Supporting Information

for

Combinatorial Self-Assembly of Cyclophilin hCyp-18 Ligands Through Rhenium Coordination

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Material

All reagents and solvents were purchased from Sigma-Aldrich, Fisher or Novabiochem and were of the higher purity available. THF was distilled from sodium/benzophenone immediately prior to use. Reaction progress and flash chromatography elution (Merck silica gel 40-63 µm) were monitored by analytical thin-layer chromatography (merck 60F<sub>254</sub>). Spots on TLC were visualized using UV light (254nm), and spots were revealed ninhydrin or phosphomolibdic acid. RP-HPLC analysis and purification were conducted on a Waters 600 Millennium chromatography system couple to a Waters diode array detector. Separations were achieved on a Vydac C18 column eluted with a binary gradient system at a flow rate of 1 mL.mn<sup>-1</sup> for analytical column and 4 mL.mn<sup>-1</sup> for semipreparative column. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AVANCE 250 NMR spectrometer and on a Bruker AVANCE 400 NMR spectrometer for the rhenium complexes; signal are described as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), b (broad), dd (doubled doublet); chemical shifts are reported in ppm relative to TMS. Electrospray mass spectrometry (ES/MS) was performed on a Quattro II (Micromass, Altricham, U.K.) or by Atheris Laboratories (Geneva).

Abbreviations: Ac, acetyl; ACN, acetonitrile; DCC, dicyclohexyl carbodiimide; DCM, dichloromethane; DIPA, diisopropylamine; DIPEA, diisopropylethylamine; DMF, dimethylformamide; DMSO, dimethylsulfoxide; ECANOx, ethyl-2-(hydroxyimino)-2-cyanoacetate; HATU, O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate; NMM, N-methylmorpholine; NMP, N-methyl-2-pyrrolidone; NS<sub>2</sub>HCl, N-bis-(thioethyl)-glycyl disulfide hydrochloride; pNA, 4-nitroaniline; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran.
General procedures for the synthesis of modules A.

Solution synthesis (A3, A4)

**Boc-Gly-R^A.** N-tert-butyloxy carbonyl-glycine (10 mmol, 1.75 g) dissolved in DCM (50 mL) was treated with proline analog R^A—H (10 mmol) and 1N DCC in DCM (12.5 mmol, 12.5 mL). The mixture was stirred overnight at room temperature. After filtration of DCU and evaporation of the solvent, the crude product was purified by silica gel flash chromatography to give Boc-Gly-R^A.

**Fmoc-Lys(Boc)-Gly-R^A.** Boc-Gly-R (2 mmol) was treated with TFA:DCM 50:50 (40 mL) for 30 min at room temperature. The solvent was removed under reduced pressure and the product was dissolved in DCM (20 mL). After neutralization with DIPEA, Fmoc-Lys(Boc)-OH (2 mmol, 0.94 g), DIPEA (4 mmol, 0.7 mL), HOBT (2 mmol, 0.306 g), and 1N DCC in DCM (3 mmol, 3 mL) were successively added. The mixture was stirred overnight and after filtration of DCU and evaporation of the solvent, the crude product was purified by silica gel flash chromatography to give Fmoc-Lys(Boc)-Gly-R^A.

**Fmoc-Lys(COCH\_2N(CH\_2CH\_2S)\_2)-Gly-R^A.** Fmoc-Lys(Boc)-Gly-R^A (1.0 mmol) was treated with TFA:DCM 50:50 (40 mL) for 30 min. The solvent was removed under reduced pressure and the product was dissolved in DCM (20 mL). After neutralization with DIPEA, N-bis-(thioethyl)glycine disulfide hydrochloride (0.89 mmol, 0.204 g), DIPEA (0.89 mmol, 0.16 mL) and 1N DCC in DCM (1.34 mmol, 1.34 mL) were successively added. The mixture was stirred overnight and after filtration of DCU and evaporation of the solvent, the crude product was purified by silica gel flash chromatography to give Fmoc-Lys(COCH\_2N(CH\_2CH\_2S)\_2)-Gly-R^A.
Fmoc-Lys(COCH$_2$N(CH$_2$CH$_2$S)$_2$-Gly-R$^A$. Fmoc-Lys(COCH$_2$N(CH$_2$CH$_2$S)$_2$-Gly-R$^A$ was treated with 20% diisopropylamine in DMF (5 mL) for 2 hrs. The solvent was evaporated in vacuo. The product was dissolved in DCM (5 -10 mL) and washed twice with acidified water (10 mL) in order to set pH to 2. The aqueous layer was freeze-dried, and the purity was checked by RP-HPLC.

Polymer-supported peptide synthesis on Oxime resin (A1, A2, A3, A5, A6).

Fmoc-Lys(COCH$_2$N(CH$_2$CH$_2$S)$_2$-Gly-[Oxime Resin]. Oxime resin (0.56 mmol.g$^{-1}$, 2.15 g, 1.20 mmol) placed in a glass reactor was successively treated as follows: (1) washing, DCM (3x); (2) coupling, Boc-Gly-OH (438 mg, 2.4 mmol), EACNOx (704 mg, 4.8 mmol) and 0.5 M DCC (6 mL) in DCM 15 mL, 20 hrs; (3) washing, DCM (3x), perform coupling twice; (4) washing, DCM:EtOH 2:1 (3x) and EtOH (3x); (5) washing, DCM (3x); (6) capping with Ac$_2$O (154 µL, 1.6 mmol) and NMM (188 µL, 1.6 mmol) in DCM (20 mL), 60 min; (7) washing, DCM (3x); (8) washing, TFA 25% in DCM (1x); (9) deprotection, TFA 25% in DCM, 30 min; (10) washing, DCM (3x); (11) washing, DCM:EtOH 2:1 (3x) and EtOH (3x); (12) washing, DCM (3x); (13) neutralize, NMM 1% in DCM (3x); (14) washing, DCM (3x); (15) coupling, Fmoc-Lys(Boc)-OH (1.0 g, 2.2 mmol), EACNOx (610 mg, 4.2 mmol) and DCC 0.5 M (6 mL) in DCM 15mL, 20 h; (16) washing, DCM (3x), perform coupling twice; (17) washing, DCM:EtOH 2:1 (3x) et EtOH (3x); then steps 7 to14; (15) coupling, NS$_2$.HCl (210 mg, 0.9 mmol), HATU (573 mg, 1.4 mmol) and DIPEA (188 µL, 1.1 mmol) in DCM

a: Boc-Gly-OH, DCC, EACNOx; b: TFA; c: Fmoc-Lys(Boc)-OH, DCC, EACNOx; d: NS$_2$.HCl, HATU; e: R$^A$-H, TEA.
The time and volume for standard washing was 1 min and 15 mL respectively.

**Lys(COCH$_2$N(CH$_2$CH$_2$S)$_2$)-Gly-$\text{R}^A$.** Fmoc-Lys(COCH$_2$N(CH$_2$CH$_2$S)$_2$)-Gly-[Oxime Resin] (255 mg, 0.1 mmol) was treated with 2.0 eq, (0.2 mmol) of $\text{R}^A$-H and 2.0 eq, of triethylamine (28 µL, 0.2 mmol) for 2 days at room temperature. After filtration, the product was purified by RP-HPLC.

**Polymer-supported peptide synthesis on Sulfamylbutyryl resin (A1, A5, A6, A7).**

![Chemical structure](attachment:image.png)

a: Boc-Lys(Fmoc)-OH, DCC, HOBT; b: piperidine; c: NS$_2$.HCl, HATU; d: ICH$_2$CN, DIPEA; e: excess $\text{R}^A$-H; f: TFA.

**Boc-Lys(COCH$_2$N(CH$_2$CH$_2$S)$_2$)-Gly-[Sulfamylbutyryl resin].** Gly-Sulfamylbutyryl (0.24 mmol.g$^{-1}$, m = 2.55 g, 0.61 mmol) placed in a glass reactor was successively treated as follows: (1) washing, DCM (3x); (2) rest 1 hr; (3) washing, DCM (3x); (4) washing, DCM (3x); (5) coupling, Boc-Lys(Fmoc)-OH (2.82 g, 6.0 mmol), HOBT (818 mg, 6.0 mmol) and DCC (1.27 g, 6.1 mmol) in DMF (15mL), 3 hrs; (6) washing, DMF (3x); (7) washing, DCM (3x); (8) washing, MeOH (2x); (9) washing, DCM (3x); (10) washing, DMF (3x); (11) washing, 20% piperidine in DMF (1x); (12) deprotection, 20% piperidine in DMF, 40 min; (13) washing, DMF (3x); (14) coupling, NS$_2$.HCl (142 mg, 0.6 mmol), HATU (359 mg, 0.9 mmol) and DIPEA (90 µL, 0.9 mmol) in DCM 5mL, 24 hrs; (14) washing, DMF (3x); (15) washing, NMP (3x); (16) activate, iodoacetonitrile (1.13 mL, 14.6 mmol) and DIPEA (540 µL, 3.0 mmol) in NMP (13 mL), 20 hrs; (17) washing, NMP (3x); (18) washing, DCM (3x); (19) washing, THF (2x).
Lys(COCH$_2$N(CH$_2$CH$_2$S)$_2$)-Gly-$\text{R}^A$. Boc-Lys(COCH$_2$N(CH$_2$CH$_2$S)$_2$)-Gly-[Sulfamylbutyryl resin] (790 mg, 0.1 mmol) was treated with 10.0 eq (1.0 mmol) of nucleophile $\text{R}^A$-H in THF (5 mL) for 2 days at room temperature. After filtration, the product was purified by silica gel flash chromatography (eluent: DCM:methanol 95:5). Pure Boc-Lys(COCH$_2$N(CH$_2$CH$_2$S)$_2$-Gly-OH (data not shown) was then deprotected with TFA:DCM 50:50 (50 mL.mmol$^{-1}$) for 1 hr at room temperature and the purity was assessed by RP-HPLC.

A1. HPLC. eluent A: H$_2$O-TFA 0.1 %, B: CH$_3$CN, 0-5 min 0 %B, 10 min 10%B, 30 min 12 %B, 35-40 min 100 %B; F = 4 mL.min$^{-1}$; tr = 15.2 min; m = 18 mg (33 %); $^1$H NMR (D$_2$O): $\delta$ 4.4 (m, 1 H, CH$\alpha$ Pro), 4.2 (bs, 3 H, CH$\alpha$ Lys + NCH$_2$CO NS$_2$), 4.0 (m, 2H, CH$\alpha$, Gly), 3.8 (m, 4 H, 2 NCH$_2$ NS$_2$), 3.6 (m, 2 H, CH$\delta$ Pro), 3.2 (m, 6 H, 2CH$_2$-S NS$_2$ + CH$_2$e Lys), 2.3 (m, 4 H CH$_3$$\beta$ + $\gamma$ Pro), 1.9 (m, 2 H, CH$_2$$\beta$ Lys), 1.6 (m, 2 H, CH$_3$$\delta$ Lys), 1.4 (m, 2 H, CH$_2$$\gamma$ Lys); $^{13}$C NMR (D$_2$O): 173.3 (C=O Pro), 166.4 (C=O Lys), 165.2 (C=O Gly), 161.4 (C=O NS$_2$), 62.5 (C$\alpha$ Pro), 56.6 (N C$_2$H$_5$CO + C -N NS$_2$), 54.5 (C$\alpha$ Lys), 49.3 (C$\alpha$ Gly), 43.2 (C$\epsilon$ Lys), 37.9 (C$\delta$ Pro), 35.2 (C-S NS$_2$), 30.3 (C$\delta$ Lys), 26.6 (C$\beta$ Lys), 23.9 (C$\beta$ Pro), 20.5 (C$\gamma$ Lys), 17.6 (C$\gamma$ Pro); ES/MS (positive ionisation) m/z = 475.25 (M+H$^+$).

A2. HPLC. Eluent A: H$_2$O-TFA 0.1 %, eluent B: CH$_3$CN, 0-5 min 0 %B, 10 min 10%B, 30 min 12 %B, 35-40 min 100 %B; F = 4 mL.min$^{-1}$; tr = 18.1 min, m = 7 mg (15%); $^1$H NMR (CD$_3$CN): $\delta$ 7.29-7.25 (m, 3H,, NH), 4.10 (m, 1 H, CH$\alpha$Lys), 3.97 (m, 2 H, NCH$_2$CO NS$_2$), 3.82 (d, 2 H cis and trans, CH$_2$$\alpha$ Gly), 3.60 (m, 4 H CH$_2$NCH$_2$ pyrrolidine), 3.38 (m, 4 H NCH$_2$CO + C-N NS$_2$), 3.0 (m, 4 H CH$_2$NCH$_2$ pyrrolidine), 1.82-1.40 (m, 4 H CH$_2$$\beta$ + $\gamma$ Lys); $^{13}$C NMR (CD$_3$CN): $\delta$ 179.0 + 169.9 + 167.9 (C=O), 58.6 (NCH$_2$CO), 57.9 (C-N NS$_2$), 54.0 (C$\alpha$ Lys), 47.0 (C$\alpha$ Gly), 46.8 + 46.3 (C-N-C pyrrolidine), 42.7 (C$\epsilon$ Lys), 38.7 (C-S NS$_2$), 36.6 (C$\delta$ Lys), 30.0 (C$\beta$ Lys), 24.6 (C-C Pyrrolidine), 21.9 (C$\gamma$ Lys); ES/MS (positive ionisation) m /z = 432.21 (M+H$^+$).

A3. HPLC. eluent A: H$_2$O-TFA 0.1 %, eluent B: CH$_3$CN, 0-5 min 0 %B, 10 min 15%B, 15 min 15 %B, 30-40 min 100 %B; F = 4 mL.min$^{-1}$; tr = 13.2 min, m = 6 mg (17 %); $^1$H NMR (CD$_3$CN): $\delta$ 7.70 (s, 1H,, NH), 7.56 (s, 1H NH), 4.08 (m, 3 H, CH$\alpha$Lys + NCH$_2$CO NS$_2$), 3.80 (s, 2H, CH$_2$$\alpha$ Gly), 3.56 (m, 8H, NCH$_2$ NS$_2$ + morpholine), 3.43-3.41 (m, 4H, CH$_2$OCH$_2$ morpholine), 3.23 (m, 2 H, CH$_2$$\epsilon$ Lys), 3.13 (m, 4 H, CH$_2$S NS$_2$), 1.88 (m, 2 H, CH$_2$$\beta$ Lys), 1.50 (m, 4 H, CH$_2$$\delta$ + $\gamma$ Lys); $^{13}$C NMR (CD$_3$CN): $\delta$ 170.0 + 167.5 (C=O), 67.1 +
67.0 (C-O-C morpholine), 58.6 (NCH₂CO), 57.9 (C-N NS₂ + morpholine), 54.0 (Cα Lys), 45.6 + 42.9 (Cα Gly), 41.9 (Cε Lys), 38.7 + 37.0 (C-S NS₂), 31.2 (Cδ Lys), 29.0 (Cβ Lys), 21.7 (Cγ Lys); ES/MS (positive ionisation) m/z = 448.19 (M+H⁺).

A4. HPLC. eluent A: H₂O-TFA 0.1 %, eluent B: ACN, 0-5 min 0 %B, 30 min 100 %B, 30-40 min 100 %B, F = 4 mL.min⁻¹; tr = 14.0 min, m = 8 mg (10 %); ¹H NMR (D₂O): δ 4.57 (2s, 2 H, cis and trans, NCH₂S thiazolidine), 4.24 (s, 2 H, NCH₂CO NS₂), 4.15 (m, 2 H, CH₂ε Lys), 4.05 (m, 1 H, CHα Lys), 3.85 (t, J = 6 Hz, 4 H, NCH₂NS₂), 3.76 (m, 2 H, NCH₂ thiazolidine), 3.23 (t, J = 6 Hz, 4 H, CH₂S NS₂), 3.13 (m, 2 H, CH₂ε Lys), 3.06 (t, J = 6 Hz, 2 H, CH₂S thiazolidine), 1.88 (m, 2 H, CH₂β Lys), 1.58 (m, 2 H, CH₂δ Lys), 1.47 (m, 2 H, CH₂ γ Lys); ¹³C NMR (D₂O): δ 156.2 (C=O), 59.0 (Cα Lys), 58.6 (NCH₂CO), 53.8 (C-N NS₂), 50.6 + 50.0 (N-C-S thiazolidine), 49.3 + 49.1 (CH₂ Gly), 44.2(Cε Lys), 40.3 + 39.7 (C-S thiazolidine), 36.4 (Cβ Lys), 35.0 + 34.8 (C-S NS₂), 31.1 (Cδ Lys), 22.1 (Cγ Lys); ES/MS (positive ionisation) m/z = 450.21 (M+H⁺).

A5. HPLC. eluent A: H₂O-TFA 0.1 %, eluent B: ACN, 0-5 min 0 %B, 30 min 100 %B, 30-40 min 100 %B, F = 4 mL.min⁻¹; tr = 16.2 min, m = 21 mg (36 %); ¹H NMR (CD₃CN): δ 7.88 (bs, 1H, NH), 7.74 (bs, 1H, NH), 6.94 (bs, 1 H, NH cyclopentylamine), 4.09 (m, 2 H, CHα Lys + N-CH cyclopentylamine), 3.84 (bs, 2 H, CH₂α Gly), 3.75 (bs, 2 H, NCH₂CO NS₂), 3.54 (bs, 4 H, NCH₂ NS₂), 3.18 (m, 2 H, CH₂ε Lys), 3.06 (m, 8H, CH₂S NS₂ + CH₂-CN-CH₂ cyclopentylamine), 1.88 (m, 2 H, CH₂β Lys), 1.68 (m, 4 H, CH₂CH₂ cyclopentylamine), 1.50 (m, 2 H, CH₂ δ Lys), 1.41 (m, 2 H, CH₂γ Lys); ¹³C NMR (CD₃CN): δ 156.2 (C=O), 59.0 (Cα Lys), 58.6 (NCH₂CO), 53.8 (C-N NS₂), 52.0 (C-NH Cyclopentylamine), 50.0 (Cα Lys), 43.4 (Cα Gly), 38.6 (Cε Lys), 37.4 (Cβ Cyclopentylamine), 33.2 (C-S NS₂), 31.0 (β Lys), 29.1 (Cδ Lys), 24.3 (Cγ cyclopentylamine), 21.7 (Cγ Lys); ES/MS (positive ionisation) m/z = 445.92 (M+H⁺).

A6. HPLC. mobile phase A: H₂O-TFA 0.1 %, mobile phase B: ACN, 0-5 min 0 %B, 30 min 100 %B, 30-40 min 100 %B, F = 4 mL.min⁻¹; m = 23 mg (54 %); ¹H NMR (CD₃CN): δ 4.06 (m, 4 H, CHα Lys + NCH₂CO NS₂), 3.70 (bs, 2 H, CH₂α Gly), 3.64 (m, 4 H, NCH₂ NS₂), 3.23 (m, 4 H, CH₂ε Lys + NCH₂ propylamine), 3.14 (m, 4 H, CH₂S NS₂), 2.93 (d, 3 H cis and trans, methylamine), 1.88 (m, 2 H CH₂β Lys), 1.44 (m, 6 H CH₂ γ + δ Lys + CH₂ propylamine), 0.90 (m, 3 H, CH₃ propylamine); ¹³C NMR (CD₃CN): δ 169.2
(C=O), 58.7 (NCH₂CO), 58.0 (C-N NS₂), 54.0 (Cα Lys), 50.9 + 50.2 (N-C propylamine), 42.6 + 42.2 (Cα Gly), 41.8 (Cε Lys), 36.4 (C-S NS₂), 34.5 (Cβ Lys), 33.8 + 33.7 (NCH₃ methylamine), 31.2 + 31.1 (CH₂ propylamine), 28.9 (Cδ Lys), 21.8 (Cγ Lys), 11.4 + 11.1 (CH₃ propylamine); ES/MS (positive ionisation) m/z = 434.16 (M+H⁺).

A7. HPLC. mobile phase A: H₂O-TFA 0.1 %, mobile phase B: ACN, 0-5 min 0 %B, 30 min 100 %B, 30-40 min 100 %B, then the column was re-equilibrated, F = 4 mL·mn⁻¹; m = 20 mg (41 %), tr = 17.0 min; \(^1\)H NMR (CD₃CN): \(\delta\) 5.89 (bs, 2 H, H cis pyrroline), 4.20 (m, 2 H, CHα Lys), 4.15 (bs, 2 H, NCH₂CO NS₂), 4.11-3.97 (m, 4 H, CH₂NCH₂ pyrroline), 3.92 (s, 2 H, CH₂α Gly), 3.64 (m, 4 H, NCH₂ NS₂), 3.27 (m, 2 H, CH₂ε Lys), 3.15 (m, 4 H, CH₂S NS₂), 1.88 (m, 2 H, CH₂β Lys), 1.44 (m, 4 H, CH₂ δ + γ Lys); \(^13\)C NMR (CD₃CN): \(\delta\) 167.5 + 165.5 (C=O), 126.6 + 126.3 (C=C), 58.9 (NCH₂CO), 58.3 (C-N NS₂), 53.3 (Cα Lys), 50.8 (N-C pyrroline), 47.7 (Cα Gly), 42.5 (Cε Lys), 34.6 (C-S NS₂), 32.6 (Cβ Lys), 31.3 (Cδ Lys), 21.8 (Cγ Lys); ES/MS (positive ionisation) m/z = 430.17 (M+H⁺).
General procedure for the synthesis of modules A’.

The hydrochloride salt NS$_2$-OH.HCl (117 mg, 0.5 mmol) was dissolved in DCM (3 mL) and neutralized with DIPEA. Then 1.0 equiv. of amine 1-11 (0.5 mmol), 1.5 equiv. of coupling agent (DCC, 155 mg, 0.75 mmol) for 1-6 and EDC (144 mg, 0.75 mmol) for 7-11 and 1.0 equiv. of DIPEA (90 µL, 0.5 mmol) were successively added. The mixture was stirred overnight at room temperature. The solvent was evaporated in vacuo and the crude product was purified by silica gel flash chromatography.

In the case of compounds A’8-A’11 the reagents used were the corresponding N-tertbutyloxycarbamate. The Boc group was removed with TFA:DCM 50:50 for 1 hr at room temperature and the product was used without further purification.

A’8 and A’9 were treated with acetyl chloride (2.2 equiv., 16 µL, 0.22 mmol) and DIPEA (3.3 equiv., 59 µL, 0.11 mmol) in DCM (2mL) for 2 hrs. Then the solvent was evaporated in vacuo and the crude products were purified by silica gel flash chromatography to give A’10 and A’11.

A’1. Eluent: dichloromethane:methanol 95:5; 78.5 mg (54 %); $^1$H NMR (CDCl$_3$): δ 7.00 + 5.87 (2s, 2H, NH$_2$), 4.53-4.49 (m, 1H, CHα prolinamide), 3.60 (s, 2H, NCH$_2$CO), 3.54-3.46
S11

(m, 2H, CH₂δ prolinamide), 3.37-3.27 (t, J = 5.3 Hz, 4H, CH₂N NS₂), 2.95-2.91 (t, J = 5.7 Hz, 4H, CH₂S NS₂), 2.32-2.42 (m, 2H, CH₂β prolinamide) 2.06-2.88 (m, 2H, CH₂γ prolinamide); ¹³C NMR (CDCl₃): δ 175.1 (C=O, prolinamide), 170.8 (C=O), 59.5 (NCH₂CO), 56.8 (Cα prolinamide), 55.9 (2C-N NS₂), 47.0 (Cδ prolinamide), 39.2 (C-S NS₂), 27.2 + 25.1 (Cβ + Cγ prolinamide); ES/MS (positive ionisation): m/z = 289.9 (M+H⁺).

A'2. Eluent: ethyl acetate:hexane 90:10; 66.3 mg (54 %); ¹H NMR (CDCl₃): δ 3.61 (s, 2H, NCH₂CO), 3.53-3.40 (m, 4H, CH₂NCH₂ pyrrolidine), 3.36 -3.32 (t, J = 5.3 Hz, 4H, CH₂N NS₂), 2.94-2.90 (t, J = 5.7 Hz, 4H, CH₂S NS₂); ¹³C NMR (CDCl₃): δ 169.1 (C=O), 57.4 (NCH₂CO), 55.9 (2C -N NS₂), 45.9 + 45.8 (2C -N pyrrolidine), 39.8 (C-S NS₂), 26.3 + 24.1 (CH₂CH₂ pyrrolidine); ES/MS (ionisation positive): m/z = 246.8 (M+H⁺).

A'3. Eluent: ethyl acetate:hexane 90:10; 91.7 mg (70 %); ¹H NMR (CDCl₃): δ 3.70 -3.66 + 3.62-3.58 (2m, 8H, CH₂ morpholine), 3.54 (s, 2H, NCH₂CO), 3.31-3.26 (t, J = 5.3 Hz, 4H, CH₂N NS₂), 2.95-2.87 (t, J = 5.7 Hz, 4H, CH₂S NS₂); ¹³C NMR (CDCl₃): δ 169.1 (C=O), 67.0 + 66.8 (2C-O morpholine), 57.0 (NCH₂CO), 55.7 (2C-N NS₂), 45.9 + 45.8 (2C-N morpholine), 39.8 (C-S NS₂); ES/MS (positive ionisation): m/z = 262.9 (M+H⁺).

A'4. Eluent: ethyl acetate:hexane 80:20; 48.8 mg (37 %); ¹H NMR (CDCl₃): δ 4.60 + 4.54 (2s, 2H, NCH₂S thiazolidine cis and trans), 3.88-3.80 (m, 2H, CH₂N thiazolidine), 3.60 + 3.57 (2s, 2H, NCH₂CO cis and trans), 3.49-3.28 (t, J = 5.3 Hz, 4H, CH₂N NS₂), 3.13-2.97 (2m, 4H, CH₂S thiazolidine), 2.94-2.84 (t, J = 5.7 Hz, 4H, CH₂S NS₂); ¹³C NMR (CDCl₃): δ 168.7 (C=O), 58.0 (NCH₂CO), 55.8 (2C-N NS₂), 49.1 + 48.7 + 48.3 + 47.9 (2C-N thiazolidine cis and trans), 39.7 (C-S NS₂), 33.9 (C-S thiazolidine); ES/MS (positive ionisation): m/z = 264.9 (M+H⁺).

A'5. Eluent: ethyl acetate:hexane 90:10; 35.1 mg (27 %); ¹H NMR (CDCl₃): δ 7.55 (s, 1H, NH), 4.33-4.17 (m, 1H, CH cyclopentylamine), 3.46 (s, 2H, NCH₂CO), 3.37-3.22 (t, J = 5.3 Hz, 4H, CH₂N NS₂), 2.99-2.87 (t, J = 5.7 Hz, 4H, CH₂S NS₂), 2.04-1.61 (2m, 8H, CH₂ cyclopentylamine); ¹³C NMR (CDCl₃): δ 171.3 (C=O), 61.0 (NCH₂CO), 57.7 (2C-N NS₂), 50.7 (C-N cyclopentylamine), 39.8 (C-S NS₂), 33.2 + 33.1 23.7 + 23.6 (CH₂ cyclopentylamine); ES/MS (positive ionisation): m/z = 260.8 (M+H⁺).
A'6. Eluent: ethyl acetate:hexane 90:10; 69.4 mg (56 %); $^1$H NMR (CDCl$_3$): $\delta$ 3.60 + 3.57 (2s, 2H, NCH$_2$CO cis and trans), 3.35-3.21 (m, 6H, CH$_2$N NS$_2$ + NCH$_2$), 3.01 (s, 3H, NCH$_3$), 2.94-2.90 (t, $J$ = 5.7 Hz, 4H, CH$_2$S NS$_2$), 1.66-1.50 (m, 2H, CH$_2$ propyl), 0.95-0.85 (q, $J$ = 6.4 Hz, 3H, CH$_3$ propyl); $^{13}$C NMR (CDCl$_3$): $\delta$ 170.3 + 170.0 (C=O), 57.5 + 57.0 (NCH$_2$CO cis and trans), 56.4 (2C-N NS$_2$), 51.0 + 49.5 (C-N propyl), 39.8 (C-S NS$_2$), 34.8 + 33.2 (NCH$_3$), 21.5 +20.4 (CH$_2$ propyl), 11.2 (CH$_3$ propyl); ES/MS (positive ionisation): m/z = 248.9 (M+H$^+$).

A'7. Eluent: ethyl acetate:hexane 90:10; 77.1 mg (63 %) ; $^1$H NMR (CDCl$_3$): $\delta$ 5.91-5.80 (m, 2H, CH=CH), 4.31-4.25 (m, 4H, CH$_2$NCH$_2$ pyrroline), 3.55 (s, 2H, NCH$_2$CO), 3.35-3.33 (t, $J$ = 5.3 Hz, 4H, CH$_2$N NS$_2$), 2.95-2.91 (t, $J$ = 5.7 Hz, 4H, CH$_2$S NS$_2$); $^{13}$C NMR (CDCl$_3$): $\delta$ 168.9 (C=O), 126.0 + 125.1 (C=C), 57.0 (NCH$_2$CO), 55.8 (2C -N NS$_2$), 53.1 + 52.7 (C -N pyrroline), 39.8 (C -S NS$_2$); ES/MS (positive ionisation): m/z = 245.2 (M+H$^+$).

A'8. A'8-Boc (86 mg) was purified with ethyl acetate:hexane 75:25; 57 mg (43 %); A'8: $^1$H NMR (CDCl$_3$): $\delta$ 4.47 (s, 2H, NCH$_2$CO), 3.84 (t, $J$ = 5.6 Hz, 4H, CH$_2$N NS$_2$), 3.47 (t, $J$ = 7.6 Hz, 2H, CONCH$_2$ cycle), 3.24 (t, $J$ = 5.6 Hz, 4H, CH$_2$S NS$_2$), 2.93 (t, $J$ = 6.8 Hz, 2H, NCH$_2$ cycle), 2.05 (m, 2H, CH$_2$CH$_2$CH$_2$); $^{13}$C NMR (CDCl$_3$): $\delta$ 172.9 (C=O), 55.9 (2C-NH$_2$CO), 47.8 (C-N NS$_2$), 39.9 (C-S NS$_2$), 36.6 (C-N), 24.7 (CH$_2$CH$_2$CH$_2$); ES/MS (positive ionisation): m/z = 248.2 (M+H$^+$).

A'9. A'9-Boc (96 mg) was purified with ethyl acetate:hexane 60:40; 43 mg (28 %); A'9: $^1$H NMR (CDCl$_3$): $\delta$ 4.44 (s, 2H, NCH$_2$CH$_2$), 3.92 (t, $J$ = 5.2 Hz, 4H, CH$_2$N NS$_2$), 3.62 (bs, 2H, CONCH$_2$ cycle), 3.20 (t, $J$ = 5.2 Hz, 4H, CH$_2$S NS$_2$), 2.90 (t, $J$ = 5.2 Hz, 2H, CH$_2$N-CO), 1.71+1.65 (2m, 4H, N-N-CH$_2$CH$_2$); $^{13}$C NMR (CDCl$_3$): $\delta$ 171.3 (C=O), 57.3 (NCH$_2$CO), 55.9 (2C-N NS$_2$), 54.8 + 49.1 (2 C-N), 39.8 (C-S NS$_2$), 23.5 (CH$_2$CH$_2$); ES/MS (positive ionisation): m/z = 262.0 (M+H$^+$).

A'10. Eluent: ethyl acetate 100%; 9.8 mg (34 %); $^1$H NMR (CDCl$_3$): $\delta$ 4.51-4.46 (bd, 2H, NCH$_2$CH$_2$), 3.67-3.60 (2s, 2H, NCH$_2$CO), 3.36 (bd, 4H, CH$_2$N NS$_2$), 2.96 (bd, 4H, CH$_2$S NS$_2$), 2.17 (m, 4H, CH$_2$CH$_2$), 1.25 (s, 3H, Ac); $^{13}$C NMR (CDCl$_3$): $\delta$ 171.3 (C=O), 55.9 (2C-...
N NS₂ + NCH₂CO), 54.8 + 49.1 (2C-N NS₂), 39.8 (2C-S NS₂), 28.2 (CH₃ Ac), 23.5 (CH₂CH₂); ES/MS (positive ionisation): m/z = 290.2 (M+H⁺).

A’11. Eluent: ethyl acetate:hexane 80:20; 27.5 mg (82 %); ¹H NMR (CDCl₃): δ 4.51 (bd, 2H, CO-NCH₂CH₂), 3.49 (s, 2H, NCH₂CO), 3.26 (bs, 4H, CH₂N NS₂), 2.87 (bs, 4H, CH₂S NS₂), 2.68 (m, 2H, CH₂N), 2.04 (s, 4H, NCH₂CH₂CH₂), 1.19 (s, 3H, Ac); ¹³C NMR (CDCl₃): δ 172.9 (C=O), 55.9 (2C -N SNS + N C H₂CO), 47.8 (C-N), 39.9 (C-S NS₂), 36.6 (C-N), 28.4 (CH₃ Boc), 24.7 (CH₂CH₂CH₂); ES/MS (positive ionisation): m/z = 262.3 (M-Ac+H⁺).

General procedures for the synthesis of modules B.

Ba. L-Cystine-p-nitroanilide was purchased from Novabiochem.

Synthesis of Bb-h (isolated as disulfides). L-Cystine-p-nitroanilide (0.125 g, 0.26 mmol) was dissolved in DCM (10mL) and neutralized with DIPEA. Then the electrophile (0.52 mmol) and DIPEA (185 µL, 1.04 mmol) were successively added and the mixture was stirred for 2-4 hrs. After removal of the solvent in vacuo, the crude product was dissolved in ethyl acetate and was washed with 10% citric acid and brine. The organic layer was dried over sodium sulfate, filtered and the solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography.

Bb.

Eluent: ethyl acetate:hexane 75:25; m = 152.4 mg (quant.); HPLC: tr = 18.4 min; ¹H NMR (CDCl₃): δ 10, 71 (s, 2H, NHₚNA), 8.23 + 7.86 (2d, J = 12 Hz, 2x4H, ar. H pNA), 7.30-7.28 (bd, 2H, N H-Ac.), 5.64 (m, 2H, CHα Cys), 3.19-3.01 (m, 4H, CH₂-S-S-CH₂), 2.21 (s, 6H, Ac); ¹³C NMR (CDCl₃): δ 171.4 (CO), 144.5 (ar. C. pNA) 125.3 + 125.0 + 119.3 (ar. C, pNA), 54.7 (Cα, Cys), 32.2 (CH₃-S Cys), 28.4 (CH₃, Ac); ES/MS (positive ionisation) m/z = 565.12 (M+H⁺).
Bc.

Eluent: ethyl acetate:hexane 30:70; m = 69 mg (39 %). HPLC: tr = 22.4 min; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 10, 81 (s, 2H, NH-pNA), 8.24 (d, \(J = 9\) Hz, 4H, ar. H pNA), 7.94-7.88 (m, 8H, 4 ar. H pNA + 4 ar. H Bz), 7.67-7.54 (m, 5H, ar.H, Bz), 7.39-7.26 (bd, 2H, NH), 6.00-5.91 (m, 2H, CH\(\alpha\) Cys), 3.38-3.13 (m, 4H, CH\(_2\)S); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 168.2 + 168.0 (CO), 143.0 + 131.9 + 128.3 + 126.2 + 124.2 + 118.6 (C ar., pNA + Bz), 54.7 (C\(\alpha\), Cys), 35.7 (CH\(_2\)S); ES/MS (positive ionisation) m/z = 689.14 (M+H\(^+\)).

Bd. (p-nitroBz-Cys-pNA)\(_2\)

Eluent: ethyl acetate:hexane 35:65; m = 65 mg (32 %). HPLC: tr = 22.7 min; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 10, 49 (s, 2H, NH-pNA), 8.47-7.82 (4d, \(J = 9\) Hz, 4x4H, ar. H p-nitro.), 7.52-7.48 (d, 2H, NH), 5.92-5.84 (bt, 2H, CH\(\alpha\)), 3.40-3.26 (m, 4H, CH\(_2\)S); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 168.2 + 168.0 (CO amide), 143.0 + 131.9 + 128.3 + 126.2 + 124.2 + 118.6 (ar. C pNA + Bz), 54.7 (C\(\alpha\), Cys), 33.3 (CH\(_2\)S); ES/MS (positive ionisation) m/z = 780.11 (M+H\(^+\)).

Be. (nicotinoyl-Cys-pNA)\(_2\)

Eluent: methanol/DCM 97/3; m = 85.8 mg (48 %). HPLC: tr = 19.9 min; \(^1\)H NMR (CD\(_3\)OD): \(\delta\) 9.00 + 8.67 (bs, 2x2H, ar. H nicotinoyle), 8.26 (m, 6H, 2 ar. H nicotinoyle + 4 ar. H pNA), 7.86-7.82 (d, \(J = 9\) Hz, 4H, ar. H pNA), 5.18 (m, 2H, CH\(\alpha\) Cys), 3.42-3.25 (m, 4H, CH\(_2\)S); \(^{13}\)C NMR (CD\(_3\)OD): \(\delta\) 171.5 (CO), 153.0 + 149.5 + 145.6 + 137.3 + 125.7 + 125.1 + 120.8 (ar. C, pNA+ nicotinoyle), 55.6 (C\(\alpha\) Cys), 34.4 (CH\(_2\)S); ES/MS (positive ionisation) m/z = 691.16 (M+H\(^+\)).
Eluent: methanol:DCM 98:2; m = 81 mg (42 %). HPLC: tr = 22.0 min; $^1$H NMR (CDCl$_3$): $\delta$ 9.83 (s, 2H, NH-pNA), 8.22 + 7.66 (2d, $J$ = 9 Hz, 2x4H, ar. H pNA), 7.35 (m, 10H, ar. H BzI), 5.32-5.27 (m, 2H, 2 NH), 3.88 (bs, 4H, CH$_2$ BzI), 3.69-3.64 (m, 2H, CH$_\alpha$), 3.24-2.92 (2m, 4H, CH$_2$ S); $^{13}$C NMR (CDCl$_3$): $\delta$ 171.4 (CO), 143.2 + 129.0 + 128.9 + 128.3 + 127.9 + 125.2+ 119.0 (ar. C), 60.8 (CH$_2$ BzI), 52.9 (C$_\alpha$ Cys), 40.3 (CH$_2$ S); ES/MS (positive ionisation) m/z = 747.24 (M+H$^+$).

Preparation of isocyanate: 1.0 eq of triphosgene (85.6 mg, 0.29 mmol) and DIPEA (310 µL, 1.74 mmol) were added dropwise to 3.0 eq of benzylamine (95 µL, 0.87 mmol) in DCM (6 mL). The mixture was stirred at 0°C for 1 hr before addition of a solution of L-Cystine-p-nitroanilide (125.6 mg, 0.26 mmol) in DCM (10 mL).

Eluent: ethyl acetate:hexane 40:60; m = 123.1 mg (63 %). HPLC: tr = 20.8 min; $^1$H NMR (CD$_3$OD): $\delta$ 8.12 + 7.79 (2d, $J$ = 9 Hz, 2x4H, ar. H pNA), 7.27 (m, 10H, ar. H BzI), 4.92 (bt, 2H, CH$_\alpha$ Cys), 4.38 (s, 4H, CH$_2$ BzI), 3.25-3.05 (m, 4H, CH$_2$ S); $^{13}$C NMR (CD$_3$OD): $\delta$ 171.5 (CO), 160.4 (CO urea), 140.9 + 129.5 + 128.2 + 127.9 + 125.6+ 120.7 (ar. C pNA), 55.9 (C$_\alpha$ Cys ), 44.7 (CH$_2$ BzI), 32.7 (CH$_2$ S); ES/MS (positive ionisation) m/z = 749.24 (M+H$^+$).

Eluent: ethyl acetate:hexane 30:70; m = 26.3 mg (13 %). HPLC: tr = 26.3 min; $^1$H NMR (CDCl$_3$): $\delta$ 10.0 (s, 2H, NH pNA), 8.20 + 7.68 (2d, $J$ = 12 Hz, 2x4H, ar. H pNA), 7.26 (m, 10H, ar. H BzI), 6.65-6.61 (m, 2H, NH), 4.85 (m, 2H, CH$_\alpha$ Cys), 4.47 (bs, 4H, CH$_2$ BzI), 3.24-2.92 (2m, 4H, CH$_2$ S); $^{13}$C NMR (CDCl$_3$): $\delta$ 171.4 (CO), 143.8 + 129.0 + 128.9 + 128.3...
+ 127.9 + 125.2 + 119.0 (ar. C pNA), 60.8 (CH₂ Bzl), 52.9 (Cα Cys), 40.3 (CH₂S); ES/MS (positive ionisation) m/z = 390.23 (M+2H⁺).

**General procedure for Bi-k.**

Para-nitroaniline (1.436 g, 10 mmol) was treated with the electrophile (10 mmol) and DIPEA (1.8 mL, 10.0 mmol) for 1 hr at room temperature. After removal of the solvent under reduced pressure, the product was dissolved in DMF (20 mL) and treated with potassium thioacetate (1.210 g, 10 mmol) overnight at room temperature. After evaporation of the solvent *in vacuo*, the crude product was dissolved in ethyl acetate and washed with 10% citric acid and brine. The organic layer was dried over sodium sulfate. After evaporation of the solvent, the crude product was purified by silica gel flash chromatography.

The pure para-nitroanilide (5 mmol) was treated with sodium methanolate (288 mg, 5 mmol) in methanol (50 mL overnight at room temperature. After evaporation of the solvent *in vacuo*, the crude product was dissolved in ethyl acetate and washed with 10% citric acid and brine. The crude product was then treated with 10 % iodide in methanol (15 mL) and the reaction was monitored by TLC. After removal of the solvent under reduced pressure the product was dissolved in ethyl acetate and washed with sodium thiosulfate and purified by flash chromatography.

Eluent: acetone:hexane 35:65; m = 1.400 g (28 %, 2 steps). HPLC: tr = 19.9 min; ¹H NMR (d⁶DMSO): δ 10.72 (s, 2H, NH-pNA), 8.14 + 7.72 (2d, J = 12 Hz, 2x4H, ar. H pNA), 3.77 (s, 4H, CH₂); ¹³C NMR (d⁶DMSO): δ 169.2 (CO pNA), 144.0 + 125.1 + 119.4 (ar. C pNA), 43.4 (CH₂S); ES/MS (positive ionisation) m/z = 422.54 (M+H⁺).
Bj.
Eluent: ethyl acetate:hexane 70:30; m = 340 mg (12 %, 2 steps). HPLC: tr = 20.5 min; $^1$H NMR (d$_6$DMSO): $\delta$ 10.63 (s, 2H, NH-pNA), 8.20 + 7.78 (2d, $J$ = 9 Hz, 2x4H, ar. H pNA), 3.02 (t, $J$ = 7 Hz, 4H, CH$_2$), 2.82 (t, $J$ = 7 Hz, 4H, CH$_2$); $^{13}$C NMR (d$_6$DMSO): $\delta$ 170.2 (CO pNA), 145.1 + 142.1 + 125.0 + 118.7 (ar. C pNA), 36.1 (CH$_2$CO), 33.0 (CH$_2$S); ES/SM (positive ionisation) m/z = 450.6 (M+H$^+$).

Bk.
Eluent: ethyl acetate:hexane 65:35; m = 1.240 g (29 %, 2 steps). HPLC: tr = 21.5 min; $^1$H NMR (CD$_3$OD): $\delta$ 9.73 (bs, 2H, NH), 8.21 + 7.88 (2d, $J$ = 10 Hz, 2x4H, ar. H NA), 2.86-2.80 (m, 4H, CH$_2$CO), 2.66-2.57 (m, 4H, CH$_2$S), 2.06-2.03 (m, 4H, CH$_2$); $^{13}$C NMR (CD$_3$OD): $\delta$ 172.1 (CO), 151.1 + 125.8 + 125.6 + 119.5 (ar. C pNA), 38.3 (CH$_2$CO), 30.5 (SCH$_2$), 25.2 (SCH$_2$CH$_2$CH$_2$); ES/MS (positive ionisation): m /z = 478.83 (M+H$^+$).

Bl.
Cystamine dihydrochloride (10 mmol, 2.298 g) was treated with 4.0 equiv. of DIPEA (40 mmol, 7.1 mL) and 4-nitrobenzoyl chloride: (20 mmol, 3.711 g) in DCM (40 mL) for 1 hr at room temperature. The crude product was washed with 10 % citric acid and brine before purification by flash chromatography (eluent: ethyl acetate:hexane 65:35): m = 1.7941 g (40 %). HPLC: tr = 18.5 min; $^1$H NMR (d$_6$DMSO): 8.81 (m, 1H, NH), 8.14 + 7.21 (2d, $J$ = 9 Hz, 2x4H, ar. H), 3.43 (m, 2H, NCH$_2$), 2.79 (t, $J$ = 7 Hz, 2H, CH$_2$S); $^{13}$C NMR (d$_6$DMSO): 165.0 (CO), 149.5 + 140.3 + 128.6 + 123.5 (ar. C), 39.2 (CH$_2$N), 37.4 (CH$_2$S); ES/MS (positive ionisation) m/z = 450.70 (M+H$^+$).
Cystamine dihydrochloride (10 mmol, 2.298 g) was treated with 4-nitro-phenyl-acetic acid (20 mmol, 3.66 g) and 1N DCC in DCM (20 mL) overnight at room temperature. The crude product was washed with 10 % citric acid and brine before purification by flash chromatography (eluent: ethyl acetate:hexane 40:60; m =0.479 g (29 %). HPLC: tr = 26.0 min; $^1$H NMR (CDCl$_3$): $\delta$ 8.21 + 7.42 (2d, $J$ = 9 Hz, 2x4H, ar. H), 6.38 (bs, 2H, NH), 3.86 (s, 2H, C(O)CH$_2$-Ph), 1.99-1.94 (m, 4H, CH$_2$N), 1.86-1.78 (m, 4H, SCH$_2$); $^{13}$C NMR (CDCl$_3$): $\delta$ 156.1 (CO), 147.2 + 142.4 + 130.4 + 123.8 (ar. C), 56.2 (C(O)CH$_2$Ph), 32.9 + 31.2 (NHCH$_2$), 28.0 + 26.4 (SCH$_2$); ES/MS (positive ionisation) m/z = 479.15 (M+H$^+$).

Triphosgene (1.499 g, 5 mmol) was added to 3.0 eq of para-nitroaniline (2.114 g, 15 mmol) and DIPEA (5.4 mL, 30 mmol) in DCM (50 mL). The mixture was stirred at 0°C for 1 hr. The corresponding isocyanate was added to a solution of cystamine dihydrochloride (7.5 mmol, 1.689 g) and DIPEA (15 mmol, 2.65 mL) in DCM. The mixture was stirred for 1 hr, and then treated as above before purification by silica gel flash chromatography. Eluent: ethyl acetate:hexane 40:60, 726.9 mg (20 %). $^1$H NMR (CDCl$_3$): $\delta$ 8.22 + 7.53 (2d, $J$ = 9 Hz, 2x4H, ar. H pNA), 6.94 (bs, 2H, NH), 4.16-4.08 (dd, 4H, CH$_2$CO, $J$ = 20 Hz, $J'$ = 9.9 Hz), 1.28-1.26 (m, 4H, SCH$_2$); $^{13}$C NMR (CDCl$_3$): $\delta$ 160.1 (CO), 147.9 + 138.8 + 125.5 + 120.3 (ar. C pNA), 54.0 (NHCH$_2$), 26.0 (SCH$_2$); ES/MS (positive ionisation); m/z = 481.25 (M+H$^+$).

**General procedure for the synthesis of Bo-p.**

Mercapto-acide (20 mmol) in THF (20 mL) was treated with iodide (2.536 g, 10 mmol) for 30 min at room temperature. The solvent was evaporated and the product was dissolved in 15 mL DCM prior to treatment with p-nitrobenzyl or m-nitrophenyl ammonium chloride (3.896 g, 20 mmol), 1N DCC in DCM (30 mL, 30 mmol) and DIPEA (14.6 mL, 60 mmol) overnight at room temperature. After removal of the solvent under reduced pressure, the crude product was washed with 10 % citric acid and brine before purification by flash chromatography
Eluents: ethyl acetate:hexane 75:25; m = 1.22 g (26 %). HPLC: tr = 26.0 min; $^1$H NMR (CDCl$_3$): $\delta$ 8.32 + 7.44 (2d, $J = 9$ Hz 2x4H, ar. H), 6.90 (bt, 2H, NH), 4.55 (d, 4H, NCH$_2$Ph), 2.83 (t, $J = 7$ Hz, 4H, CH$_2$CO), 2.69 (t, $J = 7$ Hz, 4H, CH$_2$S); $^{13}$C NMR (CDCl$_3$): $\delta$ 171.4 (CO), 145.9 + 128.2 + 123.8 (ar. C), 42.9 (NCH$_2$Ph), 32.6 (CH$_2$CO), 31.0 (CH$_2$S); ES/MS (positive ionisation) m/z = 479.9 (M+H$^+$).

Eluent: (1st purification) ethyl acetate:hexane 60:40, (2nd purification) DCM:methanol 97.5:2.5; m = 1.22 g (26 %). HPLC: tr = 25.0 min; $^1$H NMR (CDCl$_3$): $\delta$ 8.21-8.09 + 7.66-7.55 (m, 6H, ar. H), 7.16 (bt, 2H, NH), 4.31 (m, 4H,NCH$_2$Ph), 2.83 (t, $J = 7$ Hz, 4H, CH$_2$CO), 2.69 (t, $J = 7$ Hz, 4H, CH$_2$S); $^{13}$C NMR (CDCl$_3$): $\delta$ 175.4 (CO), 144.4, 129.4 + 114.2 + 110.5 (ar. C), 57.6 (NCH$_2$Ph), 33.7 (CH$_2$CO), 19.6 (CH$_2$S); ES/MS (positive ionisation) m/z = 504.33 (2M+2C=N$^+$).

**Synthesis of the Re(NS$_2$+S) complexes.**

**General Procedure.** Solutions of A$_1$-7 or A'$_1$-11 and Ba-p in methanol were treated separately with 10% PBu$_3$ in methanol (1 equiv.) for 30 min under an argon atmosphere. A$_1$-7 and Ba-p (library I) and A'$_1$-11 and Ba-p (library II) (typically 2 µmol of each component) were combined in independent vials previously flushed with argon. A fresh methanolic solution of [nBu$_4$N]ReOCl$_4$ (1 eq. 15 µL) and 10% Et$_3$N in methanol (4 equiv. 12 µL) were added successively. A brown precipitate immediately formed. After stirring for 2hrs at room temperature, the crude mixtures were centrifuged. The precipitates were washed twice with methanol, dissolved in DMSO and purified by HPLC.
**ES/M and HPLC analysis of library I.** Complexes of the 7x16 matrix were analysed diagonally.

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<th>Compounds</th>
<th>Name</th>
<th>m/z£ for</th>
<th>HPLC elution£</th>
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<td>16.7 (20)</td>
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<td>19.9 (60)</td>
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£ (M+H$^+$) analysed by ES/MS; £ HPLC: C$_{18}$ binary gradient system (A: 0.1% aqueous solution of trifluoroacetic acid; B: acetonitrile; A:B 100:0 from 0 to 5 min, 25 min linear gradient from 100:0 to 100:0 B then 0:100 for 5 min at a flow rate of 1 mL.min$^{-1}$); £ M – CO$_2$ + H$^+$.
ES/M and HPLC analysis of library II. Compounds of the 11x16 matrix were analysed diagonally.

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<th>Compounds</th>
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$^a$ (M+H$^+$) analysed by ES/MS; $^b$ HPLC: C$_{18}$ binary gradient system (A: 0.1% aqueous solution of trifluoroacetic acid; B: acetonitrile; A:B 100:0 from 0 to 5 min, 25 min linear gradient from 100:0 to 100:0 B then 0:100 for 5 min at a flow rate of 1 mL.min$^{-1}$); $^c$ M +H$_3$O$^+$. 
Spectrophotometric titration of complexes in aqueous solution.

Complexes were dissolved in DMSO or TFE (30 µL). 5µL of these solutions were diluted in water (4995 µL) and then the absorbances (A) were measured at $\lambda = 318$ nm, on a UVIKON 935 spectrophotometer. Concentration were determined using the calculated molar absorbance at 318 nm.

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Fluorimetric determination of apparent $K_d$

Fluorimetric determination of $K_d$ values was done using a JASCO FP-750 spectrofluorometer equipped with a 200 µL thermostated cell. The recombinant hCyp-18 was obtained as previously reported.$^1$ To a solution of hCyp-18 (1.1 µM, 180 µL) in HEPES buffer (35 mM, pH 7.8) was added a solution containing various concentrations of complexes dissolved in DMSO (20 µL). Measures of relative fluorescence quenching (F, %) were done at 20.0 ± 1°C.


0.1°C. The apparent $K_d$ values were obtained as the fitted points of inflection from the sigmoidal log \((100 - F)/C\) profiles.

**Competition experiment with cyclosporine A (CsA)**

To a solution of hCyp-18 (1.1 µM, 180 µL) in HEPES buffer (35 mM, pH 7.8) was added a solution containing various concentrations of CsA in DMSO (10 µL). The mixture was incubated for 2 min. Then a solution containing the complex (concentration equal to $K_d$) in DMSO (10 µL) was added. The mixture was incubated for another 2 min. Fluorescence recovery was monitored as described above.
hCyp-18 fluorescence quenching at 100 µM, F_{100µM} (%), and K_d values (µM) of library I. The K_d values were firstly obtained by measuring in duplicate the fluorescence quenching at two different complexe concentrations (10 and 100 µM).

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<sup>a</sup> % <sub>F<sub>100µM</sub></sub>; apparent <sub>K<sub>d</sub></sub> (µM); <sup>b</sup> determined from 6 independent experiments.
hCyp-18 fluorescence quenching at 100 µM, F_{100µM} (%), and K_d values of the 176 complexes (µM). The K_d values were firstly obtained by measuring in duplicate the fluorescence quenching at two different complexe concentrations (10 and 100 µM).

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|     | 43; 35; 14; 25; 3; 30; 17; 10; 21; 74; 44; 131 212 461 180 233 209 368 342 89 81 106 |
|     | 0; 7; 0; 5; 0; 0; 7; 0; 3; 0; 569 711 - - - 390 459 - |
|     | 0; 6; 0; 10; 0; 10; 0; 0; 0; 0; 329 395 - - 570 - - - - |
|     | 47; 7; 36; 13; 0; 27; 0; 20; 14; 13; 60; 138 270 190 269 - 297 - 195 270 259 80 |

^a (F; K_d); ^b determined from 6 independent experiments
Fluorimetric determination of apparent dissociation constants $K_d$ for complexes I-3e and II-8i.

Curves are the average of 2 independent experiments in duplicate. Error bars are often invisible due to the good reproducibility of the experiment.
Detailed characterization of complex I-3e.

HPLC chromatogram of crude complex I-3e on a Vydac C18 column (10µM, 4.6 mm, 250 mm) eluted with a binary gradient system (A: 0.1% aqueous solution of trifluoroacetic acid; B: acetonitrile; A:B 100:0 from 0 to 5 min, 25 min linear gradient from 100:0 to 100:0 B then 0:100 for 5 min at a flow rate of 1 mL.min⁻¹).

ES/MS (positive ionisation) mass spectra of (I-3e) and (II-8i). 30 µL of complexe in DMSO were injected then infused at 10 µL.min⁻¹, on a Quattro II (Micromass), cone voltage = 20V, Tsource = 80°C.
Figure 1: $^1$H NMR of I-e3 complex, A-3 module and B-e module in CD$_3$OD (400 MHz).
HPLC. A: H₂O-TFA 0.1%, B: ACN, 0-5 min 0%B, 30 min 100%B, 35 min 100%B, 35-40 min 100%B, then the column was re-equilibrated, F = 4 mL.min⁻¹; HPLC: tr = 18.1 min (purity > 98%); ¹H RMN (CD₃OD): δ 9.07 + 8.67 + 8.33 (bs, 3x1H, ar. H - nicotinoyl), 8.20 + 7.82 (2d, J = 9 Hz, 2x2H, ar. H pNA), 7.56 (bs, 1H, ar. H. nicotinoyl), 5.07 (m, 1H, CHα Cys), 4.28 (m, 2H, NCH₂CO NS₂), 4.13 (m, 2H, α CH₂ Gly), 3.95 (bs, 1H, CHα Lys), 3.78 (m, 10H, NCH₂ NS₂ + morpholine and CH₂ε Lys), 3.61 (m, 10H, CH₂OCH₂ morpholine + SCH₂ NS₂ + CH₂ Cys), 2.62 (m, 2H, CH₂β Lys), 1.40 (m, 4H, CHδγ + γ Lys); ES/MS (positive ionisation) m/z = 994 (60%, M+H⁺ for ¹⁸⁵Re), 996 (100%, M+H⁺ for ¹⁸⁷Re).
Detailed characterization of compound II-8i

Chromatogram of crude complex **II-8i** on a Vydac C18 column (10µM, 4.6 mm, 250 mm) eluted with a binary gradient system (A: 0.1% aqueous solution of trifluoroacetic acid; B: acetonitrile; A:B 100:0 from 0 to 5 min, 25 min linear gradient from 100:0 to 100:0 B then 0:100 for 5 min at a flow rate of 1 mL.min⁻¹).

ES/MS (positive ionisation) mass spectra of complex II-8i. 30 µL of complexe in DMSO were injected then infused at 10 µL.min⁻¹, on a Quattro II (Micromass), cone voltage = 20V, Tsource = 80°C.
H NMR of II-8i complex, A'-8 module and B-i module in CD$_3$OD (400 MHz).
II-i8

HPLC. A: H₂O-TFA 0.1 %, mobile phase B: ACN, 0-5 min 25 %B, 35 min 75%B, 36 min 100 %B, 36-40 min 100 %B, then the column was re-equilibrated, F = 4 mL.min⁻¹; HPLC: tr = 19.3 min (Purity > 98 %); 

^1^H RMN (CD₃OD): 8.19 + 7.79 (2d, J = 9 Hz, 2x4H, ar. H pNA), 3.87 (s, 2H, NCH₂CO), 3.75 (m, 6H, CH₂N NS₂ + cycle), 3.52 (t, J = 7.6 Hz, 2H, HNCH₂ cycle), 3.05 (m, 6H, CH₂S NS₂ + module B), 2.09 (m, 2H, NH cycle), 1.78 (t, J = 6.8 Hz, 2H, CH₂CH₂CH₂ cycle). ES/MS (positive ionisation) m/z = 660 (60%, M+H⁺ for ^185^Re), 662 (100%, M+H⁺ for ^187^Re)
**General method for the preparation of Acm compounds**

The disulfide (0.1 mmol) was dissolved in THF (2 mL) and treated with tributylphosphin (38 µL, 0.15 mmol) and distilled water (3 µL, 0.15 mmol) for 40 min. After removal of the solvent *in vacuo*, the crude products was dissolved in DMF (2 mL) and iodoacetamide (55 mg, 0.3 mmol) and cesium carbonate (97 mg, 0.3 mmol) were added. The mixture was stirred overnight at room temperature. After evaporation of the solvent, the crude product was purified by silica gel flash chromatography to give the corresponding acetamidomethylated derivative.

**Be(Acm)**

![Be(Acm) structure]

Eluent : DCM:methanol 95:5 ; m = 40.5 mg (50 %); ¹H NMR (CD₃OD) : δ 10.65 (bs, 1H, NH), 9.04 + 8.67 (bs, 2x1H, ar. H *p*-nicotinoyl), 8.30 (d, J = 9 Hz, 1H, H *p*-nicotinoyl), 8.24 -7.81 (AA’-BB’, 2x2H, J = 9 Hz, ar. H *p*NA), 7.54 (m, 1H, H *p*-nicotinoyl), 4.92 (m, 1H, CHα Cys), 3.27 (s, 2H, SCH₂ Acm), 3.27-3.12 (m, 2H, CH₂S); ¹³C NMR (CD₃OD) : δ 175.3 + 171.4 + 167.9 (C=O), 152.6 + 149.2 + 145.7 + 144.8 + 137.7 + 125.8 + 120.7 (ar. C, *p*NA and *p*-nicotinoyl), 55.8 (Cα Cys), 35.8 + 35.2 (CH₂S); ES/MS (positive ionisation) m/z = 404.18 (M+H⁺).

**Bi(Acm)**

![Bi(Acm) structure]

Eluent : DCM:methanol 95:5 ; m = 13.5 mg (25 %); ¹H NMR (d⁶DMSO) : δ 8.25-7.80 (2d, 2x2H, J = 9 Hz, ar. H *p*NA), 3.51 (s, 2H, SCH₂), 3.27 (s, 2H, SCH₂ Acm); ¹³C NMR (d⁶DMSO) : δ 168.7 (CO *p*NA), 145.2 + 125.1 + 118.8 (ar. C *p*NA), 23.8 (CH₂S) ; ES/MS (positive ionisation) m/z = 270.20 (M+H⁺).