

to potent anti-HCV compounds⁷ such as [Val]²[D-MeAla]³[MeVal]⁴[Ile]⁵[Gly]⁷[D-Hiv]⁸[Leu]¹⁰CsA (22 nM).

11.3.4 ADME Properties of Cyclosporine and Derivatives

Cyclosporine A displays extremely complex pharmacokinetic properties that are still being evaluated over 40 years after its discovery. Cytochrome P450-mediated metabolism and P-gp efflux transport were recognized early as key factors that affect the plasma exposure of CsA.¹⁶⁷ However, additional factors such as a saturable binding to erythrocytes,¹⁶⁸ interaction with a wide range of transporters¹⁶⁹ and a conformation-dependent solubility profile for CsA derivatives make the optimization of new CsA derivatives challenging.

CsA is a relatively hydrophobic compound that is subject to extensive metabolism by Cyp3A4 and Cyp3A5.¹⁶⁷ A comprehensive analysis of the metabolite profile of CsA following dosing to dogs and humans revealed at least nine significant species that were isolated from the bile and feces.¹⁶⁷ Primary routes of metabolism of CsA involve oxidative hydroxylation of the side chains of residues 1, 4, 6 and 9 and a demethylation of the [MeLeu]⁴ residue (Figure 11.9).¹⁶⁷ The three predominant metabolites resulted from mono-hydroxylation at the γ -carbon of the [MeLeu]⁹ side chain, hydroxylation of the terminal carbon of the Bmt side chain and a monodemethylation at the [MeLeu]⁴ residue.¹⁶⁷ Minor metabolic routes included hydroxylation at the γ -carbons of [MeLeu]⁴ and [MeLeu]⁶, an epoxidation of the MeBmt olefin and products resulting from sequential oxidations.¹⁶⁷ Tetrahydrofuran derivatives resulting from the non-enzymatic ring-closure reaction of Bmt epoxides were also isolated.^{167,170}

Limited data have been published regarding the metabolism of derivatives of CsA. Alisporivir appears to be more resistant to metabolism in humans, with up to 66% of the dose being excreted in the feces as unchanged drug,¹⁷¹ which

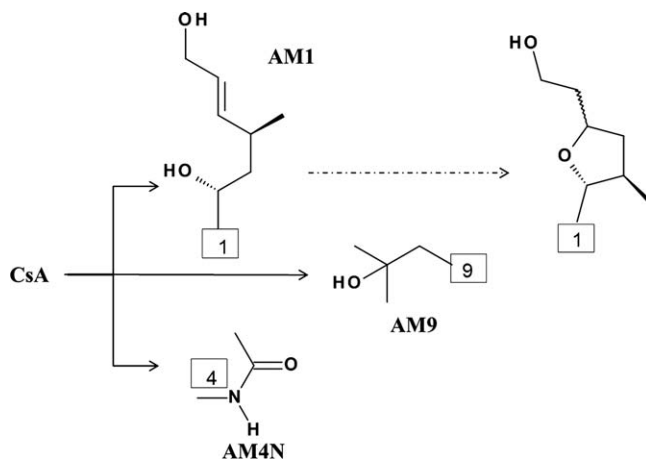


Figure 11.9 Primary human metabolites of CsA.