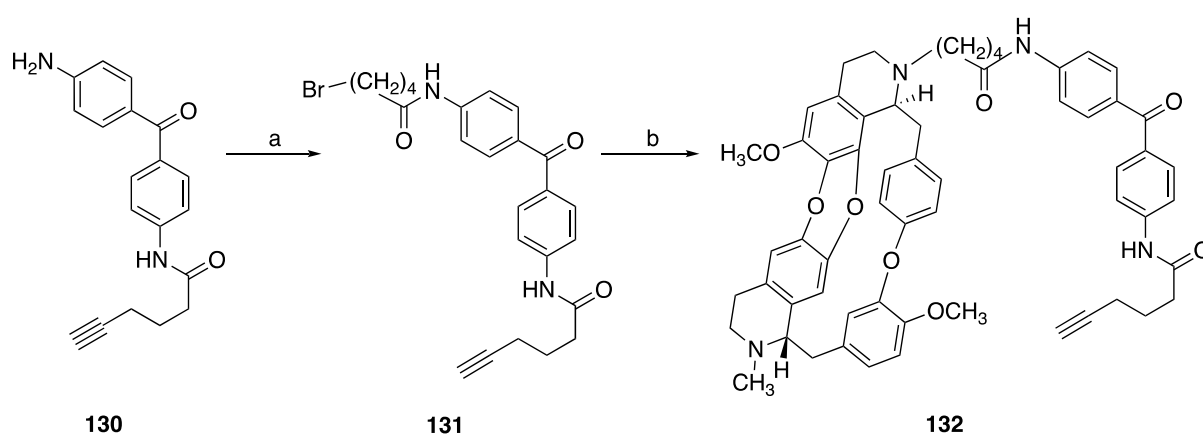


## Supplementary Information Data S3

### Synthesis of the chemical probe **132**, related to STAR Methods



**Scheme S2. Related to Figure 5A.**

a) i) HATU, DIPEA, 5-bromopentanoic acid, DMF, RT, 20min; ii) **130**, RT, 6h. b) Trilobine **1**, TEA, DMF, RT, 18 h.

#### ***N*-(4-(4-(5-bromopentanamido)benzoyl)phenyl)hex-5-ynamide (**131**)**

HATU (0.41 g; 1.08 mmol) was solubilized in dry DMF (2 mL) at RT under argon. To the solution was added 5-bromopentanoic acid (149 mg; 0.81 mmol) and DIPEA (0.2 mL; 1.13 mmol) at RT for 20 min. **130** (ref. 1) (167 mg; 0.54 mmol) was then added. The reaction mixture was stirred at RT for 6 h. The residue was diluted with ethyl acetate and washed with water and brine, and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0 to 60 % of EtOAc) in cyclohexane to afford **63** as a brown solid (145 mg; 0.31 mmol; 57 %).

<sup>1</sup>H NMR (500MHz, DMSO-*d*6)  $\delta$  10.30 (s, 1H, HNH), 10.28 (s, 1H, HNH), 7.78-7.67 (m, 8H), 3.57 (t,  $J=6.7$  Hz, 2H), 2.84 (t,  $J=2.6$  Hz, 1H), 2.48 (t,  $J=7.5$  Hz, 2H), 2.41 (t,  $J=7.4$  Hz, 2H), 2.24 (dt,  $J=2.6, 7.1$  Hz, 2H), 1.86 (p,  $J=8.2$  Hz, 2H), 1.78 (p,  $J=7.4$  Hz, 2H), 1.77-1.69 (p,  $J=7.3$  Hz, 2H).

<sup>13</sup>C NMR (125MHz, DMSO-*d*6)  $\delta$  193.4, 171.5, 171.2, 143, 131.7, 130.9, 118.2, 84.0, 71.7, 35.4, 35.2, 34.8, 31.7, 23.8, 23.6, 17.3.

MS (ESI) (m/z) calculated for C<sub>24</sub>H<sub>26</sub>BrN<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 468.1; Found: 468.2

***N*-(4-(4-(5-(((1*S*,1*S*)-1,3-dimethoxy-1-methyl-1,1,1,1,1,1,1,1-octahydro-4-oxa-1(12,1)-[1,4]dioxino[2,3-*g*:6,5-*h*']diisoquinolina-3(1,3),5(1,4)dibenzenacyclohexaphane-1-yl)pentanamido)benzoyl)phenyl)hex-5-ynamide (**132**)**

A solution of **131** (30 mg; 64  $\mu\text{mol}$ ), trilobine **1** (40 mg; 70  $\mu\text{mol}$ ) and TEA (178  $\mu\text{l}$ ; 1.28  $\mu\text{mol}$ ) in DMF (0.6mL) was stirred at RT for 18h. The reaction mixture was directly by C18 reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (05 to 95%  $\text{CH}_3\text{CN}$ ) to afford compounds **132** (22 mg; 24  $\mu\text{mol}$ ; 37 %).

$^1\text{H NMR}$  (500 MHz,  $\text{DMSO-}d_6$ )  $\delta$  10.32 (s, 1H), 10.27 (s, 1H), 8.27 (s, 1H), 7.79 – 7.72 (m, 4H), 7.72 – 7.63 (m, 4H), 7.58 (dd,  $J = 8.5, 2.3$  Hz, 1H), 7.20 (dd,  $J = 8.3, 2.2$  Hz, 1H), 7.17 (dd,  $J = 8.3, 2.6$  Hz, 1H), 7.02 (dd,  $J = 8.2, 2.7$  Hz, 1H), 6.97 (d,  $J = 8.3$  Hz, 1H), 6.87 (dd,  $J = 8.2, 2.1$  Hz, 1H), 6.64 (s, 1H), 6.49 (s, 1H), 6.46 (d,  $J = 2.1$  Hz, 1H), 6.03 (s, 1H), 4.01 – 3.96 (m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.30 – 3.24 (m, 1H), 3.13 – 2.97 (m, 3H), 2.91 – 2.74 (m, 4H), 2.69 – 2.53 (m, 6H), 2.50 – 2.35 (m, 7H), 2.29 (s, 3H), 2.25 (td,  $J = 7.0, 2.7$  Hz, 2H), 1.86 – 1.58 (m, 7H).

$^{13}\text{C NMR}$  (126 MHz,  $\text{DMSO}$ )  $\delta$  193.8, 172.4, 171.7, 164.5, 153.8, 150.0, 147.1, 146.0, 143.5, 143.4, 140.5, 139.3, 139.3, 139.1, 136.0, 135.0, 132.1, 132.1, 131.5, 131.3, 130.7, 128.9, 128.6, 128.6, 122.7, 122.2, 121.9, 120.5, 118.6, 118.6, 116.8, 115.8, 113.9, 113.1, 107.5, 72.2, 67.8, 59.4, 56.3, 56.1, 52.4, 50.3, 43.2, 43.2, 42.3, 41.5, 36.8, 35.6, 27.9, 27.6, 24.2, 23.4, 22.6, 17.8.

**HRMS** (ESI) ( $m/z$ ) calculated for  $\text{C}_{59}\text{H}_{58}\text{N}_4\text{O}_8$   $[\text{M}+\text{H}]^+$ : 951.4327; Found: 951.4336

## Reference

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