levels (**5**). A structure-guided approach using modeling and an X-ray structure of the fusion protein guided medicinal chemistry efforts to build back potency. The morpholinopropylene side chain that modulated lung tissue distribution was retained and the benzimidazole core was further elaborated with a substituted aryl group which bound in a sub-pocket and ultimately afforded picomolar fusion inhibitors with the lead compound being TMC-353121 (**6**).[52]

Detailed efficacy studies of TMC-353121 (**6**) in cotton rats and BALB/c mice were published (see Table 2.2).[53] In line with the fusion mechanism and the half-life of the compounds, efficacy in the cotton rat correlated with drug exposure in a relatively short time window after inoculation. Efficacy was observed when dosed i.v. ($10\,mg\,kg^{-1}$, range from -96 to $+24$ h), p.o. ($10–40\,mg\,kg^{-1}$, -2 h) and inhaled ($0.25–5\,mg\,mL^{-1}$, -1 h), with the best efficacy achieved by the inhalation route. A caveat to inhalation delivery is that the inoculum, which is administered intranasally, will be exposed to some extent to the fusion inhibitor and may block establishment of the infection. The maximum viral load (TaqMan, lung) was $5.67\log_{10}$ and the observed maximum viral load drop in the bronchoalveolar lavage fluid (BALF) was $1.5\log_{10}$. These rather modest numbers and the significant variability reported by Olszewska *et al.*[53] reflect the well-known limitations of the cotton rat model. Interestingly, in the BALB/c mouse, significant efficacy was observed in a therapeutic regimen ($+2$ days and $+4$ days, $10\,mg\,kg^{-1}$, viral load drop $1.0\log_{10}$), including minimal lung inflammation compared with controls. The pharmacokinetics of TMC-353121 (**6**) in BALB/c mice ($2.5\,mg\,kg^{-1}$) reported suggests very low drug levels in plasma after 2 days, although in the lung much higher exposure was observed; however, no data were reported on drug exposure after 2 days in the $10\,mg\,kg^{-1}$ arm.[53] Limited data on further progress into the clinic such as pharmacokinetic (PK) studies in higher animals were published. The development status of TMC-353121 as of 2011 was reported by Bonfanti *et al.*[52] to be undergoing further evaluation.

A recent series of patent publications described the evolution of the SAR around TMC-353121 (**6**) and disclosed an interesting hybrid between **6** and the Bristol-Meyers Squibb (BMS) lead compound **10** described below. The morpholine side chain responsible for the long lung tissue retention times can be deleted without compromising potency (see **7**, Scheme 2.3). Further potency can be built in by retaining the C2 imidazole nitrogen substitution in **8**. A polar and highly charged phosphonic acid can be introduced on the benzimidazole aminomethyl moiety, as shown in **9**. Furthermore, the right-hand benzimidazol-2-one moiety of the BMS lead compound BMS-433771 (**10**) was built into the TMC leads **6** and **8**, affording potent compounds.[48,54]

2.5.2 BMS-433771

A high-throughput screening (HTS) campaign at BMS using a cellular assay with a CPE readout afforded several hits, with a benzimidazole (see **13**, Scheme 2.4) originally designed as an analgesic and antiarrhythmic being the most attractive one.[55] Structurally, the BMS leads differ significantly from the