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New inhibitors against Herpes viruses

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Tridimensional protein modeling and virtual drug screening were performed to identify new inhibitors of Herpes virus DNA polymerase, a key enzyme in the viral replication cycle. Twelve potential inhibitors were identified, purchased and evaluated by plaque assays. Two compounds (Nos 2 and 9) were particularly active against HSV-1, HSV-2 and varicella-zoster virus (VZV) and one compound (No 3) inhibited more specifically human Cytomegalovirus (HCMV). These compounds exhibited activity against wild-type viruses and strains resistant to current antiviral agents, i.e. nucleoside and pyrophosphate analogues, with IC_{50} values between 3 and 10 μM. Furthermore, compounds 2 and 3 had good cellular permeability and metabolic stability as determined by parallel artificial membrane permeability assay (PAMPA) and microsomal stability assay, respectively. Derivatives of these compounds were also synthesized to evaluate their activity against representative strains of HSV-1, HSV-2, VZV and HCMV as well as their toxicity on different cell lines. One fluoro derivative of compound 2 (No 20) retained excellent activity against HSV-1, HSV-2 and VZV with a therapeutic index near 10 in Vero cells. In conclusion, we discovered a new class of non-nucleosidic Herpes virus inhibitors with *in vitro* activity against drug-resistant clinical isolates that warrant further pre-clinical studies.

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