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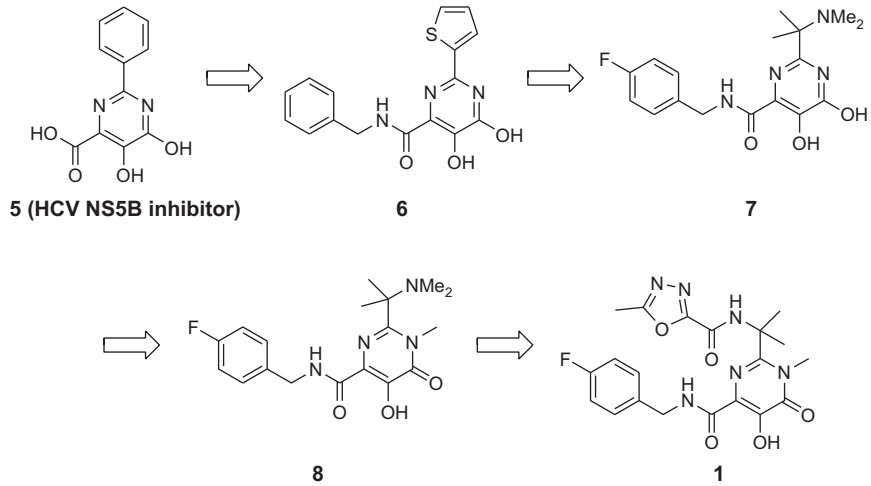

Figure 6.3 Lead progression for the discovery of raltegravir.

potency (85 nM) in an integrase strand transfer assay in return for this very simple modification. Modification of the 2-position of the pyrimidine led to further improvements and substitution of the nitrogen to form the pyrimidinone in moving from **7** to **8** was the last major structural core change of note. Finally, continued optimization around the aminomethyl C2 substituent allowed for the right balance of physicochemical properties while maintaining cell penetration and limiting protein binding effects to deliver exceptional potency. The result was raltegravir (**1**).[39]

Since the approval of RAL, the inclusion of an HIV-1 integrase inhibitor as part of highly active antiretroviral therapy (HAART) regimens has become increasingly attractive.[40,41] Integrase inhibitors have been well tolerated and among the most potent antiretrovirals discovered to date, based on nearly 5 years of post-launch experience with raltegravir, in addition to numerous clinical studies with experimental agents. In addition to exceptional viral load reduction, the class appears to result in a more rapid decrease in RNA copies, although it is still unclear if this results in a meaningful clinical benefit.[42]

Raltegravir had the notable privilege of being a first-in-class agent after several years of relative calm in the development of new antiretroviral drugs. The field was thus primed for an agent with a novel mechanism and the stage was set for a pair of identical pivotal Phase 3 trials, based on geographic regions and with a placebo control in a treatment-experienced population[43,44] that would demonstrate the superiority of raltegravir when added on to optimized background therapy (OBT) with a placebo control in a treatment-experienced population. The combined BENCHMRK 1 and 2 results at 48 and 96 weeks showed clear superiority of a 400 mg twice-daily (bid) dose of raltegravir over OBT alone. In addition to the primary endpoint of the number of patients being below either 400 or 50 copies HIV RNA per mL, a significant increase in $CD4^+$ cell numbers per mm^3 was noted for the raltegravir arms over the

Published on 17 June 2013 on http://pubs.rsc.org | doi:10.1039/9781849737814-00149
on 01/09/2013 10:32:10.