8.3.2.2 *Discovery of Lomibuvir (VX-222)*

Very little information is available on the progression of *N*,*N*-disubstituted phenylalanine derivatives (*e.g.*, **32**) identified by Shire BioChem several years ago through screening of compound libraries, suggesting that this series was abandoned. Although compounds from this class permitted the identification of a second chemotype with affinity for thumb pocket 2, data reported so far do not suggest that intrinsic potency could be improved significantly and cell-based activity for this class has not been reported.[56]

Shire BioChem was more successful with a second screening hit based on a thiophene-2-carboxylic acid structure. The initial carboxamide hit, **39** (Figure 8.10), showed only modest potency in the polymerase assay ($IC_{50} = 14\,\mu M$), but preliminary SAR studies rapidly revealed that the corresponding carboxylic acid was three times more potent and provided weak cell-based activity in the replicon ($EC_{50} = 14\,\mu M$) with modest selectivity (selectivity index, $SI = 5.7$). Further exploration of this series provided analogs with submicromolar enzymatic activity (*e.g.*, **40**) and confirmed efficacy in cell-based assays where analogs with $SI \approx 12$ were identified.[57] With these encouraging preliminary results in hand, the team's focus was directed towards further improving potency in both biochemical and cellular assays. Removal of H-bond donors by methylation often has a positive impact on cell permeation and cell-based potency. Unfortunately, in this case, *N*-methylation of the sulfonamide NH had a negative impact on intrinsic potency and did not improve replicon potency. A key discovery for the program was made when the sulfonamide linkage was replaced by a tertiary amide moiety, producing the first analogs with

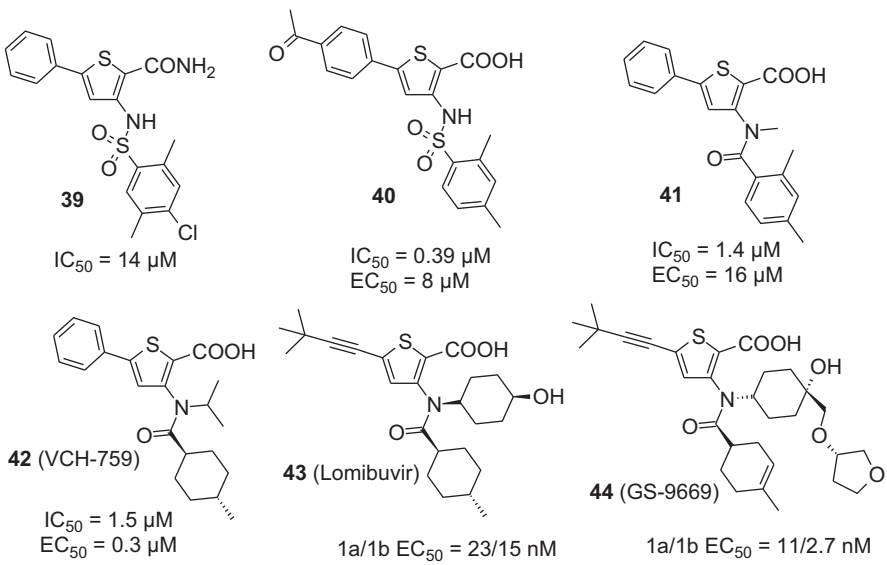

Figure 8.10 Evolution of thiophene-2-carboxylic acid thumb pocket 2 inhibitors and discovery of lomibuvir (VX-222) and GS-9669.