that have been discovered to interact with the fusion protein and the breadth of the structural chemotypes, it is very possible that multiple different binding modes and interaction points can occur with the fusion protein.

Beyond the biochemical and structural challenges, there is the common challenge of resistance development. Literature reports on the more common fusion inhibitors have identified that resistance to inhibitors can develop rapidly *in vitro* and just single mutations in the fusion protein can effectively abolish antiviral activity.[14] Despite wide differences in the structure of small-molecule inhibitors, the resistance mutations occur in the same region and cross-resistance between fusion inhibitors is common. Given that fusion inhibitors have not progressed clinically, it is not possible to determine whether the *in vitro* results will translate into the clinical setting, especially in the light of the short treatment duration in an infected individual.

Stepping beyond resistance development for a fusion inhibitor, there is also the need for inhibitors to possess broad activity across both subtypes of RSV and the various different strains within those subtypes as discussed above.

Another common preclinical challenge is the availability of relevant animal models to study the effectiveness of RSV inhibitors *in vivo*. The two most common *in vivo* models are the cotton rat model of infection and the BALB/c mouse.[15–17] These models, however, are not ideal since neither represents clinical disease in humans and, as such, the models are of limited use. Other potential animal models include sheep and calves.[15,18–24] In the latter, bovine RSV is a common ailment of calves and livestock during the winter months. The course of infection in calves is very similar to that of infant disease and, therefore, represents a potential model in late-stage optimization of compounds. To date, no small molecules have been reported in the calf model of RSV infection.

A significant challenge for RSV inhibitors, in general, not just limited to fusion inhibitors, is the ability to deliver the drugs to patients effectively. Given the diverse nature of the patient populations, from small infants to the frail elderly, consideration has to be given to the different formulation challenges. In the elderly, it is likely that oral tablets, syrups or even inhaled options for drug delivery could be utilized, whereas infants present a more significant challenge for drug formulation. Pulmonary delivery of a drug *via* inhalation is an attractive option for infants since this directly targets the organ of interest and limits systemic levels of the drug, increasing safety. However, inhaled delivery in infants is challenging since they cannot interact with the device as adults can. Additional complications include the shallow breathing of sick infants that could be inadequate to trigger delivery devices. One solution that is exemplified by viramidine, a prodrug of ribavirin (**1**), involves placing the infant inside a tent-like enclosure and then aerosolizing drug into the atmosphere. This is less than ideal and certainly not practical for a caregiver in the outpatient setting. Therefore, the challenge for infants is to develop safe and, preferably, orally bioavailable drugs that can be administered to even very young neonates. A liquid form or elixir would be ideal; however, the amount of additives needs to be minimal, since the acceptable options for very young infants are limited. Taste is also a critical aspect of drugs for infants when given orally. Other