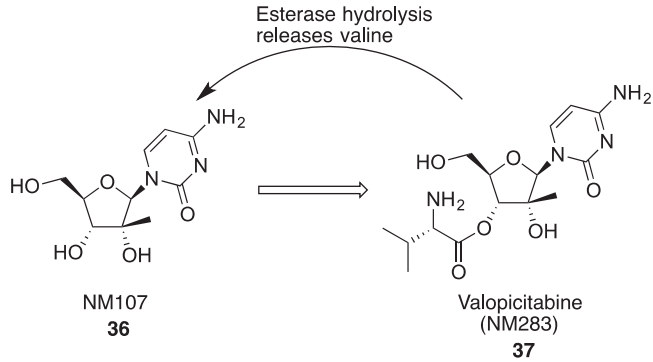

Figure 12.18 Valopicitabine (NM283) (**37**) is the valinate ester prodrug of the 2′-*C*-methylcytidine nucleoside NM107 (**36**). It was developed to improve the bioavailability of the parent drug NM107 by leveraging intestinal peptide transporters.

PK studies showed that NM107 exhibited poor oral bioavailability. Consequently, in the hope of taking advantage of peptide transporters and improve its bioavailability, the 3′-*O*-valinate ester prodrug (NM283, valopicitabine) (**37,** Figure 12.18) was developed.[99] NM283 was shown to have an apparent oral bioavailability of 34% in rats and was subsequently taken into human clinical trials. The proof of concept for the use of this prodrug strategy in humans was obtained when in a monotherapy study, NM283 demonstrated a $1.2\log_{10}$ IU mL^{-1} reduction in viral load after oral administration (800 mg bid) over 14 days and a $>4\log_{10}$ IU mL^{-1} reduction in viral load when coadministered with interferon and ribavirin.[14,15] Unfortunately, this drug was discontinued owing to adverse gastrointestinal side effects.

12.6 Conclusion

The breadth of impact of antiviral prodrugs has been significant in the development of drugs to treat viral diseases. Antiviral prodrugs have shown clinical utility for the treatment of viral diseases that include HIV, HBV, HCV, CMV, VZV, EBV, HSV and influenza. They have shown utility in improving bioavailability of a wide range of molecules that include nucleosides, nucleotides, peptide mimetics and small molecules. Even tissue targeting of nucleotide antivirals has been made possible with the use of designed prodrugs. In fact, there has been no therapeutic area where the implementation of prodrug technology has had more of an impact than it has had in the field of antivirals.

References

1. P. Ettmayer, G. L. Amidon, B. Clement and B. Testa, *J. Med. Chem.*, 2004, **47**, 2393–2404.
2. V. J. Stella, *J. Pharm. Sci.*, 2010, **99**, 4755–4765.