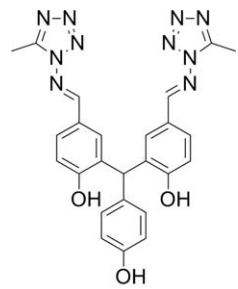
2.5.6 VP-14637, MDT-637

VP-14637 (see **26**, Scheme 2.8) was discovered in an HTS campaign at Viropharma. A small impurity in a reagent formed the active component, which was traced down and ultimately afforded **26**. SAR data disclosed so far point to a very sharp loss of antiviral activity when the tetrazole moieties are replaced by diazoles (–30× potency) or triazoles (–50× potency). Also, the hydroxy groups adjacent to the tetrazoles are key for potency (–10,000× potency with OMe), whereas the central hydroxy group has little effect. The potency range of VP-14637 was reported for clinical isolates from Europe and North America to be 0.1–80 nM (EC_{50}). MOA studies suggested an early time point in the viral life cycle and resistant mutations mapped to the F-protein.[66] Good efficacy (–1.3 to 2.8log_{10} reduction in viral titer) was observed in the cotton rat model.[67] In April 2010, Gilead Sciences and MicroDose Therapeutx announced that the companies had entered into an exclusive worldwide license and collaboration agreement for the development and commercialization of **26** using the MicroDose dry powder inhaler technology. Phase 1 studies were concluded in 2012 with high intratracheal levels and low systemic exposure (press release from MicroDose Therapeutx, 24 April 2012).

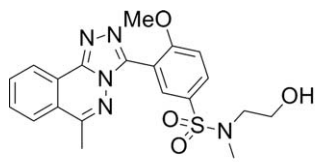
2.5.7 University of Gothenburg, Sweden

Trybala and co-workers recently identified, from screening a commercial library of small molecules (ChemBioNet), two RSV inhibitors with the structures shown in Scheme 2.9.[68] MOA studies (time of addition, resistant

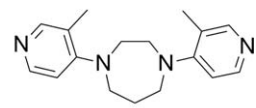


Compound **26**

Scheme 2.8 Viropharma (VP-14637)/MicroDose inhibitor (MDT-637).



Compound **27**, P13



Compound **28**, C15

Scheme 2.9 University of Gothenburg fusion inhibitors P13 and C15.