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NEW 1,1,3-TRIOXO-2*H*,4*H*-THIENO[3,4-*e*][1,2,4]THIADIAZINE DERIVATIVES ARE POTENT AND HIGHLY SELECTIVE HIV-1 INHIBITORS TARGETED AT THE REVERSE TRANSCRIPTASE

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Here we report on the development of a new group of non-nucleoside reverse transcriptase inhibitors (NNRTIs). One of the most active congeners of a series of 1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine derivatives (i.e. EA-521 or 2-benzyl-4-cyanomethylen-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine) was found to inhibit human immunodeficiency virus type 1 {HIV-1(III_B)] replication in MT-4 cells at a concentration of 1 μM. This compound was toxic for the host cells only at a 400-fold higher concentration. Some of the 1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine derivatives proved effective against a variety of HIV-1 strains, including those that are resistant to 3'-azido-3'-deoxythymidine (AZT), but not against HIV-2(ROD) or simian immunodeficiency virus (SIV/MAC251). HIV-1 strains containing the L100I, K103N, V106A, E138K, Y181C or Y188H mutation in the reverse transcriptase (RT) displayed reduced sensitivity to the compounds. EA-521 enhanced the anti-HIV-1 activity of AZT and didanosine (ddI) in a synergistic manner. HIV-1-resistant virus containing the V179D mutation in the RT was selected after approximately 6 passages of HIV-1(III_B) in CEM cells in the presence of 15 and 300 μM of EA-521. From structure-activity relationship analysis of a wide variety of 1,1,3-trioxo-2*H*-,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine derivatives, a number of restrictions appeared as to the chemical modifications that were compatible with anti-HIV activity. In contrast with most other NNRTIs but akin to nevirapine, EA-521 cannot act as an hydrogen bond donor in the RT/drug complex. Preliminary modelling studies suggest that the 4-substituent interacts with V179, and that in the case of EA-521 the 4-cyano substituent may be involved in the emergence of the V179D mutation.

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***In Vitro* Anti-Human Immunodeficiency Virus (HIV) Activity of the Chromanone Derivative, 12-Oxocalanolide A.**

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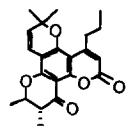
A chromanone derivative, 10,11-*trans*-dihydro-6,6,10,11-tetramethyl-4-propyl-2*H*,6*H*,12*H*-benzo[1,2-b:3,4-b':5,6-b"]tripyran-2,12-dione or 12-oxocalanolide A, a synthetic intermediate for naturally occurring anti-HIV agent (+)-calanolide A, has been discovered to be active against HIV in the *in vitro* XTT assay. 12-Oxocalanolide A has been evaluated for activity against several laboratory and clinical HIV-1 isolates with EC_{50} concentrations ranging from 0.4 - 3.0 μM. 12-Oxocalanolide A is a reverse transcriptase (RT) inhibitor, and exhibits activity against virus isolates with mutations of Y181C and P236L. Also, 12-oxocalanolide A remains fully active against 3TC-resistant isolates, with a mutation of M184I, while it has reduced activity against A17 strains, with Y181C and K103N mutations. The compound does not inhibit HIV integrase.



Conclusions:
(1) 12-oxocalanolide A may belong to the same subclass of non-nucleoside HIV-1 RT inhibitors as (+)-calanolide A.
(2) 12-Oxocalanolide A has one less chiral center than (+)-calanolide A, and, therefore, can be more easily produced, especially in larger quantities.
(3) 12-Oxocalanolide A deserves further pharmacological and toxicological evaluation.

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Betain-type fluoroalkylated oligomers are potent inhibitors of human immunodeficiency viruses type 1 (HIV-1) and other enveloped viruses

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We have examined novel betain-type fluoroalkylated oligomers for their inhibitory effects on the replication of HIV-1 and the other enveloped viruses, including herpes simplex virus type 1 (HSV-1), type 2 (HSV-2) and respiratory syncytial virus (RSV), *in vitro* and found that they are potent inhibitors of these viruses. RD6-2198, the most potent compound of this series, inhibited the replication of HTLV-III_B strain at a concentration of 0.71μg/ml with a selectivity index greater than 70 in MT-4 cells. Furthermore, EC_{50} values for HSV-1, HSV-2 and RSV were 0.51, 0.94 and 12.1μg/ml, respectively. To elucidate their mode of action, the effect of RD6-2198 on gp120-CD4 interaction was examined by using an ELISA method. The compound was found to inhibit gp120-CD4 interaction, indicating a class of viral adsorption inhibitors. RD6-2198 also inhibited binding of anti-gp120 monoclonal antibody to gp120 expressed molecules in MOLT-4/III_B (MOLT-4 chronically infected with HIV-1) cells. However, the compound did not affect binding of anti-CD4 antibody to CD4. These results suggest that RD6-2198 interacts with viral envelope and exerts its anti-HIV-1 activity through the inhibition of viral adsorption.

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Highly Potent UC Analogs With Efficacy Against NNRTI-Resistant Viruses Buckheit, R.W., Jr., Fliakas -Boltz, V., Kinjerski, T.I.., Russell, J.D., and Pallansch, L.A. Southern Research Institute, Frederick, MD, USA

Structure-activity relationships of a series of compounds related to the nonnucleoside reverse transcriptase inhibitor oxathiin carboxanilide have been described. Four new UC analogs (UC10, UC040, UC82 and UC781) have been determined to inhibit laboratory-derived and primary virus isolates at low nanomolar concentrations in both established and fresh human cells. Each of the compounds synergistically interacted with nucleoside analogs to inhibit HIV-1 replication. As a group, the UC compounds were found to be less active against viruses with the L100I, K103N and Y181C amino acid changes in the RT and, upon *in vitro* selection, yielded resistant virus with the Y181C mutation in the RT. The most potent of the three new compounds, UC781, contains a furanyl side chain similar to UC10, but differs in having an extended ether side chain instead of an oxime chain. The broad therapeutic index of UC781 (>62,000) resulted in effective inhibition of NNRTI-resistant virus isolates at high nanomolar concentrations. Further, UC781 and the NNRTI costatolide were able to synergistically inhibit HIV-1 replication when used in combination, suggesting that UC781 may interact with the RT differently than the other UC analogs.