bridge with heterocyclic moieties was explored in an attempt to improve physicochemical properties. Although several analogs exhibited good cell-based potency in both 1a and 1b replicon assays (*e.g.*, pyridine analog **27**), PK profiles were not improved relative to previously described analogs, presumably due to low solubility and poor permeability.[40] While the findings that guided further optimization of this class of thumb pocket 1 inhibitors await future publications, BMS recently disclosed the chemical structure of a clinical candidate currently in Phase 2 clinical trials in combination with SOC. BMS-791325 (**28**) is an indole-based pentacyclic thumb pocket 1 inhibitor in which the indolecarboxylic acid moiety was replaced with an *N*,*N*-dimethylsulfamide moiety that presumably reduces the potential to form reactive acylglucuronide conjugates. The molecule features a basic side chain substituent that, in combination with the ionizable acylsulfamide moiety, confers zwitterionic character to the molecule. Compound **28** has reported $EC_{50} = 3–14$ nM for genotypes 1a/1b, 3a and 5 while genotypes 2a/2b and 6 are in the 112–270 nM range. It is highly protein bound (97.8–98.8%) and the liver distribution for this compound is species dependent, ranging from 10–15-fold in rats to twofold in dogs. In an ongoing Phase 2a study, BMS-791325 (75 or 150 mg bid) in combination with PegIFN and RBV was well tolerated. During the first 12 weeks of therapy, responses were highest in the 75 mg bid group, where 92% of patients had undetectable HCV RNA at week 4 (RVR). At week 12, 77% of patients (75 mg bid group) had undetectable HCV RNA (complete early virological response, cEVR) *versus* 54% in the 150 mg dose group, which also suffered from higher discontinuation rates (15% *versus* 8%). Three of 26 patients in the 150 mg dose group experienced viral breakthrough with A421V and P495L/S resistant variants emerging in the gt1a and gt1b groups, respectively. No virologic escape was detected in the 75 mg-dose group.[41]

8.3.1.4 Discovery of TMC647055

Several groups have noted the potential of 6-indolecarboxylic acid derivatives (*e.g.*, indole-*N*-acetamide **14**) to form reactive circulating acylglucuronide conjugates and have therefore searched for suitable carboxylic acid isosteres.[42] Certain heterocycles (*e.g.*, oxadiazolones), and especially acylsulfonamides and acylsulfamides (*e.g.*, **28**), have been reported with excellent intrinsic potency and have provided opportunities to modulate physicochemical properties (*e.g.*, pK_a) and explore additional interactions with the enzyme.[43]

Recent reports from Tibotec describe the rational design of NS5B thumb pocket 1 allosteric inhibitors that combine both concepts of carboxylic acid replacement and conformational rigidification with the opportunity to exploit new biochemical space and modulate the properties of the molecules. These studies ultimately led to the discovery of TMC647055 (**29**, Figure 8.7), a macrocyclic molecule with the necessary potency and preclinical profile for selection as a clinical candidate.[44] Using knowledge derived from the overlap of publicly available X-ray structures of thumb pocket 1 inhibitors in complex with NS5B, Tibotec researchers elaborated several macrocyclization strategies