potentially with chemotypes unrelated to prototypes. In this respect, liposome assays based on fluorescent dye release,[61] or indeed those based on proton flux, as described for conductance domain peptides,[127] may be highly productive.



#### 9.2.1.5 *Influenza B and C Proton Channels*

Due to their lesser clinical importance, the proton channels of influenza B and C are less well characterised compared with AM2. The 100 amino acid NB protein of influenza B was first shown to display cation channel activity in bilayer systems, which could be inhibited by high concentrations of amantadine.[159] Like AM2, NB is a minor virion component[160] and was proposed to play the equivalent role during the life cycle. However, it is now generally accepted that the BM2 protein of influenza B is in fact the functional homologue of AM2.[43,161] BM2 has been shown to critical for virus replication and to display proton channel activity in membranes which is insensitive to amantadine. A composite solution NMR structure of this channel was reported combining the cytosolic (PDB: 2KJ1) and the TM (PDB: 2KIX) regions.[162] BM2 gating is regulated by the His19 and Trp23, equivalents of AM2 His37 and Trp41.[163–165] As described above, the amantadine-insensitive activity of BM2 has been exploited in the creation of A/BM2 chimeras during investigations of drug binding sites.[142,145] For influenza C viruses, the CM2 protein[166] is produced by an internal cleavage event from an M1–2 precursor[167,168] and has also been directly demonstrated to display channel activity,[169] to alter vesicular pH[42,170] and to promote uncoating during the entry process.[171] To date, no small-molecule inhibitors of B/CM2 or NB activity have been described, although the availability of BM2 structural information could expedite future rational development.

### 9.2.2 Human Immunodeficiency Virus Type 1 (HIV-1) Vpu

The HIV-1 pandemic has been the major driver of antiviral drug discovery in past decades and around half of all currently licensed antivirals are targeted towards this virus. As a result, highly active antiretroviral therapy (HAART) successfully prolongs the life of the majority of HIV-1 patients in the developed world and is slowly being extended to developing countries, although availability is still greatly short of demand. However, despite extensive permutations available for drug combinations, virus resistance continues to arise in response to such intense selective pressure. Even when on effective treatment, many patients exhibit low level viraemia as a result of virus shedding from infected macrophages and other long-lived infected cells such as memory T lymphocytes. Life-long HAART will therefore require many more drug combinations to continue to be available, unless a strategy can be found to target viraemia derived from virus reservoirs.

HIV-1 and related simian viruses (chimpanzee lineage) encode the Vpu accessory protein.[172,173] This small, multifunctional protein is not a virion