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Mechanism of action of ribavirin. JL Patterson and R Fernandez-Larsson. Division of Infectious Diseases Children's Hospital and Department of Microbiology and Molecular Genetics, Harvard Medical School, Boston MA 02115.

Ribavirin (1-B-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) or Virazole is a broad-spectrum antiviral agent whose molecular mode of action remains remarkably controversial. Ribavirin is and has been under clinical investigation against a variety of viral illness, including those due to influenza virus, Lassa fever, Korean hemorrhagic fever with renal syndrome (KHFS) and Human immunodeficiency virus (HIV). There has been a great deal of clinical interest in utilizing ribavirin for HIV infections. It has been reported to slow the development of AIDS in HIV infected patients. Ribavirin inhibits the human immunodeficiency virus (HIV) reverse transcriptase (RT) in an in vitro reaction. Ribavirin-5'-diphosphate was close to 40% more inhibitory than ribavirin-5'-triphosphate (RTP). Unphosphorylated ribavirin had a reduced, but detectable, effect as an inhibitor than the phosphorylated forms. The compounds seem to have a direct effect on the viral polymerase, and no chain termination was observed in the presence of RTP. Combination of any of the ribavirin derivatives tested with 3'-azido-3'-deoxythymidine (AZT, zidovudine) 5'-triphosphate resulted in an increase of its anti-HIV RT activity in the in vitro assay. Also, combination of any of the ribavirin derivatives tested with ddITP resulted in a precisely additive inhibitory effect in the in vitro assay.

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Antirhinovirus Spectrum and Mechanism of Action of R 77975.
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R 77975, a substituted phenoxy-pyridazinamine, is the prototype of a novel class of broad-spectrum antipicornavirus compounds. In an automated MTT assay, R 77975 inhibited the development of CPE of 90 out of 100 serotypes at concentrations ranging from 0.002 to 1 μg/ml. While the predecessor R 61837, a substituted phenyl-pyridazinamine, was active against 70 out of 100 serotypes at concentrations above 32 μg/ml, the new compound inhibits the same percentage of viruses at 0.040 μg/ml.

Studies on the mechanism of action showed that many, but not all susceptible rhinovirus serotypes could be neutralized by a direct contact with the antiviral compound. The infectivity could generally not be regained by dilution of neutralized virions, but was regained by organic solvent extraction of the compound for most serotypes. Neutralized viruses became stabilised to acid and heat, strongly suggesting a direct interaction of the compounds with viral capsid proteins. Mutants resistant to R 61837 were shown to bear some cross-resistance with the new compound, indicating that R 77975 too binds into the hydrophobic pocket beneath the canyon floor of rhinoviruses. The compound acts at the early stages of the replication cycle. The mode of action appears to be serotype-specific, since R 77975 was able to inhibit the adsorption of HRV9 but not that of HRV1A.