amantadine-sensitive strains,[75–77,81,152–155] some examples of inhibitors that act against resistant M2 variants also exist.[82] However, the search for potent compounds targeting the most clinically-relevant S31N channels continues.

One example of an M2 compound screen that successfully generated a hit against M2 has been published. The screen was conducted in yeast and was based on the growth-inhibitory effects of M2 expression, which was restored by amantadine.[156] The compound, BL-1743 {2-(3-azaspiro[5,5]undecano)-2-imidazoline} (Figure 9.2), caused reversible inhibition of A/Udorn 72 M2 in oocytes over a similar micromolar range to amantadine, compared with the irreversible action of the adamantane. In addition, whereas several amantadine-resistant mutations (V27S, A30T, S31N, G34E) also prevented the action of BL-1743, another, L38F, did not. Furthermore, BL-1743 selected a unique resistant variant, I35T, which, in turn, did not affect amantadine sensitivity.[157]

Hence BL-1743 potentially shares a distinct, but overlapping, M2 binding mode with adamantanes and this has prompted research into other spiranamines and/or spiropiperidines as M2-selective molecules. This has generated numerous compounds with improved antiviral potency relative to rimantadine or amantadine. A similar story holds true for derivatised adamantanes with improved antiviral potency, although both classes of compound have yet to yield variants with sub-micromolar IC_{50} values.[75,76,81,82,154,155,158] Examples of spiranamines and/or spiropiperidines have shown some activity ($IC_{50} \approx 30–80\,\mu M$) against some adamantane-resistant channels (V27A, L26F mutants, H3N2 background).[82] Other adamantane derivatives also exist with extremely limited activity against S31N channels, reducing channel activity by 22% at a high drug concentration of 100 μM, $IC_{50} \approx 250\,\mu M$;[81] however, this was less effective than high concentrations of amantadine, which reduced S31N activity by 35.6% at 100 μM with an IC_{50} of $\sim 200\,\mu M$. Recently, these two families of M2 inhibitors have been combined following molecular dynamics simulations of drug binding to the refined ssNMR TM domain structure (2KQT), to identify spiroadamantane as a compound capable of inhibiting not only Ser31-containing H3N2 M2, but also V27A- and L26F-resistant variants at low micromolar concentrations.[82] However, no activity was seen for this molecule when tested against H3N2 M2 with the S31N mutation.

This last example illustrates a shift in the field from a focus on compound-centred derivatisation towards the employment of the available atomic structures in rational programmes for the identification of novel M2-targeted compounds. This will begin to identify more potent molecules with clear site preferences and the establishment of SARs should enable clarification over the binding modes for each compound. However, as discussed above, the choice of the atomic structures employed as a template may influence outcomes with regard to which region of the channel is targeted. Ideally, templates should incorporate resistance mutations as starting points in drug discovery programmes. In parallel, screening of M2 peptide channel activity could be a means by which to identify novel inhibitors with improved characteristics,