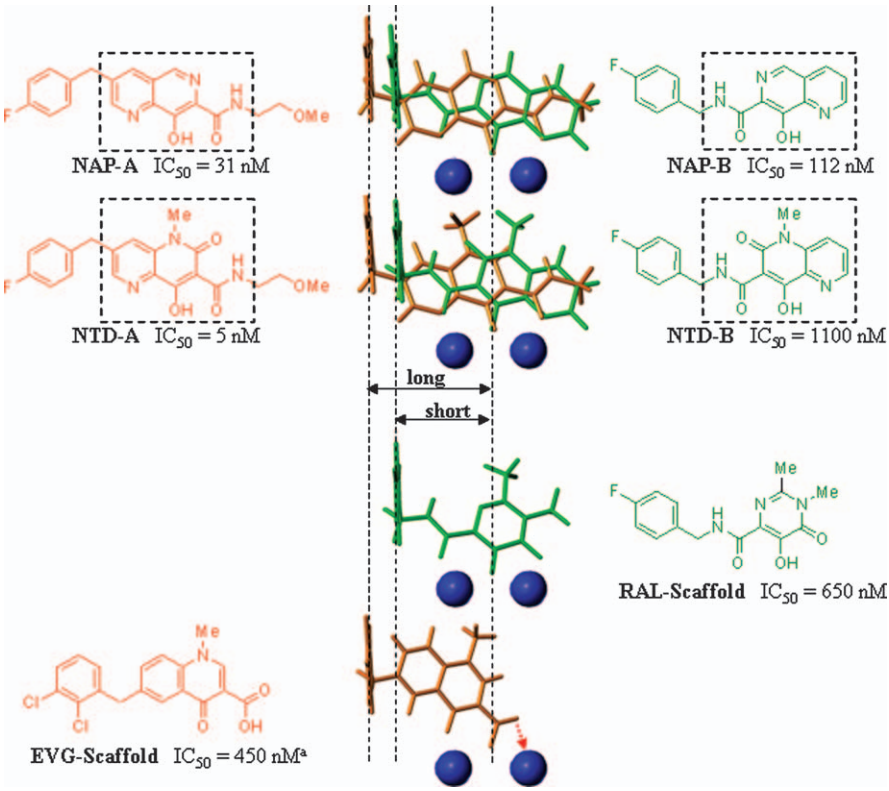

Figure 6.6 Comparison of hydrophobic region B aromatic ring spacing in pharmacophore analysis and design. The basis for increased ring spacing for optimal potency in the design of a next generation inhibitor.
[a]Data from reference 59. Reproduced with permission from reference 90. Copyright (2012) American Chemical Society.

NTD-A further extends the hydrophobic moiety and shows higher potency than NTD-B.

Additional observations with other scaffolds further supported this optimal hydrophobic positioning and, as a result, we adopted this rationale in the course of our molecular design. Interestingly, a simplified RAL scaffold, which has a short benzyl group spacing, has only weak to modest antiviral potency. However, as we saw in the RAL optimization story (referenced in Section 6.2), with additional modifications towards region C, RAL also achieved low nanomolar potency.

In contrast, the EVG scaffold extends a phenyl group similarly to the NAP-A and NTD-A structures. However, metal chelation could not be completed as effectively due to weak bidentate coordination with the carboxylic acid unit. Again, with additional modifications to the quinolone carboxylic acid scaffold, EVG achieved high potency. In recent crystallographic studies of the prototype formy virus (PFV) intasome with some HIV-1 integrase inhibitors reported by