

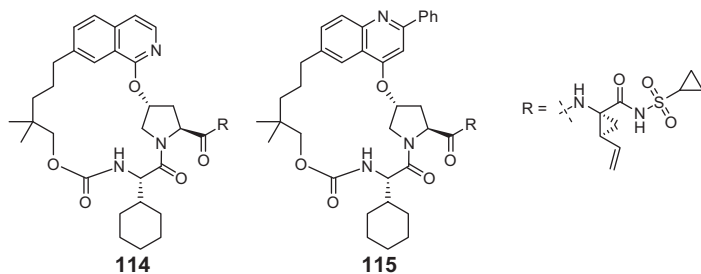
In summary, investigation of a series of P2–P4 macrocycles containing a hydroxyproline carbamate led to the identification of 5-linked isoindoline as a promising P2 substituent for a new class of HCV NS3/4a protease inhibitors. Optimization of this series, with the goals of achieving rat liver exposure and balanced activity against both the 1b and 2a genotypes of NS3/4a protease led to the identification of vaniprevir (**13**, MK-7009). Further studies of vaniprevir, including clinical investigations of the PK and efficacy profile, are ongoing.⁴³

7.4 Discovery of MK-5172

With the development of vaniprevir progressing, Merck set as a goal for the ongoing discovery program the identification of a second-generation NS3/4a protease inhibitor. While maintaining or improving the PK profile seen with vaniprevir, significant improvements in activity against the gt3a enzyme and key clinically relevant gt1 mutant enzymes were desired. An entry point for enhanced gt3a activity was provided by a consistent trend for improving gt3a activity with the addition of a large substituent to the P2 heterocycle in early compounds. For example, the gt3a activity of **114** ($K_i = 200$ nM, Table 7.19) was improved approximately fourfold with the addition of a phenyl group to give closely related compound **115** ($K_i = 45$ nM). Based on this observation, Merck undertook a systematic investigation of substituents at this position of the P2 quinoline.

In order to explore fully the SAR at the 2-position,¹⁰⁵ a significant number of analogs would be needed and using the classic Conrad–Limpach quinoline synthesis,¹⁰⁶ the substituent in the 2-position was installed in the first step (Scheme 7.5). Utilization of this synthesis would require an additional nine steps to complete each analog. Hoping to avoid this inefficiency, a more versatile route, which introduced the 2-substituent near the end of the synthetic

Table 7.19 *In vitro* activity of compounds **114** and **115**.



Compound	1b K_i (nM) ^a	3a K_i (nM) ^a	1b replicon IC_{50} 50% NHS (nM)	Rat [liver] @ 4 h (μ M)
114	0.02	200	10	21
115	0.05	45	19	7.8

^aNS3/4a protease time-resolved fluorescence assay, mean of $n \geq 3$ measurements.