benzimidazole moiety. Modeling proposed that C5 (see **18a–d**, Scheme 2.4) can be further elaborated, possibly forming productive H-bonds with Asp200. Installation of a benzylamine or benzyl alcohol (**18c** and **d**) indeed afforded potent compounds whereas a carboxylate or an aniline were much less active (**18a** and **b**). This SAR is, as mentioned above, reminiscent of pharmacophore of BABIM (**19**), a known RSV fusion inhibitor, and furthermore reflected in the recent AstraZenca series (**20**–**23**).

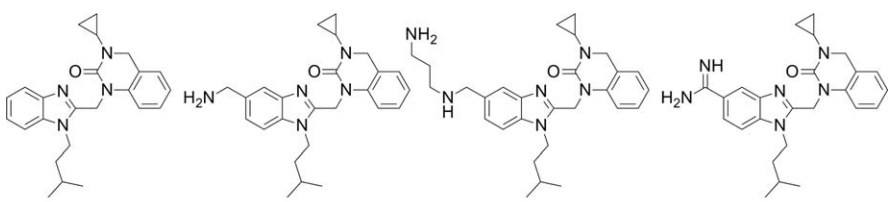
In vivo studies with **10** were performed in the cotton rat and the BALB/c mouse model. Oral dosing approaching 50 mg kg^{-1} at –1 h with intra-tracheal inoculation showed maximum efficacy (>1.0log$_{10}$ viral load drop) in the cotton rat model. In the BALB/c mouse model, prophylactic dosing as low as 5 mg kg^{-1} was efficacious.[16] Toxicity studies in three animal species were performed, enabling human clinical studies. However, BMS reported that clinical studies were not pursued owing to a change in corporate business strategy.[55]

2.5.3 AstraZeneca WO 2010/103306

AstraZeneca recently disclosed a series of quinazolinones that have striking similarity to the BMS series (see **20–23**, Scheme 2.5).[57] Compounds with high picomolar potency were disclosed, and also extensive, small-molecule X-ray and differential scanning calorimetry (DSC) data for a series of compounds. Interestingly, the installation of a basic moiety on the benzimidazole at the C5 position afforded significant potency and structurally mimics the BMS series of compounds (**18a–f**) and also the BABIM-type RSV fusion inhibitor. Improved solubility of this compound with this basic functionality was claimed. No further data regarding development status are available.

2.5.4 BTA9881

Biota claimed novel RSV fusion inhibitors in a series of patent applications, with potency in the double-digit nanomolar range (see **24**, Scheme 2.6).[58–61] The compound progressed to a Phase 1 clinical study and demonstrated good oral bioavailability and half-life. The compound was subsequently



Scheme 2.5 Selected compounds for AstraZeneca WO 2010/103306.