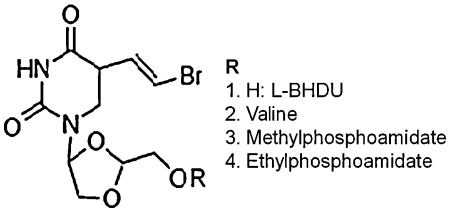

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Evaluation of Approved Antivirals for Inhibition of Xenotropic Murine Leukemia-Related Virus (XMRV) in Cell-Based Assays

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Xenotropic murine leukemia-related virus (XMRV), a retrovirus discovered in 2006, has been controversially associated with human prostate cancer and chronic fatigue syndrome (CFS). XMRV nucleic acid or proteins are found in 27% of prostate cancers and in 68% of chronic fatigue syndrome patients, and in less than 4–6% of normal controls, suggesting an association between the virus and human disease. To date there is no effective treatment for CFS. Twenty-eight drugs approved for use in humans were evaluated against XMRV replication in vitro. Drugs used to treat HIV-1 infection, as well as compounds used to treat other virus infections, were evaluated. Published literature indicates little similarity between HIV-1 and XMRV proteins: 28% homology at the amino acid level of protease, 17% homology with RT, and 14% homology with integrase; making it difficult to predict which anti-HIV agents may be effective against XMRV. Several drugs from each major class of antiretroviral agents: nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTI, NtRTI and NNRTI), integrase inhibitors (II), and protease inhibitors (PI). An in vitro assay utilizing PG-4 cells infected with XMRV collected from 22Rv1 human prostate cancer cells was developed to measure inhibition of virus replication. Efficacy and toxicity data for the approved antiviral agents will be reported, as well as evaluation of combined antiviral agents in the anti-XMRV assay.

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The Design and Synthesis of Pyrolle-Carbaldehydes as HIV-1 Integrase Strand-Transfer Inhibitors

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In silico screening of commercial databases through an optimised integrase structure identified a pyrolle-carbaldehyde with high docking scores. Virtual derivatisation of the core structure was undertaken to optimise favourable interactions and ~100 analogues were synthesised through a facile one-pot reaction. Biological evaluation of the water-soluble HCl-salt derivatives identified a number of compounds that actively inhibited the strand-transfer step as determined through direct enzymatic assays. In particular, 10 orally bioavailable compounds proved active against HIV-1 integrase in the low micromolar range (IC_{50}'s <10 μM). Here, we investigate the binding mode of these compounds within the active site of the integrase model, discuss the cytotoxicity, solubility and inhibitory activity of select compounds and establish a preliminary structure–activity-relationship.

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Identification and Characterization of Azolo-1,3-benzoxazines and Condensed Benzopyrans as Potent Non-nucleoside Inhibitors of Orthopoxviruses

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The potential use of variola virus as a biological weapon has renewed efforts in the development of antiviral agents against orthopoxviruses. Additionally, there is a growing threat from zoonotic poxvirus outbreaks, particularly monkeypox, cowpox, and vaccinia, all close relatives of variola. There are still no proven effective drugs for the treatment of severe orthopoxvirus infection. Thus, further development of new antiviral agents for the control of orthopoxviruse infections is urgently needed. During our investigation we have synthesized series of azolo-annelated 1,3-benzoxazines and condensed benzopyrans. Among compounds having activity against vaccinia poxvirus (Variola vaccinia) it is necessary to note small molecular weight fused heterocycles such as 12H-benzimidazo[2,1-b][1,3]benzoxazines, 2,3-diphenyl-5H-imidazo[2,1-b][1,3]benzoxazines and 1,5-dihydro-2H-chromeno[2,3-d]pyrimidin-2,4(3H)-diones. While a majority of these compounds moderately inhibited vaccinia virus, the 12-methyl-2-nitro- and 2-(1-adamanthyl)-12H-benzimidazo[2,1-b][1,3]benzoxazines exhibited the most potent anti-orthopoxvirus activity with an IC_{50} of 0.008 mM and 0.012 mM, respectively. A novel cascade Michael addition–intramolecular nucleophilic cyclization approach based on o-quinone methide generation as intermediates has been used for construction of these compounds.

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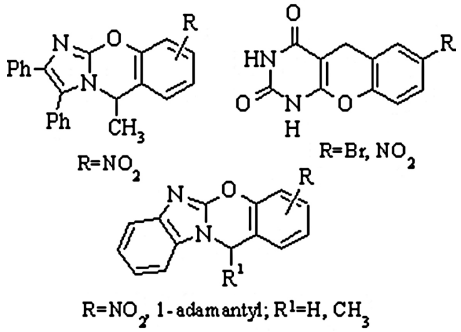

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