Figure 3. Mechanism of action of sirolimus (rapamycin). Although the pre-drug sirolimus (SRL) binds to FK506-binding protein (FKBP, which is the same molecule that is bound by FK506), the complex that is formed between SRL and FKBP binds to the mammalian target of rapamycin (mTOR). The SRL–FKBP–mTOR complex inhibits biochemical pathways that are required for cell progression through the late G1 phase or entry into the S phase of the cell cycle. Thus, unlike cyclosporine (CsA) and FK506 (which block the production of cytokines), SRL blocks cytokine signal transduction. SRL is thought to target: (1) the 70-kD S6 protein kinase p70S6K; (2) the eukaryotic initiation factor eIF-4F; (3) the G1-controlling cyclin-dependent kinase (cdk) proteins, such as the D2 cycline cdk2, the D2 cycline cdk6 or the E cycline cdk2 and (4) the kinase inhibitory protein Kip1 (p27kip), which blocks cell progression to the S phase. Abbreviations used: p34cdc2 = a kinase; PTKs = protein tyrosine kinases (fig003ssh).