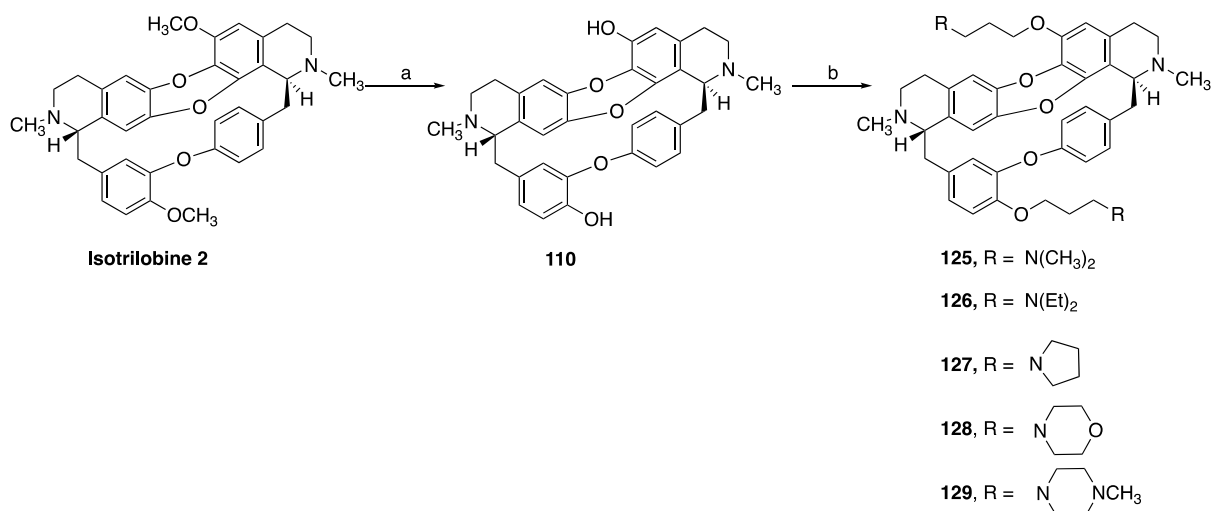


Supplementary Information Data S2

General procedure for the synthesis of compounds **125** – **129**, related to STAR Methods

Synthesis of intermediate **110**.



Scheme S1 -Related to Figure 3A.

a) i) NaH, EtSH, DMF, 0°C, 30 min; ii) isotrilobine **2**, 150°C, 30 min; b) i) NaH, DMF, 0°C, 30 min; ii) Desired chloro-derivative, 80°C, 15 h.

(1^{1S},1^{12S})-1²,1¹¹-dimethyl-1¹,1²,1³,1⁴,1⁹,1¹⁰,1¹¹,1¹²-octahydro-4-oxa-1(12,1)-[1,4]dioxino[2,3-g:6,5-h']diisoquinolina-3(1,3),5(1,4)-dibenzenacyclohexaphane-1⁶,3⁴-diol. (**110**)

To a solution of NaH (90 %) (375 mg, 15.6 mmol, 12 eq.), in dry DMF (15 mL) in a round bottom flask under argon, at 0°C, was added EtSH (0.77 mL, 10.4 mmol, 8 eq.). After a stirring at 0°C for 30 min, isotrilobine **2** was added (750 mg, 1.3 mmol, 1 eq.) and the mixture was heated at 150°C for 30 min. The mixture is quenched with few drops of saturated solution of NaHCO₃ and stirred in an open flask at RT overnight. The mixture is evaporated to dryness and the residue was purified by silica gel chromatography using a linear gradient of 1% ammonia in methanol (0 to 20% MeOH/NH₃) in dichloromethane to afford **110** as a yellow solid (605 mg, 1.10 mmol, 85 %).

¹H NMR (DMSO-*d*₆, 500 MHz) 9.48 (s, 1H), 9.33 (s, 1H), 7.57 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.22 – 7.13 (m, 2H), 7.02 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.74 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.59 (s, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 6.29 (s, 1H), 5.99 (s, 1H), 3.92 – 3.87 (m, 1H), 3.28 – 3.20 (m, 1H), 3.06 (s, 1H), 3.04 – 2.93 (m, 1H), 2.86 – 2.51 (m, 8H), 2.48 (s, 3H), 2.45 – 2.34 (m, 2H), 2.27 (s, 3H).

¹³C NMR (DMSO-*d*₆, 126 MHz) δ 153.7, 148.7, 144.3, 143.4, 139.7, 139.0, 138.9, 138.7, 135.4, 133.1, 131.1, 130.1, 128.3, 127.9, 127.7, 122.3, 121.9, 121.5, 118.6, 116.7, 116.5, 115.2, 113.4, 110.7, 67.4, 59.7, 49.9, 44.7, 42.7, 41.6, 41.1, 27.4, 23.3.

MS (ESI) (*m/z*) calculated for C₃₄H₃₃N₂O₅ [M+H]⁺ : 549.6; Found : 549.6.

General procedure Compounds 125 to 129 synthesis:

To a solution of compound **110** (75 mg, 0.14 mmol, 1 eq.) in dry DMF (4 mL) in a round bottom flask under Argon, at 0°C, was added NaH (90 %) (17 mg, 0.7 mmol, 5 eq.). After a stirring at 0°C for 30 min, the desired chloro-derivatives was added (0.42 mmol, 3 eq.) and the mixture was heated at 80°C overnight. The mixture was quenched with a minimum of saturated solution of NaHCO₃ and evaporated to dryness. A saturated solution of saturated NaHCO₃ was added to the residue and the resulting solution was extracted with EtOAc thrice. The combined organic layers were dried over sodium sulfate, filtrated and evaporated to dryness. The residue was purified by silica gel chromatography using a linear gradient of ammonia 1N in methanol (0 to 30 % MeOH/NH₃) in dichloromethane to afford the desired product as a pale-yellow solid.

3,3'-(((1¹S,1¹²S)-1²,1¹¹-dimethyl-1¹,1²,1³,1⁴,1⁹,1¹⁰,1¹¹,1¹²-octahydro-4-oxa-1(12,1)-[1,4]dioxino[2,3-g:6,5-h']diisoquinolina-3(1,3),5(1,4)-dibenzenacyclohexaphane-1⁶,3⁴-diyl)bis(oxy))bis(N,N-dimethylpropan-1-amine) (125)

Yield : 45%.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.58 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.21 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.17 (dd, *J* = 8.3, 2.7 Hz, 1H), 7.02 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.85 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.64 (s, 1H), 6.49 (s, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 5.98 (s, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 4.00 (t, *J* = 6.5 Hz, 2H), 3.95 – 3.90 (m, 1H), 3.31 – 3.12 (m, 2H), 3.08 – 2.96 (m, 2H), 2.90 – 2.71 (m, 4H), 2.68 – 2.51 (m, 3H), 2.49 – 2.49 (m, 3H), 2.49 – 2.37 (m, 3H), 2.35 (t, *J* = 7.0 Hz, 2H), 2.28 (s, 3H), 2.16 (s, 6H), 2.14 (s, 6H), 1.90 (p, *J* = 6.8 Hz, 2H), 1.84 (p, *J* = 6.8 Hz, 2H).

¹³C NMR (126 MHz, , DMSO-*d*₆) δ 153.3, 150.0, 146.0, 144.9, 139.9, 138.9, 138.8, 138.5, 135.5, 134.8, 131.1, 130.3, 128.9, 128.3, 127.9, 122.3, 121.7, 121.6, 120.3, 115.4, 114.2, 113.4, 108.3, 67.3, 67.1, 67.0, 59.6, 55.7, 55.5, 49.8, 45.2, 45.2, 44.7, 42.8, 41.6, 41.0, 27.5, 27.1, 26.9, 23.5.

HRMS (ESI) (m/z) calculated for C₄₄H₅₄N₄O₅ [M+H]⁺: 719.4167; Found: 719.4138

3,3'-(((1¹S,1¹²S)-1²,1¹¹-dimethyl-1¹,1²,1³,1⁴,1⁹,1¹⁰,1¹¹,1¹²-octahydro-4-oxa-1(12,1)-[1,4]dioxino[2,3-g:6,5-h']diisoquinolina-3(1,3),5(1,4)-dibenzenacyclohexaphane-1⁶,3⁴-diyl)bis(oxy))bis(N,N-diethylpropan-1-amine) (126)

Yield : 45%.

¹H NMR (500 MHz, DMSO-*d*₆) δ 7.61 – 7.55 (m, 1H), 7.23 – 7.18 (m, 1H), 7.16 (dd, *J* = 8.3, 2.7 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.88 – 6.82 (m, 1H), 6.61 (s, 1H), 6.48 (s, 1H), 6.43 (d, *J* = 2.1 Hz, 1H), 5.98 (s, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 3.94 – 3.89 (m, 1H), 3.29 – 3.22 (m, 1H), 3.07 – 2.96 (m, 2H), 2.89 – 2.72 (m, 4H), 2.63 – 2.51 (m, 6H), 2.49 – 2.37 (m, 12H), 2.27 (s, 3H), 1.87 (p, *J* = 6.7 Hz, 2H), 1.81 (p, *J* = 6.6 Hz, 2H), 0.99 – 0.91 (m, 12H).

¹³C NMR (126 MHz, , DMSO-*d*₆) δ 153.4, 150.1, 146.0, 145.0, 139.8, 138.9, 138.8, 138.5, 135.5, 134.8, 131.1, 130.3, 128.9, 128.3, 127.9, 122.3, 121.7, 121.6, 120.3, 116.5, 115.3, 114.2, 113.4, 108.4, 67.3, 67.0, 67.0, 59.6, 49.8, 48.7, 48.5, 46.4, 46.4, 44.7, 42.8, 41.6, 41.0, 27.5, 26.8, 26.5, 23.5, 11.8, 11.8.

HRMS (ESI) (m/z) calculated for C₄₈H₆₂N₄O₅ [M+H]⁺: 775.4793; Found: 775.4763

(1¹S,1¹²S)-1²,1¹¹-dimethyl-1⁶,3⁴-bis(3-(pyrrolidin-1-yl)propoxy)-1¹,1²,1³,1⁴,1⁹,1¹⁰,1¹¹,1¹²-octahydro-4-oxa-1(12,1)-[1,4]dioxino[2,3-g:6,5-h']diisoquinolina-3(1,3),5(1,4)-dibenzenacyclohexaphane (127)

Yield : 40%

¹H NMR (500 MHz, DMSO-*d*₆) 7.58 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.21 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.02 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.64 (s, 1H), 6.50 (s, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 5.98 (s, 1H), 4.13 – 4.09 (m, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.95 – 3.90 (m, 1H), 3.31 – 3.22 (m, 1H), 3.08 – 2.96 (m, 2H), 2.89 – 2.72 (m, 4H), 2.68 – 2.51 (m,

6H), 2.49 – 2.33 (m, 12H), 2.28 (s, 3H), 1.94 (p, $J = 6.8$ Hz, 2H), 1.88 (p, $J = 6.8$ Hz, 2H), 1.73 – 1.63 (m, 8H).

^{13}C NMR (126 MHz, , DMSO- d_6) δ 153.3, 150.0, 146.0, 144.9, 139.9, 138.9, 138.8, 138.5, 135.5, 134.8, 131.2, 130.3, 128.9, 128.3, 127.9, 122.4, 121.8, 121.6, 120.3, 116.5, 115.4, 114.1, 113.4, 108.3, 67.3, 67.1, 67.0, 59.6, 53.6, 53.6, 52.3, 52.1, 49.8, 44.7, 42.8, 41.6, 41.0, 28.4, 28.2, 27.5, 23.5, 23.1.

HRMS (ESI) (m/z) calculated for $\text{C}_{48}\text{H}_{58}\text{N}_4\text{O}_5$ $[\text{M}+\text{H}]^+$: 771.4480; Found: 771.4454

(1¹S,1¹²S)-1²,1¹¹-dimethyl-1⁶,3⁴-bis(3-morpholinopropoxy)-1¹,1²,1³,1⁴,1⁹,1¹⁰,1¹¹,1¹²-octahydro-4-oxa-1(12,1)-[1,4]dioxino[2,3-g:6,5-h']diisoquinolina-3(1,3),5(1,4)-dibenzenacyclohexaphane (128)

Yield : 35%.

^1H NMR (500 MHz, DMSO- d_6) δ 7.58 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.21 (dd, $J = 8.4, 2.3$ Hz, 1H), 7.17 (dd, $J = 8.4, 2.7$ Hz, 1H), 7.02 (dd, $J = 8.2, 2.7$ Hz, 1H), 6.98 (d, $J = 8.3$ Hz, 1H), 6.86 (dd, $J = 8.2, 2.1$ Hz, 1H), 6.64 (s, 1H), 6.50 (s, 1H), 6.44 (d, $J = 2.1$ Hz, 1H), 5.98 (s, 1H), 4.10 (t, $J = 6.4$ Hz, 2H), 4.02 (t, $J = 6.4$ Hz, 2H), 3.92 (t, $J = 3.4$ Hz, 1H), 3.57 (t, $J = 4.6$ Hz, 8H), 3.25 (dd, $J = 15.9, 2.6$ Hz, 1H), 3.08 – 2.96 (m, 2H), 2.91 – 2.71 (m, 4H), 2.66 – 2.55 (m, 2H), 2.49 – 2.33 (m, 12H), 2.28 (s, 3H), 1.93 (p, $J = 6.8$ Hz, 2H), 1.88 (p, $J = 6.8$ Hz, 2H).

^{13}C NMR (126 MHz, , DMSO- d_6) δ 153.3, 150.1, 145.9, 144.9, 139.9, 138.8, 138.8, 138.5, 135.5, 134.9, 131.2, 130.3, 128.9, 128.3, 127.9, 122.3, 121.8, 121.6, 120.4, 116.5, 115.4, 114.3, 113.4, 108.4, 67.3, 67.1, 67.0, 66.2, 59.6, 54.9, 54.7, 53.4, 53.4, 49.8, 44.7, 42.8, 41.6, 41.0, 27.5, 26.1, 25.9, 23.5.

HRMS (ESI) (m/z) calculated for $\text{C}_{48}\text{H}_{58}\text{N}_4\text{O}_7$ $[\text{M}+\text{H}]^+$: 803.4378; Found: 803.4363.

(1¹S,1¹²S)-1²,1¹¹-dimethyl-1⁶,3⁴-bis(3-(4-methylpiperazin-1-yl)propoxy)-1¹,1²,1³,1⁴,1⁹,1¹⁰,1¹¹,1¹²-octahydro-4-oxa-1(12,1)-[1,4]dioxino[2,3-g:6,5-h']diisoquinolina-3(1,3),5(1,4)-ibenzenacyclohexaphane (129)

Yield : 25%.

^1H NMR (500 MHz, DMSO- d_6) δ 7.61 – 7.55 (m, 1H), 7.20 (dd, $J = 8.3, 2.3$ Hz, 1H), 7.16 (dd, $J = 8.3, 2.7$ Hz, 1H), 7.02 (dd, $J = 8.2, 2.7$ Hz, 1H), 6.97 (d, $J = 8.3$ Hz, 1H), 6.85 (dd, $J = 8.3, 2.1$ Hz, 1H), 6.64 (s, 1H), 6.49 (s, 1H), 6.43 (d, $J = 2.1$ Hz, 1H), 5.97 (s, 1H), 4.09 (t, $J = 6.4$ Hz, 2H), 4.00 (t, $J = 6.4$ Hz, 2H), 3.94 – 3.89 (m, 1H), 3.76 – 3.68 (m, 1H), 3.30 – 3.22 (m, 1H), 3.08 – 2.96 (m, 2H), 2.90 – 2.71 (m, 4H), 2.67 – 2.52 (m, 2H), 2.49 – 2.21 (m, 14H), 2.14 (s, 3H), 1.91 (p, $J = 6.8$ Hz, 2H), 1.85 (p, $J = 6.7$ Hz, 2H).

^{13}C NMR (126 MHz, , DMSO- d_6) δ 153.3, 150.1, 145.9, 144.9, 139.9, 138.9, 138.8, 138.5, 135.5, 134.8, 131.1, 130.3, 128.9, 128.3, 127.9, 122.3, 121.8, 121.6, 120.4, 116.5, 115.4, 114.3, 113.4, 108.4, 70.3, 67.3, 67.1, 67.1, 59.6, 54.8, 54.4, 54.3, 52.8, 52.7, 49.8, 45.8, 44.7, 43.5, 42.7, 41.6, 41.0, 27.5, 26.4, 26.2, 23.5.

HRMS (ESI) (m/z) calculated for $\text{C}_{50}\text{H}_{64}\text{N}_6\text{O}_5$ $[\text{M}+\text{H}]^+$: 829.5011; Found: 829.4996