

The Mechanism of Action of Antirhinoviral 9-Benzylpurines. J.W.T.SELWAY and J.L.KELLEY. Wellcome Research Laboratories, Beckenham, Kent, U.K., and Burroughs Wellcome Co., Research Triangle Park, NC 27709, U.S.A.

Rhinoviruses are the major etiological agents of the common cold. With over 100 antigenically distinct sero-types the development of a vaccine seems remote and, therefore, these viruses are an attractive target for chemotherapy. Novel derivatives of 9-benzylpurine are selective for certain rhinovirus serotypes with activity in the range 0.3-10.0 μ M. 6-Dimethylamino-9-(4-methylbenzyl)-2-trifluoromethyl-9H-purine (BW B429U) was chosen for mechanism studies. BW B429U inactivates, irreversibly, sensitive virus and requires to be present at the time of infection for optimum inhibitory activity. Mutants resistant to BW B429U shared cross-resistance with mutants resistant to capsid binding compounds. The mechanism of action is similar to that of 4',6-dichloroflavan (BW683C) and other "capsid binders" which stabilise the virion and prevent conformational changes essential for the release of viral RNA. The rhinovirus capsid has been shown to be a valid target for chemotherapy and the 9-benzylpurines are another structural type which prevent uncoating and inhibit rhinovirus replication.

In Vitro Antiviral Spectrum of LY253963. J. D. Nelson*, D. C. DeLong, J. Terry, J. Tang, B. Warren, E. Wu, D. W. White, C. Gale, and W. A. Spitzer, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana, 46285.

LY253963 (the sodium salt of 1,3,4-thiadiazol-2-ylcyanamide) is a unique antiviral agent having broad spectrum in vitro activity. LY253963 is active in vitro against both A and B strains of influenza with an average IC_{50} (plaque reduction) of approximately 1 μ g/ml. In addition, LY253963 is very active when tested against various members of the paramyxovirus family. While the compound is active against ECHO 25, other members of the picornavirus family (including rhinovirus and poliovirus) are not affected. The in vitro spectrum of LY253963 includes DNA viruses, being active against vaccinia and certain members of the herpes virus family; however it is not active against Adeno 21. While the mechanism of action is not known, it has been noted that the in vitro activity may vary from cell line to cell line. Reversal of the in vitro activity was attempted by the addition of various metabolites or pseudometabolites to the testing milieu. Of more than 250 compounds examined, only 5-fluorouracil and certain guanosine derivatives reversed or partially reversed the antiviral activity.