

JC virus replication in human fetal brain SVG cells with an EC_{50} value of $0.045 \mu\text{M}$. Moreover, intracellular viral DNA levels were reduced by 60%, consistent with the proposed mechanism of action.⁹⁵ Furthermore, CMX001 was active against JC virus in progenitor-derived astrocytes and in COS-7 cells. The EC_{50} value was 5.55 nM and the CC_{50} value was 184.6 nM .⁹⁶

CMX001 was used in a recent case of a patient with progressive multifocal leukoencephalopathy and idiopathic $CD4+$ lymphocytopenia caused by JC virus.⁹⁷ At admission, the patient had extremely low $CD4+$ lymphocyte counts and presented with slurred speech and partial paralysis. An MRI revealed multiple white matter lesions throughout the brain, consistent with a demyelinating process that was confirmed by brain biopsy, establishing progressive multifocal leukoencephalopathy as the diagnosis. *In situ* hybridization for JC viral genome sequences was positive and the JC viral load was reported as $3600 \text{ copies mL}^{-1}$. Intravenous CDV was administered for 2 weeks followed by oral administration of CMX001. In addition, the patient received antibiotic therapy (mefloquine) to prevent opportunistic infection and an experimental interleukin-7 to boost $CD4+$ cell counts. Administration of CMX001 correlated with reduced JC virus DNA in the blood and clinical improvement.⁹⁷

CMX001 shows promise as an antiviral compound for the treatment of DNA virus infections. The antiviral activity in humans against several viral pathogens provides a path to establish effective dosing strategies that can be extrapolated to infections with OPVs. The broad-spectrum activity and high genetic barrier to resistance provide impetus for continued development of CMX001 for treatment of OPV infections.

4.4.3 ST-246

ST-246 is a tricyclononene carboxamide identified by high-throughput screening of a chemical compound library for inhibitors of OPV replication (Figure 4.4).⁵¹ Over 350 000 compounds were screened for their ability to inhibit vaccinia virus-induced CPE. A total of 759 compounds were identified that inhibited vaccinia virus-induced CPE by $>50\%$ and could be grouped into nine distinct chemical series.

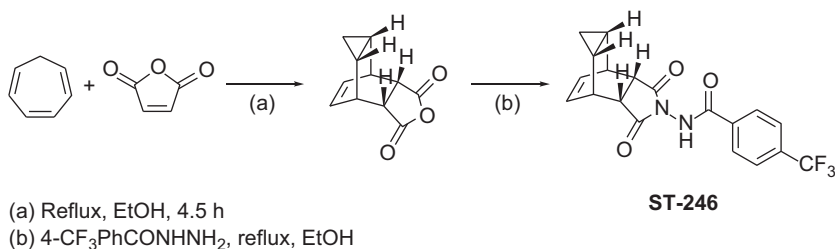


Figure 4.4 Synthesis of ST-246. Chemical synthesis adapted from Bailey *et al.*⁹⁸