would otherwise serve to clear the infection and place Cyp inhibition as a potentially important immunotherapy approach to virology.

11.3 Modification of Cyclosporine to Treat Viral Diseases

11.3.1 Factors Affecting Cyclophilin Binding and Selectivity

As discussed in Section 11.1.2, the Cyp binding domain comprises of residues 9, 10, 11, 1 and 2 on the CsA scaffold. Hence modifications to these residues tend to have a significant effect on Cyp binding, whereas modifications to residues in the CaN binding domain (4, 5, 6 and 7) typically have less influence (Figure 11.6).

The MeBmt group at position 1 plays a key role in that it resides in the Cyp binding domain, yet its side chain drapes across the CsA scaffold and ultimately into the CaN binding domain. In general, modifications to MeBmt tend to decrease Cyp binding. Removing or altering the stereochemistry of the 4-methyl group reduces activity, as does introducing a second methyl group at this position.[94,95] Likewise, removing, replacing or capping the 3′-hydroxy group as an ester also reduces potency.[96,97] The butenyl chain appears crucial for binding, as reducing the double bound to a fully saturated butane chain slightly diminishes Cyp binding.[96] More significant changes, such as truncation of the butene chain, cause a significant decrease in activity;[98] however, modification of the 8′-carbon, including simple homologation or oxidation, can

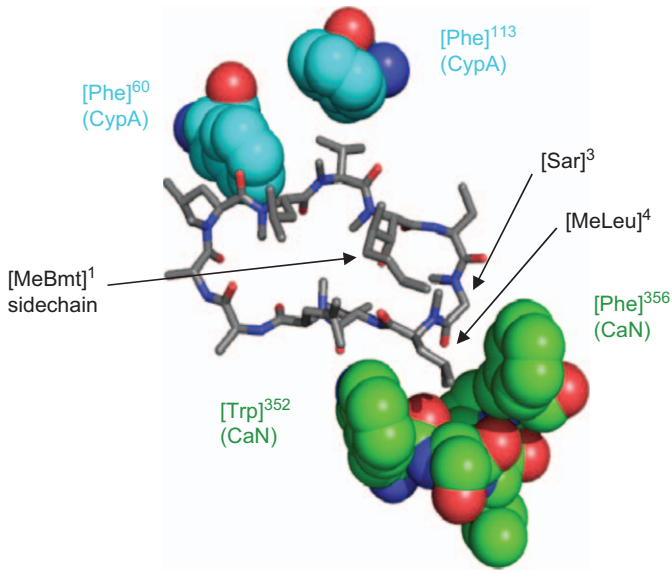

Figure 11.6 Structure of CsA bound to both CypA and CN. The side chain of [Val][11] is bound in a hydrophobic pocket of CypA whereas [Leu][4] binds tightly to CN.