viroporin-targeted drugs. However, the fact that resistant variants are selected at all suggests that even prototype inhibitors exert a selective pressure on the virus, meaning that druggable sites almost certainly exist on viroporin molecules. As such, prototype inhibitors serve to highlight regions on viroporin molecules suitable for further exploration through targeted drug discovery or which may select high-affinity ligands through library screens. This view is supported by the reported nanomolar potency of the BIT225 molecule {*N*-[5-(1-methyl-1*H*-pyrazol-4-yl)-naphthalene-2-carbonyl]guanidine, Biotron, Australia; see Table 9.2} in certain systems, which was selected through a limited screening programme in bacteria. Although this molecule shares some traits of prototypes with reported activity against both p7 and Vpu, it appears more potent in cell culture models for HIV-1[86] and a pestivirus model for HCV,[87] although its binding mode and ability to select resistance are not yet apparent. Results of both HIV-1 and HCV clinical trials are currently pending. As more information is obtained on viroporin biochemistry and atomic structures, there is every chance that novel molecules will be generated that show significant improvements over existing prototypes, suitable for drug development and incorporation into modern antiviral regimens.

9.1.5 Non-ion Channel Functions of Viroporins: Confounding Factors in the Study of Virus-coded Ion Channels

The variability and small coding capacity of many viruses require that their limited number of gene products be capable of functional redundancy. As such, it is not surprising that many viroporins display additional roles during the virus life cycle that are separate to ion channel activity. In addition, their small size often means that overlapping regions and residues can be involved in both aspects, leading to great difficulty in the interpretation of mutagenesis studies and in ascribing phenotypes to either the lack of channel activity or other interactions. In addition, viroporins produced following the cleavage of polyprotein precursors (*e.g.* picornavirus 2B, HCV p7) add a further layer of complexity as mutations can affect the production or topology of the protein. As such, although this chapter does not discuss these additional aspects of viroporin function in great detail, it is pertinent always to consider that phenotypes reported for particular mutations may well result from an indirect effect on viroporin activity or indeed not apply to channel function in any regard.

9.2 Viroporins Encoded by Pathogenic Human RNA Viruses with Known Small-molecule Inhibitors

9.2.1 Influenza A Virus M2: Clinical Precedent and Prototype Viroporin

Influenza A virus represents one of the most prevalent human viral infections. Although ‘seasonal’ influenza epidemics cause around 500 000 deaths each year