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Thiadiazole Derivatives as Highly Potent Inhibitor of Human Immunodeficiency Virus Type 1 (HIV-1)

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We have examined thiadiazole derivatives for their inhibitory effects on HIV-1 replication in various cell cultures and found that they are highly potent and selective inhibitors of HIV-1. MT-4, U937 and peripheral blood lymphocyte (PBL) cells were used in the anti-HIV assays. Several virus strains of HIV-1, including a laboratory strain, clinical isolates, AZT-resistant mutants, and nonnucleoside reverse trnscriptase inhibitor (NNRTI)-resistant mutants and HIV-2 were used for the assays. The anti-HIV activities were determined by the inhibition of virus-induced cytopathic effect in infected cells or the reduction of p24 antigen in culture supernatants. The 50% effective concentration (EC_{50}) and the 50% cytotoxic concentration (CC_{50}) were calculated by the standard method. RD4-2024, the most potent compound in this series, inhibited HIV-1 replication in variety cell cultures at a concentration of 4-13nM. Its selectivity index (ratio of CC_{50} to EC_{50}) was greater than 10,000. RD4-2024 was also highly inhibitory to various clinical isolates and AZT-resistant mutants of HIV-1. Whereas the compound could not inhibit the replication of the NNRTI-resistant mutants and HIV-2. Studies on their mechanism of action revealed that the thiadiazole derivatives inhibited the activity of recombinant HIV-1 RT. The 50% inhibitory concentration (IC_{50}) of RD4-2024 was 800nM when poly(rC)-oligo$(dG)_{12-18}$ was used as the template-plimer. Furthermore, this compound did not affect the activity of HIV-2 RT. Taken together, we have concluded that the thiadiazole derivatives belong to the family of NNRTIs such as nevirapine, HEPT, and αAPA .

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QSAR Study of Nucleoside Analogs with Anti-HIV Activity Using Molecular Similarity Analysis and Structure-Activity Maps

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The correlations between molecular structure and anti-HIV activity of nucleoside analogs have been investigated using molecular similarity analysis and structure-activity maps. Molecular descriptors such as molecular topology number (NAB), maximum common substructure (MaCS), minimum common superstructure (MiCS), and molecular similarity index (MSI) have been used in the molecular similarity analysis. NAB denotes the number of atoms and bonds in a molecule. The maximum common substructure (MaCS) of two molecules is defined as a substructure, with the greatest value of NAB, common to both molecules. A minimum common superstructure (MiCS) is defined as the union of two molecules. MaCS and MSI quantify the similarity between two molecular structures. A topological approach using these descriptors (NAB, MaCS, MiCS and MSI) to perform quantitative molecular similarity analysis (QMSA) and quantitative structure activity relationship (QSAR) study of the structure and anti-HIV activity of nucleoside analogs is described. Structure-activity maps are also used to examine the structure and anti-HIV activity relationships of nucleoside analogs including dideoxynucleoside analogs, acyclic and carbocyclic nucleoside analogs.