8.3.1.3 Discovery of BMS-791325

More recently, the virology group at Bristol Myers Squibb (BMS) has begun reporting on the discovery of their own version of conformationally rigidified polycyclic indole thumb pocket 1 inhibitors.[39] Early examples include lactam-bridged analogs such as **25** (Figure 8.7). Hybridization with Boehringer Ingelheim's cinnamic acid right-hand sides (*e.g.*, **26**) resulted in compounds with 10–20-fold increases in replicon potency ($EC_{50} = 10$ nM for **26**). The results were rationalized with X-ray crystal structure data maintaining the typical dihedral angle between the indole and C2 aromatic substitution ($\sim 46^{\circ}$), a hydrogen bond between the indole C6 amide and R503 and an interaction of the cinnamic acid carboxylate with the side chain of R498.[39]

Early inhibitors displayed poor PK profiles in rats, due in part to high clearance. In a subsequent report, replacement of the phenyl ring at the C2

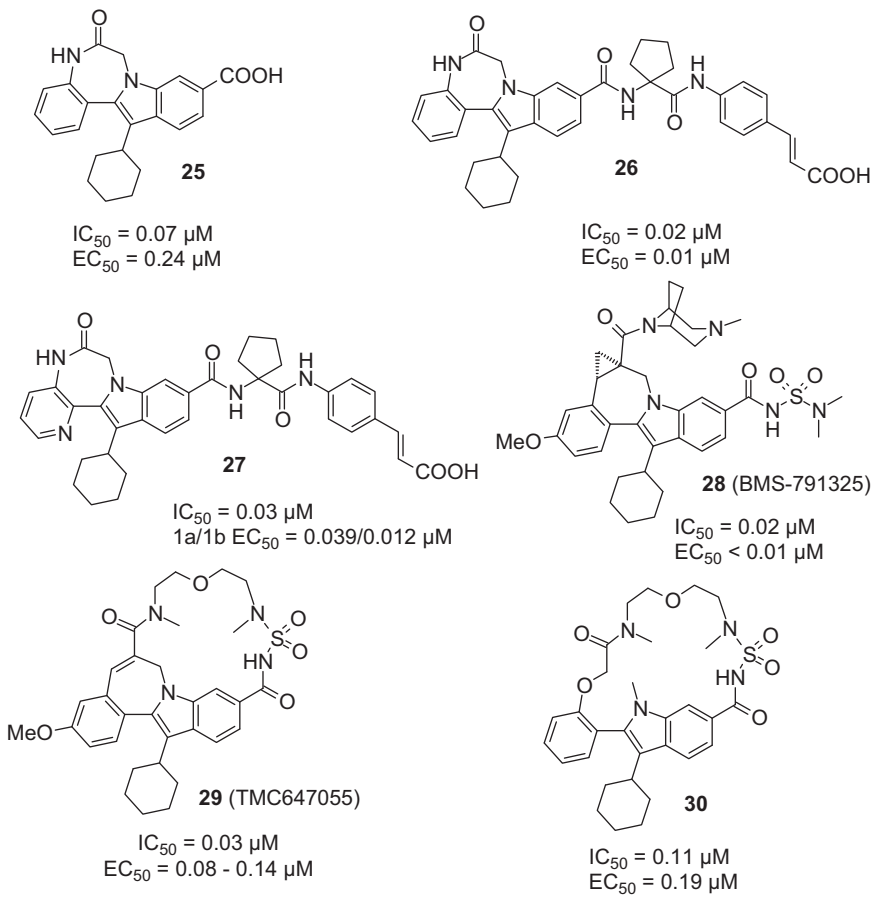

Figure 8.7 Constrained polycyclic indole inhibitors from Bristol Myers Squibb and Tibotec.