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a proline-rich sequence in the HIV-1 capsid domain of Gag,[41–43] where residues 85–93 of HIV-1 capsid bind to the active site of CypA, as later revealed by X-ray crystallography.[44] Subsequent studies with CypA in the presence of mutated Gag or competitive Cyp A inhibitors have shown that neither viral budding nor Gag processing are affected; however, virions produced under such conditions were less infectious than those possessing CypA.[44] CypA is then incorporated into nascent HIV-1 virions during the assembly and budding process. As these HIV virions now infect new T cells, CypA from the virion delivered to the new cell facilitates uncoating of the capsid and supports efficient reverse transcription of the viral genome.[45]

More recent studies, however, have suggested that CypA in the infected target cell, and not CypA from HIV-1 virions, is more important to HIV-1 infectivity.[46–48] It was then also found that CypA in the target cell increases HIV-1 infectivity by inhibiting host cell restriction factors mounted as part of an innate immune response that ordinarily combats invading retroviruses.[49] In particular, CypA was found to inhibit tripartite motif 5α (TRIM5α)-mediated restriction of post-entry HIV-1 before reverse transcription *via* binding to HIV-1 capsid, which binds to TRIM5α in the same region that it binds to CypA.[49,50] Reducing the CypA–capsid interaction by either mutations altering binding of CypA to capsid or by the introduction of a CypA inhibitor such as CsA has been shown to increase HIV-1 susceptibility to TRIM5α restriction.[49] Other recent studies have suggested that CypA binds to HIV-1 viral protein R (Vpr), which undergoes *cis–trans* isomerization of proline residues in its N-terminal region. This activation by CypA ultimately governs the functional expression of Vpr, which is needed for translocation of virus to the nucleus and induction of cell cycle arrest and apoptosis in infected T cells.[51,52]

In summary, there are several stages in the HIV-1 life cycle that involve CypA, some understood more clearly than others. Clearly, a CypA inhibitor that bound to CypA alone and not CaN would potentially be an effective anti-HIV therapeutic. Such compounds have been developed and are discussed in Section 11.3.

11.2.2 Hepatitis C Virus

The demonstration of *in vitro* anti-HCV activity, using a sub-genomic replicon cell culture system, for CsA but not for a different CaN inhibitor, FK-506, provided early support for a role of Cyps in HCV replication.[53,54] Clinical studies in HCV-infected patients showing superior virologic response to CsA in combination with interferon-α2b versus interferon-α2b alone[55,56] further implicated Cyp inhibition as an approach to HCV therapy. A definitive role for Cyps in HCV replication was demonstrated by Watashi *et al.* using a set of chemically modified CsA derivatives (Figure 11.4).[56] Both immunosuppressive {CsA (**1**) and [8′-HO-MeBmt][1]CsA (**2**)} and non-immunosuppressive {[MeAla][6]CsA, [MeVal][4]CsA (**3**) and [MeIle][4]CsA (**4**, NIM-811)} derivatives demonstrated potent inhibition of HCV RNA replication while closely related compounds {CsH (**5**) and PSC 833 (**6**)} that do not bind CypA were inactive in