clearances of 12, 21 and 6% Q_h (% hepatic blood flow) and good bioavailability (54–70 %). The compound was favorably distributed to the liver target organ in rats with a liver/plasma ratio of ~9.

Based on its preclinical and safety profile, BILB 1941 was evaluated in 5 day multiple rising dose monotherapy in gt1-HCV-infected patients, where it produced significant (up to 2.5$\log_{10}$ reduction in viremia) and HCV subtype-dependent antiviral activity when dosed at 450 mg q8h.[30] Unfortunately, increased virological response was limited by gastrointestinal intolerance, which precluded testing of the compound at higher doses. This proof-of-concept trial suggested that more potent analogs could result in a more consistent antiviral response, and efforts at Boehringer Ingelheim were subsequently focused on identifying analogs with improved potency against both gt1a and gt1b replicons, while maintaining a favorable PK profile. These efforts culminated in the discovery of a follow-up compound, BI 207127 (**17**, Figure 8.4; 1b/1a $EC_{50} = 11$ and 23 nM), which maintained replicon potency <100 nM across genotypes 1–6.[31] BI 207127 given as monotherapy at doses up to 1200 mg q8h for 5 days exhibited strong and dose-dependent antiviral activity (>3$\log_{10}$) and a low frequency for emergence of resistance mutations in gt1-HCV-infected patients.[32] In combination with PegIFN-α2a and ribavirin, BI 207127 decreased HCV RNA in gt1-HCV patients in a dose-dependent manner [5.6$\log_{10}$ in treatment-naïve (TN) and 4.2$\log_{10}$ in treatment-experienced (TE) patients] at a dose of 600 mg administered tid for a period of 28 days. Breakthroughs were not observed in the TN group and 3/30 TE patients experienced rebound due to a P495 mutation.[33] BI 207127 has also been investigated in a Phase 2 trial in an interferon-free combination with protease inhibitor faldaprevir and ribavirin. In a 4 week study with BI 207127 (600 mg tid) + faldaprevir (120 mg qd) + RBV (1000–1200 mg d^{-1}), 100% of patients achieved a lower limit of quantification (25 IU mL^{-1}) independent of gt1-HCV subtype, and the combination was generally well tolerated. In a larger Phase 2b study of faldaprevir (120 mg qd) + BI 207127 (600 mg bid) + RBV, 68% SVR_{12} was achieved after 28 weeks of treatment in all gt1 TN patients; this included an 82% SVR_{12} among all gt1b (IL28B: CC and non-CC) and gt1a (IL28B: CC only).[34b] The data support further evaluation of these two drugs in interferon-free regimens for the treatment of HCV infection, including patients with cirrhosis and phase 3 trials are currently ongoing.[34]

In 2006, Japan Tobacco reported the discovery of a new series of conformationally constrained tetracyclic indolecarboxylic acid derivatives with improved potency. The novel thumb pocket 1 inhibitors exhibited low serum shifts in replicon assays performed in the presence of human serum albumin.[35] Installation of a bridge between the indole nitrogen and the *ortho*-position of an aromatic ring at C2 provided rigidification of the dihedral angle between the indole scaffold and the C2 substituent. The optimal three-atom tether and dihedral angles approximating 50° (similar to the bioactive conformation revealed in the crystal structure of a tetracyclic analog in complex with NS5B) provided up to 10-fold gains in biochemical potency (see, for example, **18**, Figure 8.6).[35a]