The design of inhibitors based on the isomerase mechanism of Cyps led to bicyclic lactams that mimic the ground state of a proline-bearing peptide, along with bicyclic amines in which a tertiary amine mimics a 'twisted amide' transition state.[15] The ground-state mimic (**15**) was found to bind more efficiently to CypA ($K_d = 1.5\,\mu M$ *versus* $K_d = 77\,\mu M$) for this series of derivatives. A series of small-molecule inhibitors based on aryl 1-indanyl ketones was designed by Schiene-Fischer to mimic the 'twisted amide' of a putative transition state and led to compounds (**16**) that not only bound tightly to CypA (K_i 520 nM) but also demonstrated selectivity for CypA over CypB.[12,13] Very minimal ligands for CypA were developed by Walkinshaw and co-workers by combining a 'twisted amide' concept with a hydrophobic group designed to mimic [MeVal][11] of CsA; however, the affinity of these ligands was poor (>25 mM).[186]

A successful application of fragment-based ligand design identified simple dimedone inhibitors in which the dimethyl group was shown to mimic the isopropyl group present in [MeVal][11]of CsA while one of the carbonyls mimics the [MeLeu][10] carbonyl.[187] Further structure-aided elaboration of these weak ligands led to potent inhibitors of CypA such as **17** (K_D 11 μM), which demonstrated activity against *Caenorhabditis elegans* consistent with inhibition of CypA.[188]

Virtual screening efforts using the key residues in CypA known to be involved in binding CsA ([Trp][121], [Arg][55], [Asn][102], [Gln][63], [Asn][102]) have been employed by a number of groups. A series of thioureas with good potency against CypA (IC_{50} 0.48 μM) were reported by Wu *et al.*[189] as potential neuroprotective/neurotrophic agents, while Chavanieu and co-workers[190] and Jiang and co-workers[191] identified very potent diarylureas ($IC_{50} < 0.05\,\mu M$) (*e.g.* **18**) that showed activity in HIV-1 infection assays.

Further studies by Jiang's group using virtual screening in conjunction with surface plasmon resonance to screen for non-CsA-based CypA inhibitors[192–194] identified substituted anilides with modest potency as inhibitors of CypA ($IC_{50} \sim 3\,\mu M$), which showed evidence of immunosuppression. Subsequent elaboration of these leads using X-ray structural data resulted in potent ligands for CypA. Finally, high-throughput screening of diverse chemical libraries has identified new ligands for Cyps[195,196] with modest affinity; however, no further modification of these starting points has been described.

One final compound mentioned in this section is sanglifehrin A (**19**) (Figure 11.10). Although it is not a small molecule, it is a natural product found to have 60-fold higher affinity for Cyp ($IC_{50} = 6.9$ nM) than CsA itself ($IC_{50} = 420$ nM),[197] and there have been several recent reports of sanglifehrin and synthetic derivatives as potential Cyp-inhibiting drugs, including anti-HIV-1 and/or anti-HCV activity therapeutics.[198–206]

In conclusion, there are several examples of non-CsA-based CypA inhibitors in the recent literature, some of which show CypA binding comparable to that of CsA itself. These synthetically feasible small molecules could foster drug discovery programs towards CypA inhibitors tailored for specific diseases through specific Cyp isoforms, and may have the added benefit of being devoid of CsA-related toxicity.