binding,[95,96] as does MeVal.[2] The 11-position is especially sensitive to Cyp binding, consistent with this residue occupying the 'proline binding region' which is central to the catalytic activity of the protein. Substitution of [MeVal][11] with MeIle, aMeIle or MeLeu completely abolishes Cyp binding,[96] as does MeThr,[104] while [MeAla][11]CsA exhibits only 8.5% of CsA's Cyp binding affinity.[95,96]

### 11.3.2 Removing Immunosuppressive Potential

In Section 11.2, it was noted that Cyp inhibition alone, and not CaN inhibition, is requisite for inhibiting replication of viruses such as HIV-1 and HCV. Furthermore, one would correctly surmise that inhibiting CaN would be counterproductive towards antiviral therapy since this would compromise the host immune response to an invading virus. Hence, an ideal Cyp-inhibiting antiviral drug should be designed such that it retains high binding affinity for Cyp, but not CaN.

Amino acid 4, where [MeLeu][4] ordinarily resides in CsA, has a profound influence on CaN binding, presumably due to a tight 'aromatic sandwich' that the amino acid side chain must snugly fit into between CaN residues [Trp][352] and [Phe][356]. The first derivative modified at this position found to exhibit a huge disparity between CypA and CaN binding is [MeIle][4]CsA, NIM811.[125] [MeIle][4]CsA was found to have no immunosuppressive activity, while retaining the same affinity for CypA as CsA itself.[125] Subsequent synthesis of analogs revealed that [MeVal][4]CsA (**3**) exhibited a >2500-fold decrease in immunosuppressive activity, with a concomitant twofold increase in Cyp binding.[110] Similarly, substituting [MeLeu][4] with [4′-HOMeLeu][4]CsA (**7**, Figure 11.8) *via*

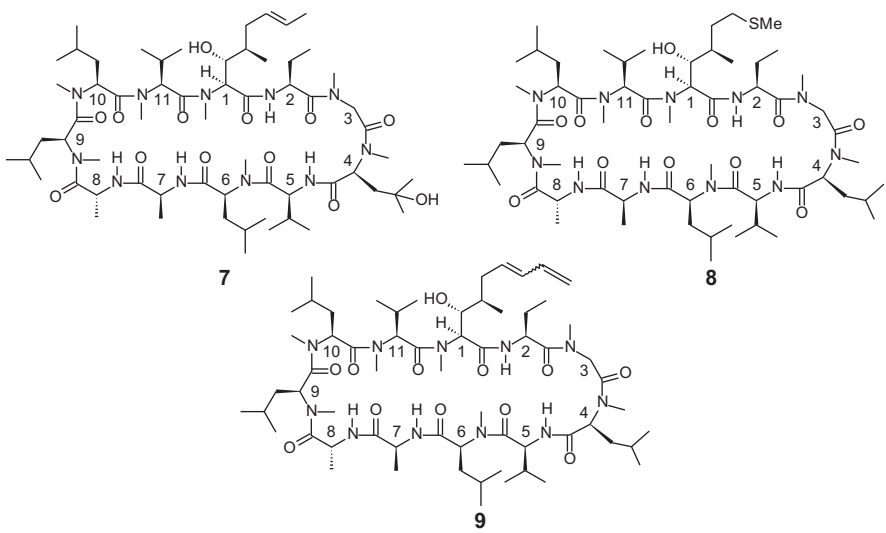


**Figure 11.8** Modification of [Leu][4] generally leads to a loss of CN binding, whereas [Bmt][1] modification is less predictable.