**Table Ts3.** Analyses of the 3D structures of the cyclophilins.

| No. | PDB | Res(Å) | Length | NID | B-factor | Description | Reference |
|---|---|---|---|---|---|---|---|
| **Human/vertebrates** | | | | | | | |
| 1 | 2CPL | 1.63 | 165 | 3586 | 15E,44K,81E | hCyPA | 16 |
| 2 | 1CWA | 2.10 | 165 | 3591 | 69RHGEK,144R | hCyPA/CsA | 25 |
| 3 | 1YND | 1.60 | 164 | 3519 | 13DGEP,69RHN,148RN,153SK | hCyPA/(Sanglifehrin A) | 52 |
| 4 | 1ZKF | 2.55 | 165 | 3528 | 80G,81E,82K | hCyPA/(Suc-AGPF-pNA) | 29 |
| 5 | 2X7K | 1.15 | 166 | 2757 | - | hPPIL1 (CGI-124) | R1 |
| 6 | 1XYH | 2.60 | 160 | 3396 | 156AN | hCyPJ (PPIL3) | R2 |
| 7 | 1CYN | 1.85 | 178 | 3704 | 7GP,51EKG,77R | hCyPB/CsA | R3 |
| 8 | 2RMC | 1.64 | 182 | 3867 | 48D,182D,184H | mCyPC/CsA | R4 |
| 9 | 2BIT | 1.71 | 164 | 3664 | 44K,68TNHNG,147SKS,150GRK | hCyPF | R5 |
| 10 | 2Z6W | 0.96 | 164 | 3668 | 13NGK,144S,149S,153SK | hCyPF/CsA | R6 |
| 11 | 1MZW | 2.00 | 173 | 3756 | 50E,52RKDGVP,112M,161P | hCyP19 (hCyPH) | 18 |
| 12 | 1QOI | 2.00 | 173 | 3747 | 53KD,83D | hCyP19 | R7 |
| 13 | 1ZMF | 1.88 | 162 | 3729 | 150NKP,215YGKK,239SGP | hCyP33 (AA:137-301) | R8 |
| 14 | 1IIP | 2.00 | 297 | 6916 | 100GE,123A | bCyP40 orthogonal | R9 |
| 15 | 1ZKC | 1.65 | 187 | 4205 | 414EDPKT,423KE | CLD of hCyP60 (AA:271-457) | 54 |
| 16 | 2A2N | 1.65 | 164 | 3700 | 567HST,573D | CLD of hCyP73 | R10 |
| 17 | 2GW2 | 1.80 | 173 | 3976 | 68V,85R,126I | CLD of hCyP88 | R11 |
| 18 | 2HE9 | 2.00 | 172 | 3844 | 54GKK,70NG,80E,160A | CLD of hCyP157 | R12 |
| **Invertebrates/Parasites** | | | | | | | |
| 1 | 1DYW | 1.80 | 172 | 3869 | 87GEK | CeCyp3 (CeCyP18d) | R13 |
| 2 | 1E3B | 1.85 | 172 | 3839 | 87GE,111G | CeCyP3/(Complex-Au) | R14 |
| 3 | 1H0P | 1.75 | 182 | 4154 | 67P,70E,189IAVDT | CeCyP5 | R15 |
| 4 | 1A58 | 1.95 | 177 | 3837 | none | BmCyP18 | R16 |
| 5 | 1C5F | 2.47 | 177 | 3858 | 51KIS | BmCyP18/CsA | R17 |
| 6 | 1Z81 | 2.80 | 186 | 4066 | 99I,156I,182L | PyCyP23/p | R18 |
| 7 | 2B71 | 2.50 | 169 | 3844 | 101GKS,105YGEY | PyCyP18 | R18 |
| 8 | 1QNG | 2.10 | 170 | 3933 | 45KIGSRGKN | PfCyP18/CsA | R19 |
| 9 | 2FU0 | 1.80 | 155 | 3563 | 62SGDGTG,73GN,106FFIT | PfCyP87 | R18 |
| 10 | 2HAQ | 1.97 | 166 | 3376 | 50K,103GE,170NSH | LdCyP18 (CyPA) | R20 |
| 11 | 2CMT | 1.50 | 164 | 3650 | 43F,73F,76VKGDGT | SmCyP18 | R21 |

All the X-ray files were taken from the PDB server whereas the structures were analyzed with the methods recently described [19]. The numbers of the intra-molecular distances (NID) between the AAs in $i \geq i+2$ sequence positions and at atomic distances $d_{ij} \leq 4.5$ Å are dependent on the size of the CLD and structure resolution. In average, about 3700 inter-atomic interactions take place within 2.7-4.5 Å that contribute to the overall stability of the CLD. The residues having higher than the average flexibility (Debye/Waller B-factors) are explicitly indicated. **Abbreviations:** NID, the number of intramolecular interatomic distances calculated between the $i \geq i+2$ AA residues (AAs) in the distance range ($2.7$ Å $\geq d \leq 4.5$ Å); B-factor, the AAs that have a

higher flexibility than average; b, *Bos taurus*; Py, *Plasmodium yoelii*; Pf, *Plasmodium falciparum*; Ld, *Leishmania donovani*; Bm, *Brugia malayi*; Ce, *Caenorhabditis elegans;* Sm, *Schistosoma mansoni.* The chemical name of Sanglifehrin A: (3S,6S,9R,10R,11S,12S,13E,15E,18S,21S)-18-{(1E,3E,7S,8S)-9-[(2S,3R,4S,5S,6R,9S,11S)-9-ethyl-4-hydroxy-3,5,11-trimethyl-8-oxo-1-oxa-7-azaspiro[5.5]undec-2-yl]-8-hydroxy-1,7-dimethylnona-1,3-dienyl}-10,12-dihydroxy-3-(3-hydroxybenzyl)-6-isopropyl-11-methyl-9-(3-oxobutyl)-19-oxa-1,4,7,25-tetraazabicyclo[19.3.1]pentacosa-13,15-diene-2,5,8,20-tetrone.

## References


R1. Stegmann CM, Luhrmann R, Wahl MC (2010) The crystal structure of PPIL1 bound to cyclosporine A suggests a binding mode for a linear epitope of the SKIP protein. PLoS One 5:e10013

R2. Huang LL, Zhao XM, Huang CQ, Yu L, Xia ZX (2005) Structure of recombinant human cyclophilin J, a novel member of the cyclophilin family. Acta Crystallogr D Biol Crystallogr 61:316-321

R3. Mikol V, Kallen J, Walkinshaw MD (1994) X-ray structure of a cyclophilin B/cyclosporin complex: comparison with cyclophilin A and delineation of its calcineurin-binding domain. Proc Natl Acad Sci USA 91:5183-5186

R4. Ke H, Zhao Y, Luo F, Weissman I, Friedman J (1993) Crystal structure of murine cyclophilin C complexed with immunosuppressive drug cyclosporin A. Proc Natl Acad Sci USA 90:11850-11854

R5. Schlatter D, Thoma R, Kung E, Stihle M, Muller F, Borroni E, Cesura A, Hennig M (2005) Crystal engineering yields crystals of cyclophilin D diffracting to 1.7 Å resolution. Acta Crystallogr D Biol Crystallogr 61:513-519

R6. Kajitani K, Fujihashi M, Kobayashi Y, Shimizu S, Tsujimoto Y, Miki K (2008) Crystal structure of human cyclophilin D in complex with its inhibitor, cyclosporin A at 0.96-Å resolution. Proteins 70:1635-1639

R7. Reidt U, Reuter K, Achsel T, Ingelfinger D, Luhrmann R, Ficner R (2000) Crystal structure of the human U4/U6 small nuclear ribonucleoprotein particle-specific SnuCyp-20, a nuclear cyclophilin. J Biol Chem 275:7439-7442

R8. Wang T, Yun CH, Gu SY, Chang WR, Liang DC (2005) 1.88 Å crystal structure of the C domain of hCyP33: a novel domain of peptidyl-prolyl cis-trans isomerase. Biochem Biophys Res Commun 333:845-849

R9. Taylor P, Dornan J, Carrello A, Minchin RF, Ratajczak T, Walkinshaw MD (2001) Two structures of cyclophilin 40: folding and fidelity in the TPR domains. Structure 9:431-438

R10. Davis T, Walker JR, Newman EM, Mackenzie, F, Butler-Cole, C, Finerty, PJ Jr, Weigelt J, Sundstrom M, Arrowsmith C, Edwards A, Bochkarev A, Dhe-Paganon S (2007) Structural Genomics Consortium (SGC). Crystal structure of the peptidylprolyl domain of human PPWD1 (2A2N), http://www.rcsb.org/pdb

R11. Stegmann CM, Seeliger D, Sheldrick GM, de Groot BL, Wahl MC (2009) The thermodynamic influence of trapped water molecules on a protein-ligand interaction. Angew Chem Int Ed Engl 48:5207-5210

R12. Davis T, Walker JR, Newman EM, Mackenzie F, Butler-Cole C, Finerty PJ Jr, Weigelt J, Sundstrom M, Arrowsmith C, Edwards, A, Bochkarev A, Dhe-Paganon, S (2007) Structural Genomics Consortium (SGC). Structure of the PPIase cyclophilin-type domain of the human NK-tumor recognition protein (2HE9), http://www.rcsb.org/pdb

R13. Dornan J, Page AP, Taylor P, Wu S, Winter AD, Husi H, Walkinshaw MD (1999)

R15. Picken NC, Eschenlauer S, Taylor P, Page AP, Walkinshaw MD (2002) Structural and biological characterisation of the gut-associated cyclophilin B isoforms from *Caenorhabditis elegans*. J Mol Biol 322:15-25

R16. Taylor P, Page AP, Kontopidis G, Husi H, Walkinshaw MD (1998) The X-ray structure of a divergent cyclophilin from the nematode parasite *Brugia malayi*. FEBS Lett 425:361-366

R17. Ellis PJ, Carlow CK, Ma D, Kuhn P (2000) Crystal structure of the complex of *Brugia malayi* cyclophilin and cyclosporin A. Biochemistry 39:592-598

R18. Vedadi M, Lew J, Artz J, Amani M, Zhao Y, Dong A, Wasney GA, Gao M, Hills T, Brokx S, Qiu W, Sharma S, Diassiti A, Alam Z, Melone M, Mulichak A, Wernimont A, Bray J, Loppnau P, Plotnikova O, Newberry K, Sundararajan E, Houston S, Walker J, Tempel W, Bochkarev A, Kozieradzki I, Edwards A, Arrowsmith C, Roos D, Kain K, Hu, R (2007) Genome-scale protein expression and structural biology of *Plasmodium falciparum* and related *Apicomplexan* organisms. Mol Biochem Parasitol 151:100-110

R19. Peterson MR, Hall DR, Berriman M, Nunes JA, Leonard GA, Fairlamb AH, Hunter WN (2000) The three-dimensional structure of a *Plasmodium falciparum* cyclophilin in complex with the potent anti-malarial cyclosporin A. J Mol Biol 298:123-133

R20. Venugopal V, Sen B, Datta AK, Banerjee R (2007) Structure of cyclophilin from *Leishmania donovani* at 1.97 Å resolution. Acta Crystal F63:60-64

R21. Gourlay LJ, Angelucci F, Baiocco P, Boumis G, Brunori M, Bellelli A, Miele AE (2007) The three-dimensional structure of two redox states of cyclophilin A from *Schistosoma mansoni*. Evidence for redox regulation of peptidyl-prolyl cis-trans isomerase activity. J Biol Chem 282:24851-24857