Table S1: Proton chemical shift assignments of the Debio 025 and partial ^{13}C assignment deduced from the natural abundance [^{1}H,^{13}C]-HMQC.

Table S2: **A**: Energy minimization of the 9 possible rotamers for residue N-EthVal4 in Debio 025: initial and final total energy and initial and resulting dihedral angles in the minimization process. The dihedral angles are defined in the figure joined to Table 3, represented as red quarters, and are abbreviated in the table N-Eth for the angle defined by C-N/C1-C2 and V for the angle HA-CA/HB-CB ($\chi 1$). **B**: measured distances from the HN_{CH2} of the N-Ethyl moiety of Val4 in the four different minimized rotamers of Debio 025 in interaction with CypA. Distances are given as shortest between 2 chemical group protons or average of all the distances between the involved protons. The distances derived from the integrated NOE cross peaks (NOE) in NOESY with 50 msec and 200 msec mixing times are in blue. Stars denote that HαEthVal4 and HβMeβmt1 resonances are superimposed in the spectrum. **Figure joined to Table S2**: Representation of the N-EthVal4 rotamer (NEth -88.2 V+72.6) that best corresponds to the observed NOEs, the measured average distances for this rotamer are highlighted in green..

Figure S1: Extracted strips from a 2D [^{1}H,^{1}H]-NOESY spectrum of -[^{2}H,^{15}N]-CypA-Debio 025 in D_2O buffer. NOE cross-peaks are labelled. These strips illustrate the intra-Debio 025 NOE contacts.

Figure S2: Histograms of the combined [^{1}H, ^{15}N]-delta chemical shift (C.S., in ppm) upon addition of Debio 025 (A) or CsA (B) to [^{15}N]-CypA reported along the sequence. The difference between the delta chemical shift observed after addition of Debio 025 or CsA is reported in histogram C (Δ(delta C.S.). Horizontal lines show the color coding corresponding to the arbitrary values chosen to illustrate the Δ(delta C.S.) on the molecular surface of CypA (**Fig. 4**).

Figure S3: Superimposed strips from 3D [^{1}H,^{15}N]-HSQC NOESY spectra of [^{2}H,^{15}N]-CypA-Debio 025 (in black) or [^{2}H,^{15}N]-CypA-CsA (in red) in H_2O buffer. NOE cross-peaks are labelled. These strips illustrate the inter-molecular (Debio 025 or CsA with CypA) NOE contacts.

Figure S4: Superimposition of the structures of CsA in complexes The CsA molecules are represented in stick models, with N in blue, Oxygen in red and carbon atoms in yellow for CypA-CsA (1CWA), in blue for CypA-CsA-CaN (1M63) and in gray for CypB-CsA (1CYN) complexes. Superimposition of the structures was performed with the backbone atoms of the Cyp molecules.