demonstrates the remarkably subtle effects that translocation of a single methyl group can have on a complex scaffold such as CsA. The [MeVal]^{4}CsA derivative served as the starting point for the discovery of the potent non-immunosuppressive anti-HIV-1 compound [D-Ala]^3[EtVal]^{4}CsA) (alisporivir).[73,144] Addition of a methyl group to the [Sar]^3 position may serve to affect conformation distribution patterns and improve CypA binding while the homologation of the [MeVal]^4 residue to [EtVal]^4 would be expected to diminish metabolic demethylation of this position, a major metabolism route of CsA itself.

After position 4, little anti-HIV-1 has been published involving modification of positions 5–11. Both [MeVal]^{5}CsA and the metabolite [4′-HOMeLeu]^{9}CsA exhibit anti-HIV-1 activity roughly equipotent to CsA, while [MeAla]^{6}CsA shows about a threefold decrease in anti-HIV-1 activity.[129–132] Beyond this, there is a report of anti-HIV-1 activity with [3′-HOMeLeu]^1[MeAla]^4[MeAla]^{6}CsA, in which costimulation of IL-2 production is observed, lowering HIV-1 infectivity in drug-exposed cells.[145,146]

11.3.3.2 Anti-HCV SARs

The [MeBmt]^1 residue, due to the relative ease of synthetic access, has been investigated by several groups that have included claims to anti-HCV activity,[126–128,147–157] although to date no anti-HCV SAR has been published.

The 2-position, not being as amenable to synthetic modification, has been addressed only sparingly for anti-HCV activity. Astellas Pharma has looked at analogs of CsC ([Thr]^{2}CsA) with additional modifications at either the 1- and/or 9-positions[158] or the 3-, 4-, 5- and 10-positions.[159] In the case of the former, [Thr]^2[5′-HOMeLeu]^{9}CsA was reported to have an $EC_{50} < 3\,\mu M$, whereas for the latter, nine [Thr]^2[Leu]^5[Leu]^{10}CsA analogs were found to exhibit $EC_{50} < 0.5\,mg\,mL^{-1}$. These compounds possessed modifications at position 3 (D-SerOMe, D-Ala, D-Abu or D-MeThrO-*t*-Bu) and/or 4 (MeThr, MeThrOMe, MeThrO-*t*-Bu, MeIle, MeVal or MePhe).

As was the case with anti-HIV-1 analogs, [Sar]^3 has been explored heavily owing to its relative ease in synthetic modification to analogs well tolerated for CypA binding (Table 11.1). Scynexis has prepared [Sar-*O*/*S*-alkyl]^{3}CsA analogs with either [MeLeu]^4 or the preferred [4′-HOMeLeu]^4, many of which exhibited EC_{50}s $< 400\,nM$, the value observed for CsA.[136] The most potent examples from this set included [Sar-D-OMe]^{3}CsA (60 nM), [Sar-D-SMe]^3[4′-HOMeLeu]^{4}CsA (40 nM), [Sar-D-OMe]^3[4′-HOMeLeu]^{4}CsA and [Sar-D-$OCH_2CH{=}CH_2$]^3[4′-HOMeLeu]^{4}CsA. Scynexis subsequently explored [Sar-*O*/*S*-CH_2aryl]^{3}CsA analogs and found several derivatives, including **10**, **11**, [Sar-D-OCH_2-furan-3-yl]^{3}CsA (250 nM) and [Sar-D-OCH_2Ph]^{3}CsA (260 nM), to be more potent against HCV than CsA itself. A recent patent from S & T Global claims [Sar]^3 substitution with a methylene (–CH_2–) bridging the 2′-α-carbon to the *O*/*S*-$(CH_2)_{2,3}$-dialkylamine side chain to give compounds (*e.g.* **12**) with good activity against a subgenomic HCV replicon and improved stability in MeOH at $\geq 50\,^{\circ}C$.[139]