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Synthesis and Structure-Activity Relationship of Thiadiazole Derivatives, Novel Nonnucleoside Inhibitors of HIV-1

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In our extensive synthesis and screening program for anti-HIV compounds, we have recently found that a novel series 1,2,5-thiadiazole derivatives are highly potent and selective inhibitors of HIV-1 replication. In the screening assays, MT-4 cells were infected with HIV-1_{IIIB} and incubated in the presence of varying concentrations of the test compounds. After a 4- or 5-day incubation period, the number of viable cells were determined by the MTT method. Approximately 200 compounds were synthesized and examined for their anti-HIV-1 activities in MT-4 cells. Among them, more than 100 compounds proved inhibitory to HIV-1 replication at concentrations that were significantly lower than their cytotoxic thresholds. 4-Phenyl-1,2,5-thiadiazole-3-yl N,N-dimethylcarbamate was the first compound of which anti-HIV-1 activity was identified. Its 50% effective concentration (EC_{50}) and the 50% cytotoxic concentration (CC_{50}) were 23 and 183μM, respectively. Introduction of chlorine atoms into the 2,6-positions of the phenyl group led to significant increase of activity (EC_{50}=240nM). Furthermore, with regard to the carbamate group, the compounds having N-methyl-N-propylcarbamate moiety showed the most potent anti-HIV-1 activity. Consequently, the obtained compound 4-(2,6-dichlorophenyl)-1,2,5-thiadiazole-3-yl N-methyl-N-propylcarbamate (RD4-2024) inhibited HIV-1 replication in MT-4 cells at a concentration of 13nM. Its selectivity index (ratio of CC_{50} to EC_{50}) was greater than 10,000. This compound appears to be worth pursuing as a candidate drug for the chemotherapy of HIV-1 infections.

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Mechanism of Anti-Human Immunodeficiency Virus (HIV) Action of Selected ATA-Polymer Analogues

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Various aurintricarboxylic acid (ATA) polymer analogues were prepared by substituting certain salicylic acid derivatives and carbonyl compounds for salicylic acid and formaldehyde in the ATA polymerization reaction. These compounds proved inhibitory to the replication of HIV and several enveloped viruses, showing the highest activity against HIV and HCMV [50% effective concentration (EC_{50}): 0.5 and 1.1 μg/ml for HIV and HCMV, respectively]. They inhibited syncytium formation between persistently HIV-1 and HIV-2-infected HUT-78 cells and uninfected MOLT-4 cells at EC_{50} values ranging from 2 to 50 μg/ml. Under similar experimental conditions, ATA had an EC_{50} of 2 μg/ml for HIV-1- and 0.4 μg/ml for HIV-2-induced syncytium formation. The novel ATA polymer analogues were equipotent to ATA in their inhibition of adsorption of HIV-1(III_B) and recombinant gp120 to MT-4 cells. By flow cytometric/immunofluorescent techniques we could demonstrate that the derivatives also prevented the binding of anti-gp120 monoclonal antibody to HIV-1 gp120 and most of them interfered with the interaction between OKT4A monoclonal antibody and the CD4-receptor of MT-4 cells. In conclusion, the anti-HIV activity of the novel series of ATA polymer analogues is due to the inhibition of virus adsorption to $CD4^+$ cells, resulting from an interaction with both the HIV-1 gp120 and the cellular CD4 receptor. This is in contrast with other polyanionic derivatives such as dextran sulfate that solely interact with HIV-1 gp120.