result, virtually all viroporin inhibitors described to date originate from three chemical classes, namely adamantanes, amilorides and alkylated imino sugars. Adamantanes were, of course, identified for influenza A viruses,[5] imino sugars were explored as HIV-1 therapeutics targeting glycosylation[73] and amiloride is a well-known inhibitor of the epithelial Na^+ channel, commonly used as a diuretic in hypertensive patients.[74] Table 9.2 shows a list of prototype viroporin inhibitors, their targets and resistance polymorphisms where known. The majority of prototypic viroporin inhibitor studies merely applied one or more variants of such molecules with little or no idea regarding modes of action. Surprisingly, this small repertoire of molecules appears promiscuous in its ability to block channels from multiple unrelated viruses, including examples from all three classes of viroporins to a greater or lesser extent. However, with the exception of some adamantane variants which are effective at low micromolar concentrations against certain influenza strains,[75–77] the majority of prototype viroporin inhibitors are only effective at concentrations of tens to hundreds of micromoles. Further studies have generally involved the derivatisation and modification of prototype scaffolds rather than rational design or screening, even where atomic structures are available.

At first glance, the wide-ranging effects of individual prototype inhibitors may seem appealing for drug discovery, indicative that 'magic bullet' compounds might be possible to generate targeting multiple viroporins. However, derivatives rarely improve on the relatively low potency of prototypes to any great extent, indicating that the molecular fit and binding of such molecules within prospective binding pockets may be inefficient. Even for M2, where atomic structures exist, the structure–activity relationships (SARs) for the multiple adamantane derivatives generated to date are not clear. Indeed, there is even controversy surrounding the binding modes of amantadine and rimantadine themselves as a result of conflicting structural studies where either lumenal[78,79] or peripheral binding sites[80] were proposed. Such ambiguity is likely a result of adamantane structures comprising small hydrophobic cages capable of fitting within multiple protein cavities, where their amine extensions H-bond with nearby residues. This, in turn, is probably also responsible for the promiscuity of these molecules and their relatively low potency; although capable of binding to multiple sites, they probably do not do so with the same affinity as would a theoretical molecule designed to fill the entire cavity and make multiple stabilising contacts with the protein. This view is supported by the enhanced potency of certain adamantane derivatives with bulky R groups, which can also inhibit some amantadine-resistant M2[81,82] and p7 channels.[63] Given the relatively similar potency and promiscuity of prototypic imino sugars and amilorides, the same scenario is likely to apply.

The non-targeted nature of the current prototype viroporin inhibitor repertoire is also reflected by their clinical efficacy. On the one hand, adamantanes serve as a clinical precedent for viroporins as drug targets, yet their limited clinical benefits and the rapid selection of resistant polymorphisms with seemingly little or no fitness cost to the virus, whether it be influenza A[83] or HCV,[84,85] has generated significant scepticism regarding the potential of