

11.4 New Opportunities for Cyclophilin Inhibitors as Antiviral Agents

11.4.1 Non-cyclosporine Cyclophilin Inhibitors

Attempts to discover ‘small-molecule’ inhibitors of Cyps, using either the protein or ligand structures, have appeared over the last 10 years (Figure 11.10).^{179–182} Early attempts to use peptide substrates as starting points identified Succ-Ala-Ala-Pro-Phe-*p*-NO₂-anilide, which is known to bind CypA with a K_m of 870 μM .¹⁸³ Replacing the central Ala-Pro core with a (*Z*)-alkene *cis*-Pro (**14**) mimetic resulted in a compounds with an IC₅₀ of 6.5 μM . The demonstration that a CypA–Gag interaction is crucial for effective replication of HIV-1 led to an effort to use Gag sequences as inhibitors of CypA. A pentapeptide Dav-His-Ala-Gly-Pro-Ile-NHBn was found to have higher affinity for CypA ($K_d = 3 \mu\text{M}$) than the entire capsid protein ($K_d = 16 \mu\text{M}$).¹⁸⁴ More recently, a virtual screening exercise performed by Zhang and co-workers identified short peptides (Trp-Gly-Pro, Trp-Ala-Gly-Pro and Tyr-Gly-Pro) that showed inhibition of CypA PPIase activity with potency (33 nM) comparable to that of CsA (10 nM).¹⁸⁵

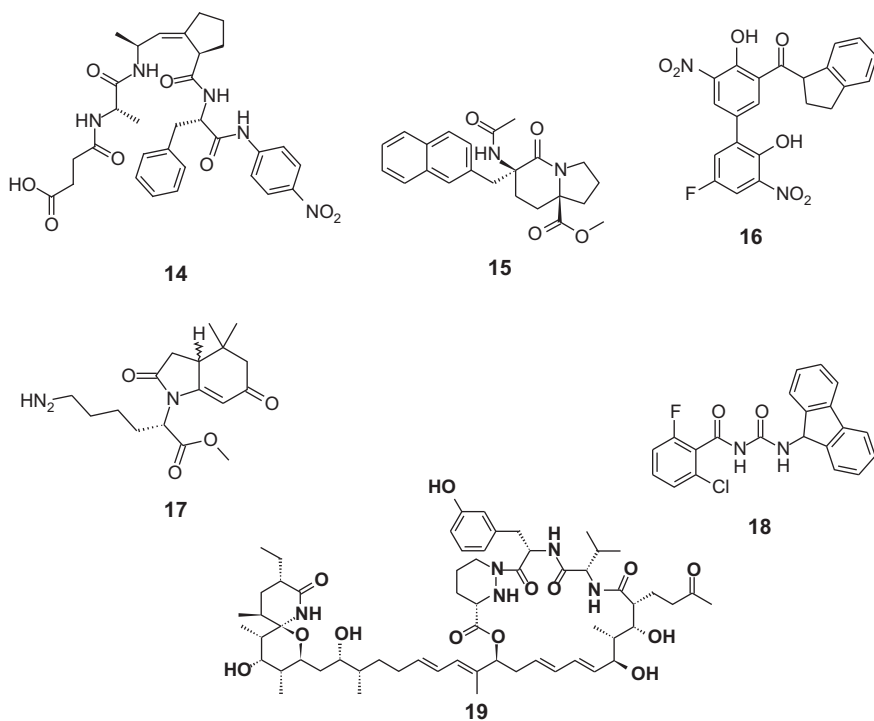


Figure 11.10 Non-CsA inhibitors of CypA.