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Synthesis, Activity against Human Immunodeficiency Virus and Cytotoxicity in Cell Cultures of 5'-Carboxyphosphonyl Derivatives of Dideoxynucleosides.

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5'-Carboxyphosphonyl derivatives of nucleoside analogs which are potent anti-HIV agents, AZT, ddC and d4T, were synthesized. These are: 3'-azido-5'-carboxyphosphonyl-2',3'-dideoxythymidine (CP-AZT), 5'-carboxyphosphonyl-2',3'-dideoxycytidine (CP-ddC), and 5'-carboxyphosphonyl-2',3'-didehydro-2',3'-dideoxy-thymidine (CP-d4T). The anti-HIV activity of the CP- analogs was determined by Focal immunoassay using human HeLa CD_4 (HT4-6C) cells and Reverse Transcriptase assay using human peripheral monocytes/macrophages (PBM) and MT-2 cells. CP-AZT was five-fold and 20 fold less active than AZT in MT-2 cells, PBM and HT4-6C cells. The most significant drop (approx. 1000 fold) in anti-HIV activity was observed for CP-d4T (ED_{50} 40 μM) in HT4-6C cells. CP-ddC activity was 75 fold (ED_{50} 0.75 μM) and 125 fold (ED_{50} 7.5 μM) lower in MT-2 and PBM, respectively. Toxicity of CP-AZT, CP-ddC and CP-d4T was lower than the parent nucleosides.

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Synthesis, Activity against Human Immunodeficiency Virus and Cytotoxicity of Derivatives of 5-Hydroxymethyl-2'-Deoxyuridine.

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5-Hydroxymethyl-2'-deoxyuridine (**1**) is a moderate inhibitor of human immunodeficiency virus (HIV) in replicating T-cell culture which prolonged the life of mice implanted with Friend Leukemia Virus Complex. 3'-Fluoro-2',3'-dideoxy-5-hydroxymethyluridine (**2**), 2',3'-dideoxy-5-hydroxymethyluridine (**3**) and 2',3'-dideoxy-2',3'-didehydro-5-hydroxymethyluridine (**4**) were synthesized to improve the activity of **1** against HIV. The antiviral activity of compound **2**, **3** and **4**, FddT and d4T (positive controls) against HIV was determined by Focal immunoassay using HeLa CD_4 (HT4-6C)cells. The average concentrations required to inhibit HIV by 50% (ED_{50}) for **1**, d4T and FddT were 9 μM, 0.05 μM and 1.3 μM, respectively. Compounds 2-4 were devoid of anti-HIV activity. Compounds **2-4** have low cytotoxicity (CC_{50} for HT4-6C cells >3000 μM).

AZT showed high affinity for the human cellular thymidine kinase (TK), its IC_{50} value for the enzyme was about 11 μM. When assayed under the same conditions, the IC_{50} values for **1**, d4T and **4** were approximately 311 μM, 3470 μM and >4,000 μM, respectively. Thus one possible reason for the loss of anti-HIV activity of the derivatives of **1** may be the result of very low affinity for cellular TK.

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The Thiocarboxanilides UC-781 And UC-82 Are Potent HIV-1-Specific Reverse Transcriptase Inhibitors That Inhibit A Broad Spectrum Of Drug-Resistant HIV-1 Strains

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The thiocarboxanilide derivatives UC-10, UC-781 and UC-82 containing a 2-methyl-substituted furanyl (UC-10; UC-781) or thienyl (UC-82) ring linked to the thiocarboxy group and a t-butyl oxime ether (UC-10) or pentenyloxyether (UC-781; UC-82) chain linked to the 4-chlorophenyl ring in meta position were synthesized by scientists at Uniroyal Chemical Ltd. and are potent and selective inhibitors of HIV-1. UC-781 and UC-82 inhibit wild-type HIV-1/III_B at a 50% effective concentration (EC_{50}) as low as 0.002 μg/ml. They also markedly inhibit mutant virus strains, including those viruses containing the 100 Leu → Ile, 103 Lys → Asn, 106 Val → Ala, 138 Glu → Lys or 181 Tyr → Cys mutation in their reverse transcriptase. The 50% EC_{50} values for the mutant virus strains ranged from 0.004 to 0.006 μg/ml (for the 106 Ala and 138 Lys mutant strains) and from 0.014 to 0.023 μg/ml (for the 103 Asn and 181 Cys mutant strains). The UC-781 and UC-82 derivatives select for mutant virus strains with only minimal resistance. They proved to knock-out virus from the cell cultures at concentrations that were 10- to 50-fold lower than those required for the parent thiocarboxanilide UC-10, nevirapine and BHAP U90152 to knock-out the virus. Addition of 50% human serum to the virus-infected cell cultures only slightly reduced the antiviral efficiency of the thiocarboxanilides, and the compounds proved highly stable in human serum for at least 24 hours. Moreover, UC-10 was able to efficiently protect human $CD4^+$ lymphocytes from destruction by HIV-1 in SCID/hu PBL mice. The thiocarboxanilides should be considered as attractive candidate drugs to be further investigated in clinical trials in HIV-1-infected individuals.

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Structure - Activity Relationship of Non-nucleoside RT inhibitor, Thiadiazole derivatives

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We have recently reported that 1,2,5-thiadiazole (TDA) derivatives are highly potent inhibitors of HIV and HIV-1 reverse transcriptase (RT). We expected that *N*-carbamate and phenyl moieties are essential substitution components for the inhibition activity of HIV-1 RT. In order to understand the relationship between inhibitory properties and the moieties at these sites, the quantitative structure-activity relationship (QSAR) was calculated using CoMFA method for the TDA derivatives and non-nucleoside RT inhibitors (NNRTIs), nevirapine and L696229. The followings were elucidated from the results: (1) There is a low steric bulk tolerance region at the *para* position of 4-phenyl-TDA, and there are high steric bulk tolerance regions *ortho* and *meta* positions of 4-phenyl-TDA. (2) The carbonyl oxygen atom of TDA was overlaid on the amide oxygen atom of nevirapine and L696229. This oxygen atom may interact with RT and have a key role in inhibiting the RT activity. (3) The phenyl ring of TDA derivatives was not overlaid on nevirapine and L696229. This interaction mode may be different from the mode of the two NNRTIs. These results suggest that TDA derivatives might inhibit the activity of the NNRTIs-resistant RT.