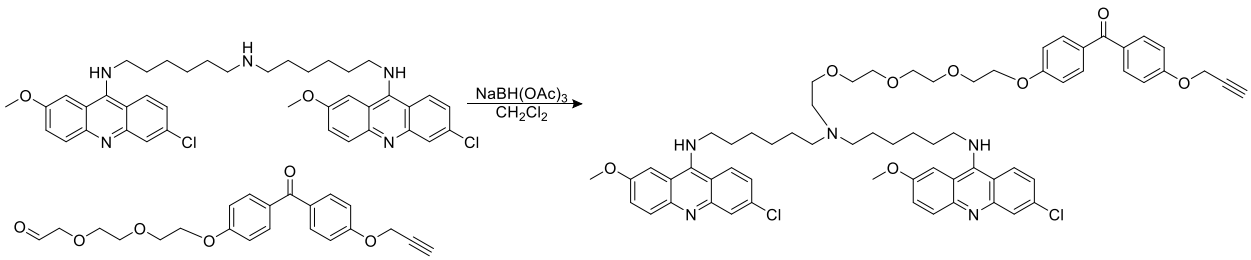
(4-(2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethoxy)phenyl)(4-(prop-2-yn-1-yloxy)phenyl)methanone

(4-hydroxyphenyl)(4-(prop-2-yn-1-yloxy)phenyl)methanone[6] (1.021g, 4.052 mmol) was added to a round bottom flask, under an argon atmosphere, followed by K_2CO_3 (1.104g, 8.1 mmol, 2.0 eq). 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (1.551g, 4.46 mmol, 1.1 eq)[7] was dissolved in absolute ethanol (8 mL, 0.5M), and added to the reaction vessel. The reaction was heated to reflux under a condenser for 16 hours. The reaction was halted upon consumption of the tosylate starting material as determined by TLC (R_f 0.2, EtOAc). The reaction was concentrated under reduced pressure to a yellow-white paste, which was dissolved in a mixture of 15 mL of water and 15 mL of EtOAc. The layers were separated, and the aqueous layer was washed 2 x 25 mL EtOAc. The combined organic layers were washed once with brine and dried over anhydrous Na_2SO_4. Evaporation under reduced pressure yielded a yellow clear paste (2.06g). The crude material was purified by column chromatography (45mm x 150mm, SiO_2, EtOAc, R_f 0.18) affording a translucent paste (1.314g, 76%). IR λ (neat/cm^{-1}): 2873, 1644, 1600, 1507. HRMS (ESI) Calc. (M+H) $C_{24}H_{29}O_7$ 429.1913, found 429.1933. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80-7.77 (4H, m, ArH), 7.04 (2H, d, *J*= 8.7 Hz, ArH), 6.98 (2H, d, *J*= 8.7 Hz, ArH), 4.78 (2H, d, *J*=2.4 Hz, CH_2), 4.22 (2H, t, *J*=4.81, CH_2), 3.90 (2H, t, *J*= 4.84, CH_2), 3.76-3.61 (m, 12H, CH_2), 2.56 (1H, s, CH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.47, 162.27, 160.77, 132.35, 132.22, 131.68, 130.85, 114.49, 114.24, 78.05, 76.27, 71.00, 70.81, 70.73, 70.48, 69.70, 67.75, 61.87, 56.00.



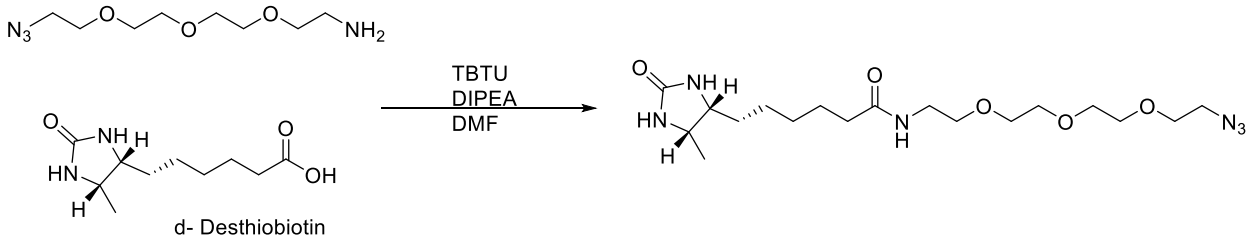
2-(2-(2-(2-(4-(4-(prop-2-yn-1-yloxy)benzoyl)phenoxy)ethoxy)ethoxy)ethoxy)acetaldehyde

In a flame dried round bottom flask under an argon atmosphere, a solution of freshly distilled oxalyl chloride (0.308 mL, 3.6 mmol, 1.2 eq) in dichloromethane(20 mL), cooled to -78°C, was treated with DMSO (0.51 mL, 7.2 mmol, 2.4 eq), and bubbling of the resulting mixture was observed. The reaction mixture was stirred for 30 min at -78°C, and then treated with a solution of (4-(2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)ethoxy)phenyl)(4-(prop-2-yn-1-yloxy)phenyl)methanone (1.284g, 3 mmol, 1.0 eq) in dichloromethane. Prior to addition, the alcohol was dried azeotropically with benzene and then placed under high vacuum for 16 hours to remove water. The resulting solution was stirred at -78°C for 1 hour and then treated with freshly distilled triethylamine (2.01 mL, 15.0 mmol, 5.0 eq). The resulting mixture was slowly warmed to 23°C and stirred at 23°C for 16 hours. The progress of the reaction was determined via TLC by consumption of the starting alcohol (TLC R_f 0.18, EtOAc) and the appearance of a new TLC spot for the aldehyde product (R_f 0.6, EtOAc). The reaction mixture was then washed 3 x 20 mL with saturated aqueous NH_4Cl, 1 x 20 mL brine, and the resulting organic solution dried over anhydrous Na_2SO_4. The filtrate was concentrated under reduced pressure, and the residue treated with toluene, which was then evaporated to remove dimethyl sulfide. The crude aldehyde was used without further purification in the next reaction. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (1H, s, CHO), 7.8-7.5 (4H, m, ArH), 7.04 (2H, d, J= 9.0 Hz, ArH), 6.98 (2H, d, J=8.0 Hz, ArH), 4.75 (2H, d, J= 2.0 Hz, CH_2), 4.18 (2H, t, J= 4.35, CH_2), 4.13 (2H, s, CH_2), 3.87 (2H, t, J= 3.86, CH_2), 3.76-3.61, (10H, m, CH_2), 2.56(1H, s, CH).



DQ661-alkyne ((4-((18-((6-chloro-2-methoxyacridin-9-yl)amino)-12-(6-((6-chloro-2-methoxyacridin-9-yl)amino)hexyl)-3,6,9-trioxa-12-azaoctadecyl)oxy)phenyl)(4-(prop-2-yn-1-yloxy)phenyl)methanone)

In a flame dried round bottom flask under an argon atmosphere, a suspension of DQ660 (320mg, 0.458 mmol) in 2 mL of dichloromethane was treated with a solution of 2-(2-(2-(2-(4-(4-(prop-2-yn-1-yloxy)benzoyl)phenoxy)ethoxy)ethoxy)ethoxy) acetaldehyde (558mg, 1.31 mmol, 2.9 eq) in 3.5 mL of dichloromethane, bringing the reaction to a final concentration of 0.08 M. The two components were stirred for 15 minutes at 23°C and the resulting orange mixture became homogeneous. $NaBH(OAc)_3$ (388mg, 1.832 mmol, 4.0 eq) was added as a solid to the reaction mixture and the resulting mixture was stirred for 16 hours at 23°C, until the DQ 660 was consumed as observed by TLC. The reaction mixture was then diluted with dichloromethane (50 mL) and stirred with an equal volume of 2N NaOH (50 mL) for 1 hour at 23°C. The layers were separated and the aqueous layer was washed with 2 x 20 mL of dichloromethane. The combined organic layers were washed once with brine and dried over anhydrous Na_2SO_4. Evaporation under reduced pressure afforded an orange paste, which was purified by column chromatography (35mm x 150mm, SiO_2, 5% MeOH:94% EtOAc:1%TEA) to yield an orange paste (200mg, 39%). IR λ (neat/cm^{-1}): 2921, 2848, 1756, 1719, 1627, 1594, 1558, 1254. HRMS(ESI) calc. (M + H) $C_{64}H_{72}N_5O_8Cl_2$ 1108.4758, found 1108.4749. ^{1}H NMR (500 MHz, $CDCl_3/CD_3OD$): δ 8.05 (2H, s, ArH), 8.00 (4H, t, J= 9.0 Hz, ArH), 7.77-7.74 (4H, m, ArH), 7.42 (2H, dd, J=9.2 Hz, J= 2.5 Hz, ArH), 7.30 (2H, dd, J=9.3 Hz, J=2.5 Hz, ArH), 7.23 (2H, d, J=2.6 Hz, ArH), 7.03 (2H, d, J=8.9 Hz, ArH), 6.94 (2H, d, J=8.3, ArH), 4.75 (2H, d, J= 2.4 Hz, CH_2), 4.17 (2H, t, J=5.0 Hz, CH_2), 3.95 (6H, s, OMe), 3.85 (2H, t, J=3.8 Hz, CH_2), 3.70-3.56 (14H, m, CH_2) 2.59 (2H, t, J=6.5 Hz, CH_2), 2.55 (1H,s, CH), 2.36 (4H, t, J= 7.0 Hz, CH_2), 1.72 (4H, m, CH_2), 1.39 (8H, m, CH_2), 1.27 (4H, m, CH_2). ^{13}C NMR (126 MHz, $CDCl_3/CD_3OD$): δ 194.23, 162.03, 160.57, 155.88, 149.712, 148.187, 134.67, 132.108, 131.99, 131.39, 130.62, 128.11, 124.36, 124.32, 123.99, 117.80, 115.70, 114.26, 113.97, 99.21, 77.80, 76.02, 70.80, 70.58, 70.32, 69.71, 69.45, 67.52, 55.78, 55.45, 54.58, 53.21, 50.54, 31.65, 27.08, 26.98, 26.77.



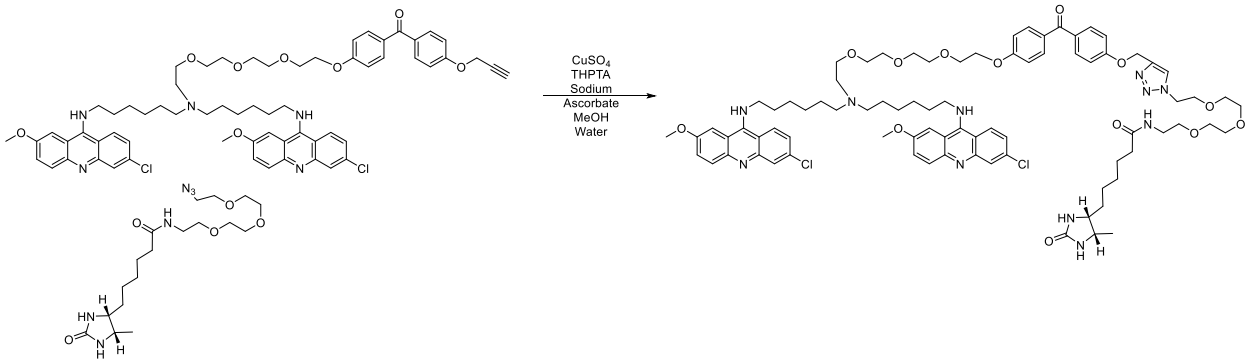
d- Desthiobiotin

Desthiobiotin Azide

To a flame dried round bottom flask, d-desthiobiotin (200mg) was added, followed by TBTU (449mg,). The solids were placed under an atmosphere of argon and dissolved in dimethylformamide (2mL). The solution was stirred and and 2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethan-1-amine (305mg, ,1.5 equiv)[6] was added as a solution in dimethylformamide (1mL). Then after stirring for 5 min, DIPEA (488 uL, ,4.0 equiv). The reaction is stirred for 24 hours until the starting desthiobiotin is consumed, as observed by TLC (Rf = 0.1, 10:1 chloroform:methanol). The reaction is quenched by pouring onto 30 mL of brine, and is extracted with ethyl acetate (3x30mL). The combined organic layers were then washed with water (5x10mL, second aqueous fraction). TLC analysis revealed the product was found exclusively in the water wash (second aqueous fraction). The second aqueous fraction was then extracted with ethyl acetate (5x50mL), dried over anhydrous sodium sulfate and concentrated to a brown oil. NMR analysis

reveals the crude is mostly dimethylformamide and product. The crude product was then purified by column chromatography [SiO2, 20 mm x 180 mm, gradient elution of increasing methanol in chloroform (2% for 100 mL, 4% for 100 mL, and 6% for 200 mL). The product was isolated as a purple-translucent oil (163mg, 42%) ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.16 (s, 1H), 3.91 – 3.82 (m, 1H), 3.74 – 3.54 (m, 13H), 3.50 – 3.36 (m, 4H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.66 (t, *J* = 7.3 Hz, 2H), 1.56 – 1.23 (m, 7H), 1.14 (d, *J* = 6.5 Hz, 3H).^{13}C NMR δ_c ($CHCl_3$): 15.7, 25.2, 25.8, 28.6, 29.5, 35.84, 39.1, 50.7, 51.4, 56.1, 70.0(2C), 70.1, 70.5, 70.7, 77.4, 164.2, 173.2. HRMS (ESI): $C_{18}H_{35}N_6O_5$, calc. for $C_{18}H_{36}N_6O_5$ [M+H] = 415.2669, found: 415.2666.

DQ661 Photoaffinity/Biotinylated Probe



N-(2-(2-(2-(2-(4-((4-(4-((18-((6-chloro-2-methoxyacridin-9-yl)amino)-12-(6-((6-chloro-2-methoxyacridin-9-yl)amino)hexyl)-3,6,9-trioxa-12-azaoctadecyl)oxy)benzoyl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-6-((4R,5S)-5-methyl-2-oxoimidazolidin-4-yl)hexanamide

To a solution of DQ661-alkyne (58mg, 0.052 mmol) and desthiobiotin-azide(33mg, 0.08mmol, 1.5 eq) in 250 µL of MeOH in a resealable vial was added 200 µL of a solution that was 20 mM in $CuSO_4$ (0.65mg, 0.004mmol) and 44 mM in THPTA (3.9mg, 0.009mmol; Tris(3-hydroxypropyltriazolylmethyl)amine) which had been treated with 2 mg (10 µmoles) of sodium ascorbate to discharge the blue color before addition to the reaction mixture. The resulting mixture was stirred for 20 hours at 23°C. The reaction mixture was concentrated to a paste under reduced pressure and the residue partitioned between chloroform (5mL) and water (5mL). The water was extracted 6 x 5 mL with 3:1 chloroform: isopropanol, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 94 mg of crude product, which was chromatographed (20 mm x 150 mm, SiO_2, 10% MeOH: 90%CH_2Cl_2). The resulting product required further purification (RP-HPLC). The chromatographed product (36mg) was purified as the TFA salt by RP-HPLC (C_{18}, gradient elution using 35%-53% acetonitrile in water with 0.1% TFA over 15 min) yielded a yellow film (18 mg, 23%). IR λ (neat/cm^{-1}): 3040, 1652, 1447, 1197, 1123. HRMS (ESI) calc ([M+2H]/2) $C_{82}H_{106}Cl_2N_{11}O_{13}$ 761.8713, found 761.8740. ^{1}H NMR (500 MHz, CD_3OD): δ 8.51 (2H, d, *J* = 9.3 Hz, ArH), 8.18 (1H, s, ArH), 7.86 (4H, dd, J = 12.5 Hz, J = 2.5 Hz, ArH), 7.81 – 7.77 (6H, m, ArH), 7.72 (2H, dd, *J* = 9.0 Hz, *J* = 2.5 Hz, ArH), 7.57 (2H, dd, *J* = 9.3, *J* =2.1 Hz, ArH), 7.06 (2H, d, *J* = 8.7 Hz, ArH), 6.94 (2H, d, *J* = 8.7 Hz, ArH), 4.61 (2H, t, J = 4.3 Hz, CH_2), 4.26 (2H, t, *J* = 4.5 Hz, CH_2), 3.99 (6H, s, OMe), 3.92-3.88 (4H, m, CH_2), 3.85 – 3.78 (4H, m, CH_2), 3.73 – 3.56 (18H, m, CH_2), 3.49 (2H, t, *J* = 5.5 Hz, CH_2), 3.18 – 3.13 (4H, m, CH_2), 2.92 (4H, t, J= 8.0 Hz), 2.17 (2H, t, *J* = 8.0 Hz, CH_2), 1.97 (4H, q, *J* = 7.6 Hz), 1.72-1.58 (13H, m), 1.50 – 1.29 (14H, m), 1.35 (2H, q, *J* = 6.5 Hz), 1.10 (3H, d, *J* = 6.5 Hz, CH_3).^{13}C NMR (126 MHz, CD_3OD): δ 194.32, 174.82, 171.61, 164.75, 162.33, 161.82, 156.61, 142.74, 140.39, 131.87, 131.82, 130.26, 130.08, 127.25, 125.03, 123.57, 120.20 ,117.27, 114.03, 113.72, 70.33, 70.09, 70.03, 69.98, 69.82, 69.28, 69.14, 68.89, 67.61, 65.51, 64.26, 61.09, 60.16, 60.14, 55.96, 55.28, 53.06, 52.54, 52.08, 51.28, 50.11, 48.90, 38.89, 35.48, 31.36, 29.31, 29.12, 28.80, 25.96, 25.79, 25.42, 23.08, 22.31, 19.50, 19.47, 14.25, 14.04, 13.06.

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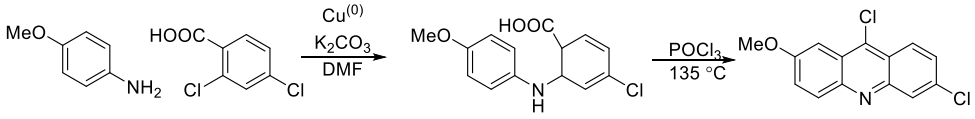
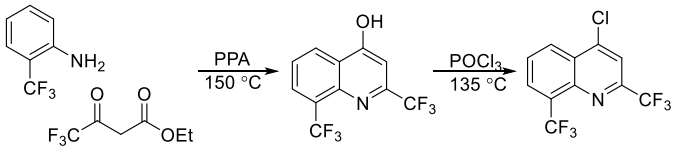
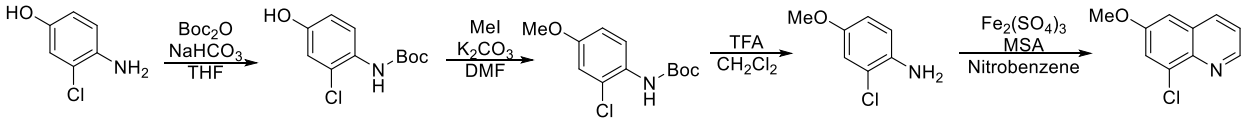
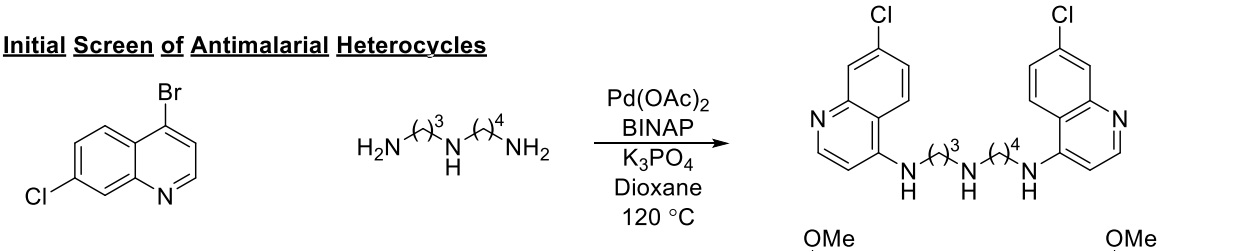
Synthesis of Heterocycles

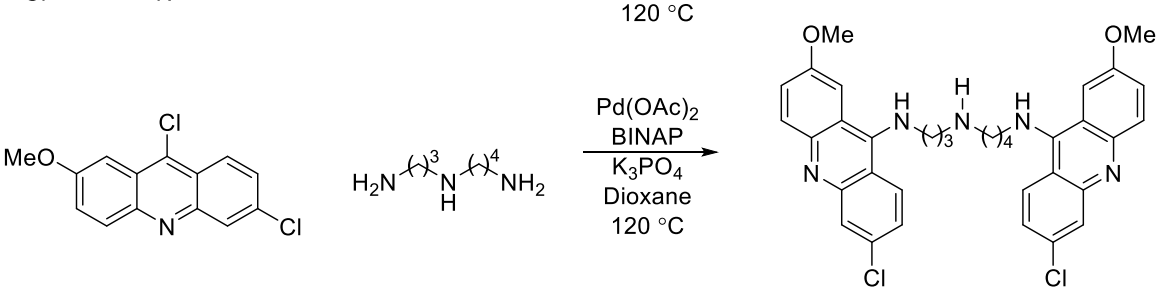


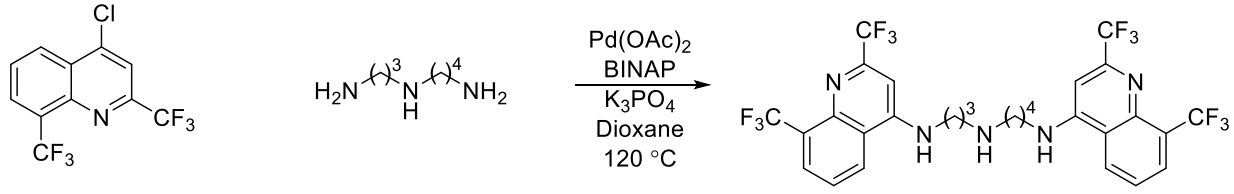


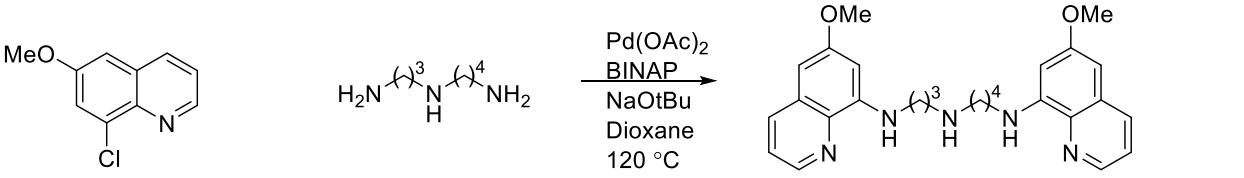


Initial Screen of Antimalarial Heterocycles









Expansion of Dimeric Quinacrine Library