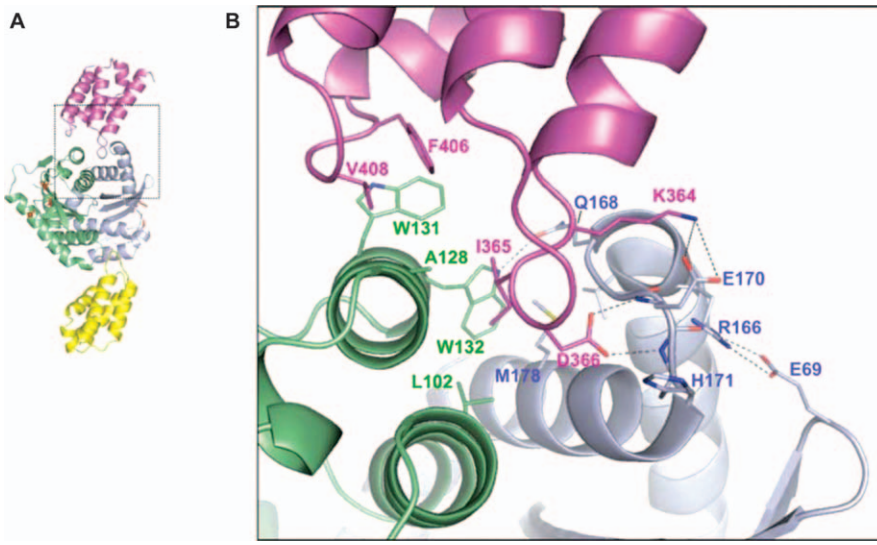

Figure 6.14 Crystal structure of the LEDGF/p75-IN Interaction. (A) Integrase-binding domain of LEDGF/p75 (in magenta and yellow) binding with the integrase CCD (in blue and green). (B) Highlighting key residues of the CCD–IBD interaction: a bidentate hydrogen bond of D366 with IN residues H171/E170 and I365 interacting with a hydrophobic pocket formed by IN residues A128, W132, L102 and M178.
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of 200 000 commercially available compounds that afforded 25 hits for further evaluation. This led to a series of 2-(quinolin-3-yl)acetic acid derivatives that inhibited the IN-LEDGF/p75 interaction *in vitro* and also demonstrated micromolar antiviral activity in HIV-1 infected cells with no appreciable cytotoxicity. Their most potent compound (LEDGIN 6, **39**, Figure 6.15) did not affect integrase–DNA binding, was a very weak strand-transfer inhibitor ($IC_{50} = 19\,\mu M$) and was inactive in 3′ processing ($IC_{50} > 250\,\mu M$). *In vitro* resistance passaging of **39** selected for a single point mutation A128T, which is located at the edge of the LEDGF/p75 binding pocket (Figure 6.14B). The binding mode was unambiguously assigned, with a co-crystal structure of **39** revealing that the compound occupies the LEDGF/p75 pocket located at the CCD dimer interface. Furthermore, **39** demonstrated no significant cross-resistance with reverse transcriptase, entry or integrase-resistant virus strains. Conversely, an IBD-resistant strain of virus (A128T/E170G) was fully resistant to **39** but suffered no loss in susceptibility to the other antiviral agents tested. Although the lack of antiviral potency for these early inhibitors prevented further development, these compounds did offer valuable insight into the potential for this new class of integrase inhibitors.

Independent of the findings reported by Debyser's group, Boehringer Ingelheim published a patent claiming *tert*-butoxy(4-phenylquinolin-3-yl)acetic acid (tBPQA) derivatives as inhibitors of HIV replication.[128] This series was