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Abstract

Variola virus, the causative agent of smallpox, is a potential bioweapon. The development of new antiviral compounds for smallpox prophylaxis and treatment is critical, especially because the virus can acquire resistance to the drugs that are currently available. We have identified novel small chemical inhibitors that target DNA synthesis of vaccinia, the prototypical poxvirus. Robotic high-throughput screening of 49663 compounds and follow-up studies identified very potent inhibitors of vaccinia DNA synthesis, with IC₅₀ values as low as 0.5 μM. Cell-based assays showed that 16 inhibitors effectively blocked vaccinia infection with minimal cytotoxicity. Three inhibitors had selectivity indexes that approximate that of cidofovir. These new non-nucleoside inhibitors are expected to interfere with components of the vaccinia DNA synthesis apparatus that are distinct from cidofovir. On the basis of the high sequence similarity between the proteins of vaccinia and variola viruses, these new inhibitors are anticipated to be equally effective against smallpox.