benzimidazoles pursued by J&J, but shows some similarities with the well-known RSV fusion inhibitor BABIM.[19] The initial lead, which has an excellent potency, an EC_{50} of 220 nM, a high CC_{50} of 83 μM and no cross-reactivity against Sendai, parainfluenza, vesicular stomatitis viruses, HIV and HSV, was advanced into a rigorous medicinal chemistry campaign with the goal of identifying an orally bioavailable inhibitor. Initial SAR exploration focused on the benzimidazole substitution while keeping the parent methylenebenzotriazole unchanged. A wide range of functionalities, including lipophilic, anionic, cationic and uncharged polar groups, were tolerated provided that an ethylene spacer between the core was present. The most potent substitution, *N*-isoamyl (**14**), was moved forward into a second round of optimization interrogating the benzotriazole moiety. In part due to synthetic accessibility, but with the key advantage of having an additional vector for functionalization, the triazole was replaced with a benzimidazol-2-one. In this second round of optimization, potency was further improved from double-digit to single-digit nanomolar EC_{50}. Reoptimization of the benzimidazole *N*-substitution revealed a series of low single-digit nanomolar compounds (**15**). This set of compounds was studied in both the cotton rat and the BALB/c mouse model and, despite exploring multiple routes of delivery (p.o., i.p., s.c.), no efficacy was observed. Proof of concept in an animal model was deemed critical at this point. This was achieved by delivering the compound *via* small-particle aerosol (SPA) delivery in collaboration with Baylor College (Houston, TX). SPA delivery requires highly water-soluble compounds (10 mg mL^{-1}) and the lead molecules were probed for tolerance of polar groups. The benzimidazol-2-one *N*-position was elaborated with a benzyl moiety, which tolerated a wide variety of polar charged functionalities and delivered animal proof of concept with **16** (log_{10} viral load reduction: 2 at 2 mg mL^{-1} concentration in the aerosol).[56] This set the stage for further medicinal chemistry optimization to improve potency and *in vivo* exposure following p.o. delivery. Following SAR for potency, human liver microsome stability and Caco-2 permeability, several key structural changes were introduced, including replacing the isoamyl group with *n*-butanol, installing a nitrogen atom in the benzimidazol-2-one ring and installing a cyclopropyl group as the *N*-substituent, affording the clinical candidate BMS-433771 (**10**). PK (i.v., p.o.) in mouse, rat, dog and monkey was disclosed and the compound showed good absorption, with high to intermediate clearance. Allometric scaling predicted a human half-life of 8 h and, with an estimated 50% oral bioavailability, a human dose of 500 mg was predicted. A scalable and efficient synthesis of **10** was developed to support clinical and preclinical material supply.[55]

Interestingly, resistant mutations induced by **10** map to K394R, which is identical with what was found for TMC-353121 (**6**). Elegant MOA studies using a radiolabeled photoaffinity probe (see **17**, Scheme 2.4,), tagged Y198, which is located in the N-terminal heptad repeat adjacent to the fusion peptide. Y198 lines a hydrophobic pocket inside the deep groove of the HR-N57 heptad repeat trimer. Modeling studies of the BMS series of fusion inhibitors suggested binding in this pocket and was in line with the SAR seen on the right-hand