which would likely make stabilising hydrophobic contacts with adamantyl cages if drugs bound to the periphery. Conversely, conductance domain solution structures in detergent micelles display narrowed lumenal apertures, which would therefore disfavour drug binding at this site.[149] The conductance domain structure from bilayers (2LOJ) does not suffer greatly from either of these issues and likely represents the most physiologically relevant system in which to study drug interactions,[72] although, unfortunately, a drug-bound version of this structure has not yet been determined.

Another consideration is the format in which adamantane–drug interactions are studied. Several divergent studies point to the weaker allosteric binding occurring only following drug partitioning within the bilayer,[79] yet systems such as SPR[146] and patch clamping of oocyte membranes[142] transiently introduce compounds at relatively (with respect to the number of channels present in the membrane) high concentrations in the aqueous phase, likely favouring rapidly measurable lumenal interactions. By contrast, notwithstanding differences between peptides, structural studies are usually performed at roughly equimolar ratios of drug and protein, possibly favouring lumenal interactions due to less membrane partitioning. The exception to this is the allosteric rimantadine-bound solution structure (2RLF), where an $\sim$50:1 drug:protein molar ratio was used, potentially favouring saturation within the micelle and resultant peripheral binding.[80] In patients, adamantane concentrations within the plasma rarely exceed 2–3 μM,[150,151] yet it is not clear either how these drugs partition within aqueous and membranous compartments in the body or how they arrive at the respiratory epithelium to exert their antiviral effects.

Perhaps the greatest obstacle to resolving these issues is the characteristic properties of amantadine and rimantadine themselves. Neither molecule was specifically selected to target M2, as reflected by their potency in cell culture. Their small size and amphiphilic properties lend themselves to promiscuous, yet relatively inefficient, binding within both solvent and membrane-exposed cavities. They therefore act as poor structure probes as their selectivity to a particular binding site is difficult to determine; it should be remembered that *in silico* docking and/or molecular dynamic simulations of drug–protein interactions in a membrane environment are technically challenging and are often not comparable to those in solution. However, while the controversy over the potential binding of prototype adamantanes to M2 may continue, it does serve to illustrate that two regions on the M2 channel complex are potentially amenable to targeted drug design.

9.2.1.4 *Improving on Amantadine: the Search for Modern Influenza Drugs and Their Potential as New Therapies*

Efforts to improve upon the amantadine and rimantadine M2 inhibitors have primarily concerned the derivatisation of these prototype molecules, adding one or more R groups of varying size and molecular composition. Although this has defined several potent series of compounds that principally act against